AusPAR Attachment 1

Extract from the Clinical Evaluation Report for Buprenorphine

Proprietary Product Name: Transtec and three additional trade names

Sponsor: Mundipharma Pty Ltd

First round April 2015
Second round 28 September 2015
About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website [https://www.tga.gov.au](https://www.tga.gov.au).

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
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<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACPM</td>
<td>Advisory Committee on Prescription Medicines</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AUCinf</td>
<td>Area under the concentration-time curve extrapolated to infinity</td>
</tr>
<tr>
<td>AUClast</td>
<td>Area under the concentration-time curve from the time of dosing to the last quantifiable concentration</td>
</tr>
<tr>
<td>AUC t1-t2</td>
<td>Area under the curve from time t1 to time t2</td>
</tr>
<tr>
<td>AUCcum</td>
<td>Cumulated area under the curve</td>
</tr>
<tr>
<td>BUP</td>
<td>buprenorphine</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>Ce</td>
<td>threshold concentration = MEC = minimum effective concentration</td>
</tr>
<tr>
<td>c (conc.)</td>
<td>Concentration</td>
</tr>
<tr>
<td>CMI</td>
<td>Consumer medicines information</td>
</tr>
<tr>
<td>Cmax</td>
<td>Maximum observed concentration</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRO</td>
<td>Contract Research Organisation</td>
</tr>
<tr>
<td>C.V.</td>
<td>Coefficient of variation</td>
</tr>
<tr>
<td>FAS</td>
<td>Full analysis set</td>
</tr>
<tr>
<td>GC/MS</td>
<td>gas chromatography / mass spectrometry</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>h, hrs</td>
<td>hour(s)</td>
</tr>
<tr>
<td>ITT</td>
<td>intention-to-treat</td>
</tr>
<tr>
<td>IV, i.v</td>
<td>intravenous(ly)</td>
</tr>
<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>LLOQ</td>
<td>lower limit of quantification = LLQ</td>
</tr>
<tr>
<td>LLQ</td>
<td>lower limit of quantification = LLOQ</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>MAOI</td>
<td>mono amino oxidase inhibitor</td>
</tr>
<tr>
<td>MEC</td>
<td>minimum effective concentration = ce; for buprenorphine this is assumed at 100 pg/mL</td>
</tr>
<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency (UK)</td>
</tr>
<tr>
<td>µg</td>
<td>microgram = µg</td>
</tr>
<tr>
<td>µg/h</td>
<td>micrograms per hour = µg/h</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>mg/h</td>
<td>milligrams per h</td>
</tr>
<tr>
<td>NA</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NRS</td>
<td>Numeric Rating Scale</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-Steroidal Anti-Inflammatory Drug</td>
</tr>
<tr>
<td>PD</td>
<td>Pharmacodynamics</td>
</tr>
<tr>
<td>PI</td>
<td>Product information</td>
</tr>
<tr>
<td>PIL</td>
<td>Patient information leaflet</td>
</tr>
<tr>
<td>PK</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td>PP</td>
<td>Per protocol</td>
</tr>
<tr>
<td>pg</td>
<td>picogram</td>
</tr>
<tr>
<td>pg/mL</td>
<td>picogram per millilitre</td>
</tr>
<tr>
<td>QTc</td>
<td>QT interval corrected for heart rate</td>
</tr>
<tr>
<td>RR</td>
<td>relative risk</td>
</tr>
<tr>
<td>SADR</td>
<td>serious adverse drug reaction</td>
</tr>
<tr>
<td>SAE</td>
<td>serious adverse event</td>
</tr>
<tr>
<td>SAF</td>
<td>safety (analysable set)</td>
</tr>
<tr>
<td>SD</td>
<td>standard error of the mean</td>
</tr>
<tr>
<td>SL</td>
<td>Sublingual</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of product characteristics (SPC)</td>
</tr>
<tr>
<td>SPC</td>
<td>Summary of product characteristics (SmPC)</td>
</tr>
<tr>
<td><strong>t</strong>(\frac{1}{2},z)</td>
<td>half-life</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>t_{lag}</strong></td>
<td>lag-time (first time of occurrence of concentration above LLOQ)</td>
</tr>
<tr>
<td><strong>TD</strong></td>
<td>Transdermal</td>
</tr>
<tr>
<td><strong>TDP</strong></td>
<td>Transdermal patch</td>
</tr>
<tr>
<td><strong>TdP</strong></td>
<td>Torsade de Pointes</td>
</tr>
<tr>
<td><strong>t_{max}</strong></td>
<td>time to reach (C_{\text{max}})</td>
</tr>
<tr>
<td><strong>TTS</strong></td>
<td>Transdermal therapeutic system</td>
</tr>
<tr>
<td><strong>TTS50</strong></td>
<td>20 mg transdermal patch = BUP-TDP35 (\mu g/h)</td>
</tr>
<tr>
<td><strong>TTS75</strong></td>
<td>30 mg transdermal patch = BUP-TDP 52.5 (\mu g/h)</td>
</tr>
<tr>
<td><strong>TTS100</strong></td>
<td>40 mg transdermal patch = BUP-TDP 70 (\mu g/h)</td>
</tr>
<tr>
<td><strong>ULQ</strong></td>
<td>upper limit of quantification</td>
</tr>
<tr>
<td><strong>VRS</strong></td>
<td>Verbal rating scale</td>
</tr>
<tr>
<td><strong>WHO</strong></td>
<td>World Health Organisation</td>
</tr>
</tbody>
</table>
1. **Introduction**

This is a major variation application to register additional strengths and a different dosing frequency of a buprenorphine transdermal drug delivery system, under the proposed trade name of Transtec and three additional trade names. Three dose strengths are proposed (20 mg, 30 mg and 40 mg with the proposed release rates of 35 µg/h, 52.5 µg/h and 70 µg/h respectively) and a dosing frequency of 96 hours. The indication proposed by the sponsor is the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.

Buprenorphine is a potent opioid analgesic used in the treatment of chronic and acute pain and in the treatment of opiate dependence. It is a semi synthetic compound derived from thebaine, a natural opium alkaloid, and structurally similar to morphine, although several molecular differences confer specific properties on buprenorphine. It is commonly described as having partial agonist action at the mu-opioid receptors.

Buprenorphine was first synthesized in the late 1960s, and introduced into worldwide clinical practice in a parenteral formulation in the late 1970s. Sublingual and transdermal formulations subsequently became available. Formulations of buprenorphine for intravenous and sublingual administration were first registered for use in Australia in 1991 with the indication of short-term (not more than one week) relief of moderate to severe pain. A transdermal form, Norspan (from the same sponsor as the current application), was registered in Australia in April 2005 for the indication of moderate to severe pain. Sublingual dosing forms are also available for the management of opiate dependence.

The proposed indication of the new dosing strengths and regimen is the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.

The following dosage forms and strengths currently registered in Australia are shown in Table 1 below.

---

1 Temgesic Product Information accessed February 2015
2 Norspan Product Information. Date of last amendment 25 August 2009.
Table 1: Currently registered forms of Buprenorphine

<table>
<thead>
<tr>
<th>Trade name</th>
<th>Dosage form</th>
<th>Strengths</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temgesic</td>
<td>Sublingual, Intravenous</td>
<td>0.2 mg tablet, 0.3mg ampoule</td>
<td>Acute moderate to severe pain</td>
</tr>
<tr>
<td>Norspan*</td>
<td>Transdermal patch changed every 7 days</td>
<td>5, 10, 15, 20, 25, 30, 40 µg/h</td>
<td>Moderate to severe pain</td>
</tr>
<tr>
<td>Bupadex</td>
<td>Sublingual tablet</td>
<td>0.2, 4, 8 mg</td>
<td>Management of opiate dependence</td>
</tr>
<tr>
<td>Subutex</td>
<td>Sublingual tablet</td>
<td>0.4, 2, 8, 16 mg</td>
<td>Management of opiate dependence</td>
</tr>
<tr>
<td>Bupradone, Subuxone</td>
<td>Sublingual, combination with naloxone</td>
<td>various</td>
<td>Management of opiate dependence</td>
</tr>
</tbody>
</table>

*Same sponsor as current application. Patch structurally the same as the subject of this submission, except for different application time, lower dose strengths and indication.

The product is for transdermal administration only, with dose to be adjusted, by changing the patch strength, according to clinical response. Three dosing strengths are provided, 20 mg (35 µg/h), 30 mg (52.5 µg/h) and 40 mg (70 µg/h), and a dosing interval of 72 to 96 hours advised.

The draft Product Information (PI) advises that opioid naïve patients, patients who have previously received a non-opioid or weak opioid, and patients switching from a strong opioid should start with the lowest transdermal patch strength, 20 mg (35 µg/h). Patients who have previously been treated with high doses of strong opioids (such as 120 mg of oral morphine) may start at the next patch strength, 30 mg (52.5 µg/h).

Due to the slow onset of action with the first patch, the previous analgesic(s) should be administered during the first 12 hours. A dosing interval of 96 hours at most is recommended with the suggestion that changing the patch twice a week on specific days (for example always on Monday morning and Thursday evening) may be optimal. Non-opioid analgesics should be continued if possible and analgesics for breakthrough pain provided, with a recommended regimen of one to two buprenorphine 0.2 mg sublingual medications per day. The patch dose should be individually titrated until analgesic efficacy is attained. If analgesia is inadequate at the end of an application period, or excessive doses of breakthrough medications have been required (0.4 to 0.6 mg sublingual buprenorphine), the dose may be increased by either applying an additional same strength patch or by switching to the next patch strength. A maximum dose of 2 x 40 mg patches (140 µg/h) is recommended.

Use in children (aged less than 18 years) is not recommended. No dose adjustment is required in the elderly or in renal failure. Patients with liver disease should be closely monitored.

Comment: The proposed patch strengths supplement the currently registered buprenorphine patches (Norspan), with substantially lower dose strengths available in the Norspan formulation (see Table 1 above). The recommendation of the draft Transtec PI that all patients, from the opioid naïve to those on moderate doses of opioids, commence on the Transtec 35 µg/h strength patch does not consider the availability of lower patch strengths in the Norspan formulation (see description below). Given the high rate of discontinuations seen in the clinical studies due to opioid type adverse events in opioid naïve patients, it may be more appropriate that opioid naïve patients commence at lower patch strengths, such as 20 µg/h, and gradually titrate upwards based on clinical response.
patients commence on a lower strength Norspan patch; the Australian Therapeutic Guidelines: Analgesic\textsuperscript{3} recommend initiating patients on a 5 µg/h strength patch. The full range of buprenorphine patches (both seven day and four day formulations) should be considered when determining the most appropriate starting point for patients already receiving opioids.

The PI proposes a maximum dose of two 70 µg/h patches although the maximum dose used in the clinical trials was 70 µg/h and the higher dose was rarely reported as being used in the post-marketing surveillance studies. The rationale for the maximum dose of 2 x 70 µg/h patches provided in the clinical overview is that this would allow for the additional SL buprenorphine tablets used in the clinical studies and because this dose would correspond to 240 mg of oral morphine. This was not further substantiated by an estimate of the additional buprenorphine tablets taken in the studies and whether this equated to a second 40 mg patch. Nor was there any reference for the statement regarding equipotency to 240 mg of morphine.\textsuperscript{4} An upper dose limit of one 70 µg/h patch would be more in keeping with the dose tested in the studies.

2. Clinical rationale

Chronic pain is a common clinical problem that is often difficult to treat. It may be divided into cancer related, neuropathic and nociceptive groups, according to the type of cause, or more simply into cancer related and non-cancer related. An accepted way to treat moderate to severe chronic pain is to combine a strong opioid in a prolonged release formulation together with an immediate release formulation for managing breakthrough pain.

The World Health Organisation (WHO) proposed a simple stepwise approach to chronic pain (Fig 1): commencing with Level 1 non-opioid drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol, progressing to Level 2 with weak opioids for mild to moderate pain and then escalating to WHO Level 3 by adding a strong opioid for moderate to severe pain. At each level, drug administration was to be regular and options for breakthrough pain provided. This ladder was proposed in 1994 for use in cancer pain and has since also been used for chronic pain of all causes. Terminology related to the WHO Pain Relief Ladder is used throughout the dossier.

\textsuperscript{3} Chronic pain: pharmacological management pp113-134. Therapeutic Guidelines: Analgesic, Version 6, 2012

\textsuperscript{4} This issue was resolved during the second round of evaluation.
Buprenorphine is a potent opioid analgesic that has been used for several decades in the treatment of moderate to severe acute (for example, post-operative) pain, acute and chronic cancer pain, and severe chronic non-cancer pain. In some countries, including Australia, buprenorphine has also been used in the management of opioid dependence, with doses well above the analgesic range.

In nonclinical tests, buprenorphine has been demonstrated to act as a partial agonist at the mu-opioid receptor with ceiling effects for both analgesia and respiratory depression. In clinical studies, the ceiling effect was confirmed for respiratory depression but not for analgesia. It is postulated that the therapeutic doses required for analgesia fall well short of the potential analgesia ceiling.

Transdermal delivery systems provide a convenient method for the regular delivery of analgesic medications and may avoid the peaks and troughs in serum drug levels seen with other routes of administration, thereby improving pain control. Passive transdermal diffusion of medication occurs over a number of days, maintaining a constant therapeutic dose. The physicochemical properties of buprenorphine (for example, high lipophilicity, low molecular weight, water solubility) together with its high affinity and slow dissociation from the mu-opioid receptors make it an appropriate agent for transdermal delivery.

Buprenorphine is absorbed by passive diffusion down a concentration gradient from the drug matrix, across the skin, into the subcutaneous tissue and thence into the bloodstream. The
stratum corneum is the main limiting factor to absorption. The composition of patches of all strengths is the same except for physical size. The amount of buprenorphine absorbed per hour is proportional to the surface area of the drug matrix in contact with the skin: the greater surface area of drug containing matrix in the higher strength patches enables a higher rate of drug absorption.

The dossier describes three dose strengths containing 20, 30 and 40 mg of buprenorphine with nominal in vivo release rates of 35 µg/h, 52.5 µg/h and 70 µg/h. The ‘hourly release rate’ used to describe each patch strength is the average rate of buprenorphine absorption from the patch over the entire dosing period. The clinical development programme of pharmacokinetic, controlled clinical trials and long-term safety and efficacy data from open follow-up studies, post marketing surveillance studies is briefly described.

Comment: The clinical rationale for the submission is acceptable and consistent with the recommended approach to chronic pain with the subject of the submission proposed as a WHO Level 3 opioid.

The dossier prefers to refer to the different patches by their ‘release rate’. This is the nominal average in vivo absorption rate. The term ‘release rate’ suggests an active controlled process by the patch, rather than the passive diffusion that is occurring. It also implies a consistency in absorption over time and between patients. It may be more correct to refer to the patches by the total amount of buprenorphine contained within the patch and the application time.\(^5\)

The Seven Day Norspan Patch: Another buprenorphine product using the same transdermal delivery system, but with a seven day application time, was registered in Australia in 2005 under the tradename Norspan. This patch is not discussed in the dossier but needs to be considered given the close relationship between the two patch formulations and frequent reference to the 7 day product in this evaluation. The Norspan patches available at the time of Australian registration were 5, 10 and 20 µg/h with higher strength patches (30 µg/h and 40 µg/h) becoming available recently. The dosing interval for Norspan patches is 7 days and the indication is ‘moderate to severe pain’. The seven day patch has been marketed in the USA since 2010 as Butrans that is sponsored by Purdue Pharma LP and manufactured by [information redacted].\(^6\) The manufacturer of the buprenorphine patch that is the subject of the current submission is [information redacted] and the Australian sponsor is Mundipharma Pty Ltd.

\(^5\) Definition of patch strength is given as the mean dose delivered per unit time consistent with EU guidelines. The overall drug content in the patch (in mg) is not an indicator of a patch strength, as it does not provide any information of what amount of drug is delivered to the body (this depends not only on drug content but also on the patch characteristics, for example, formulation and excipients, etcetera). Also, patches always contain a larger amount of drug than intended to be delivered: the excess of drug is needed to achieve and maintain the desired release rate. For example the range of daily dose of buprenorphine absorbed from the 40mg patch was estimated to be 0.04 to 5.0mg. The sponsor’s estimate was for a mean daily dose with the 40 mg patch was 1.7 mg buprenorphine daily. It is important to note that the residual buprenorphine in the patches is similar to the residual in Norspan patches because most of the active drug is not absorbed from either product over the application course.

\(^6\) http://www.drugs.com/pro/butrans-patch.html
Figure 3: Description of the Norspan, Butrans patch

Absorption of buprenorphine from a matrix patch worn over seven days is greater during the first few days of wear compared to the last few days. The use of a shorter dosing interval, such as 3 or 4 days, enables higher plasma concentrations to be achieved by exploiting this higher flux during the first few days. As an example, the 20 mg patch is common to both Norspan and Transtec and the area of active matrix in each is 25 cm²:

- When worn for 3 days, the average absorption rate is 35 µg/h (or 0.84 mg/day)
- When worn for 7 days, the average absorption rate is 20 µg/h (or 0.48 mg/day).

Transtec patches are square (20 mg patch, 35 µg/h) or rectangular (30 mg patch, 52.5 µg/h and 40 mg patch, 70 µg/h) beige coloured, matrix patches with rounded corners. Each patch consists of a protective liner and functional layers, proceeding from the outer surface towards the surface adhering to the skin, the layers are:

1. a beige coloured web backing layer of polyethylene terephalate (PET)
2. an adhesive matrix rim without buprenorphine (provides a seal around the active drug matrix)
3. a separating layer (‘foil’) of PET over the adhesive matrix
4. the buprenorphine containing adhesive matrix
5. a release liner, this is removed and discarded before use.
Table 2: Patch strength and size

<table>
<thead>
<tr>
<th>Purported Release Rate</th>
<th>Amount of Buprenorphine</th>
<th>Area of Active Matrix</th>
<th>Approximate size of patch as worn</th>
</tr>
</thead>
<tbody>
<tr>
<td>35 µg/h</td>
<td>20 mg</td>
<td>25 cm²</td>
<td>52 cm²</td>
</tr>
<tr>
<td>52.5 µg/h</td>
<td>30 mg</td>
<td>37.5 cm²</td>
<td>70 cm²</td>
</tr>
<tr>
<td>70 µg/h</td>
<td>40 mg</td>
<td>50 cm²</td>
<td>88 cm²</td>
</tr>
</tbody>
</table>

Comment:

- This formulation was used in the clinical trials and is the same formulation as the currently registered Norspan patches.
- Buprenorphine ‘release rates’ calculated prior to clinical testing were found to be an over estimation in clinical pharmacokinetic studies. Example: the 20 mg patch release was found to have an average release rate of 35 µg/h rather than the estimated 50 µg/h. Many of the studies provided in the dossier use a terminology based on the initial estimates of release rates (TTS50, TTS70 and TTS100), as will be evident in tables and figures taken from the study reports.
- The dosing interval used in the clinical studies was 72 hours. An additional pharmacokinetic study and two population pharmacokinetic studies⁷ were performed with the objective of showing bioequivalence for 72 hour and 96 hour dosing intervals.
- The post-marketing surveillance studies report patients wearing ⅛, ¼ and ½ of the 20 mg patch despite the advice in the CMI: ‘Do not cut or divide the patch’.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The clinical dossier documented a clinical development programme of pharmacology and efficacy studies. Much of the information regarding pharmacokinetics, pharmacodynamics, assessment of the use in special populations (renal disease, liver disease, pregnant or lactating females) and safety was extrapolated from pre-existing literature or experience of buprenorphine delivered by other routes.

Comment: Much of the clinical dossier appears to have been written and assembled almost 10 years ago, in 2005. The clinical overview, although dated August 2014, contains little information and no references more recent than 2005. The Summary of Clinical Safety is dated 15 November 2005 and has not been updated. The Risk Management Plan is dated 31 October 2014. There were considerable discrepancies and inconsistencies across the three documents. In particular, the Risk Management Plan describes two major new safety issues. Neither of these are discussed in the clinical overview and only one is discussed in the summary of clinical safety.

⁷ Correction: there were 2 studies one was a population PK study and the other was a Wagner –Nelson analysis.
[Information redacted] sponsored Phase III studies and post marketing surveillance studies that were performed after 2005 (and described in the PSURs) were not included in the dossier.

None of the research involving the closely related 7 day buprenorphine patch was included in the dossier, despite the active and ongoing research programme conducted by [information redacted]8.

The submission contained the following clinical information:

- 5 clinical pharmacology studies, with 5 providing pharmacokinetic data and 2 providing limited pharmacodynamic data. An additional pharmacodynamics study ('thorough QT study') located in an appendix to a PSUR has also been included.
- 1 population pharmacokinetic study and a Wagner-Nelson analysis.
- 6 efficacy and safety studies with
  - 3 placebo controlled efficacy/safety studies
  - 1 one placebo controlled withdrawal efficacy / safety study
  - 2 active controlled efficacy/safety studies
- 1 post-hoc analysis of the 3 placebo controlled efficacy/safety studies.
- 2 uncontrolled extension studies.
- 10 non interventional post-marketing surveillance studies, 2 with comparator arms (tramadol, fentanyl patch).
- 17 Periodic Safety Update Reports (PSURs) in 29 volumes covering the years 2002 to 2013.
- 74 publications were provided in the clinical overview, including
  - 30 publications supporting the pharmacology of buprenorphine; 8 publications describing use of opioids and/or buprenorphine in special populations
  - 4 related to safety aspects of buprenorphine
  - 3 publications supporting the use of transdermal buprenorphine in chronic pain
  - 1 publication on the use of naloxone in buprenorphine overdose.

Comment: None of these articles were published more recently than 2005.

The submission also contained a Clinical Overview; Summary of Biopharmaceutics, Summary of Clinical Pharmacology, Summary of Clinical Efficacy, Summary of Clinical Safety and list of literature references.

Comment: There were some technical issues with the clinical dossier that slowed the evaluation process. These included:

- non-functioning hyperlinks in the electronic documents
- some electronic documents did not allow copying and pasting of text
- none of the electronic documents allowed searching within the contents
- not all cited references were provided. One frequently cited reference was only provided in German9.

8 Data from the 7 day patch was made available where it was relevant in response to TGA questions.
9 Where the TGA notified the applicant, this was corrected.
3.2. Paediatric data

The submission did not include paediatric data and the sponsor describes no paediatric development plan. The draft PI states: ‘As Transtec has not been studied in patients under 18 years of age, the use of the medicinal product in patients below this age is not recommended’.

Comment: Chronic pain states, including cancer related, are not unusual in children with management preferably through a multi-disciplinary and multi-modal approach, with pharmaceutical agents one element of this. The post-marketing surveillance studies provided in the dossier report the use of the buprenorphine patches in children as young as 21 months. Off label use in children can therefore be expected. Research in the use of opioids for chronic pain states in children, especially long acting opioids that do not require oral or parenteral administration, could be of clinical benefit.

3.3. Good clinical practice

The submission states that the clinical trials, which were all conducted in Europe, were conducted in accordance with Good Clinical Practice (ICH GCP) (CPMP/EWP/612/00). Review of the study reports supports this.

4. Pharmacokinetics

Limited pharmacokinetic studies were performed with considerable reliance placed on the existing literature regarding buprenorphine delivered by other routes to describe both pharmacokinetic and pharmacodynamic characteristics.

4.1. Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 3 shows the studies relating to each pharmacokinetic topic.
Table 3: Submitted pharmacokinetic studies

<table>
<thead>
<tr>
<th>PK topic</th>
<th>Subtopic</th>
<th>Study ID</th>
<th>Primary aim of study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK in healthy adults</td>
<td>General PK - Single dose</td>
<td>LAB91206</td>
<td>PK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HP5303/01</td>
<td>Dose proportionality</td>
</tr>
<tr>
<td></td>
<td>- Multi-dose</td>
<td>HP5303/04</td>
<td>72h vs 96h wear time</td>
</tr>
<tr>
<td></td>
<td>Bioequivalence - Single dose</td>
<td>HP5303/02</td>
<td>PK with repeated dose</td>
</tr>
<tr>
<td></td>
<td>- Multi-dose</td>
<td>HP5303/01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Food effect</td>
<td></td>
<td>Not applicable</td>
</tr>
<tr>
<td></td>
<td>Factors affecting absorption</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td>PK in special populations</td>
<td>Target population § - Single dose</td>
<td>WIS-BUP 02 PK</td>
<td>PK with repeated dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic impairment</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td></td>
<td>Renal impairment</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td></td>
<td>Neonates/infants/children/adolescents</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td></td>
<td>Elderly</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td></td>
<td>Other special pop’a</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td>Genetic/gender-related PK</td>
<td>Males vs. females</td>
<td>WIS-BUP 02 PK</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other genetic variables</td>
<td></td>
<td>Not included</td>
</tr>
<tr>
<td>PK interactions</td>
<td>Any</td>
<td></td>
<td>Not included</td>
</tr>
</tbody>
</table>

Table 3: Submitted pharmacokinetic studies (Continued)

<table>
<thead>
<tr>
<th>Population PK analyses</th>
<th>Subtopic</th>
<th>Primary aim of study*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects</td>
<td>PP0017P</td>
<td>Bioequivalence of 72 and 96h wear times</td>
</tr>
<tr>
<td>Healthy subjects</td>
<td>FK761</td>
<td>Bioequivalence of 72 and 96h wear times</td>
</tr>
<tr>
<td>Target population. Other</td>
<td>Not included</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates the primary aim of the study.
† Dose proportionality of different strength patches
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

Table 4 lists pharmacokinetic results that were excluded from consideration due to study deficiencies.

Table 1: Pharmacokinetic results excluded from consideration

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Subtopic(s)</th>
<th>PK results excluded</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIS-BUP02PK</td>
<td>Pharmacokinetics of multiple dosing</td>
<td>Steady state and lack of accumulation with multiple dosing not demonstrated</td>
</tr>
</tbody>
</table>
4.2. **Summary of pharmacokinetics**

Buprenorphine is a potent opioid analgesic that has been in clinical practice for several decades. It is available in parenteral, sublingual (buccal) and transdermal preparations for the treatment of moderate to severe pain. Higher doses of buprenorphine are used for the substitution treatment of opioid dependence.

4.2.1. **Physicochemical characteristics of the active substance**

The following information is derived from the sponsor’s summaries, unless otherwise specified.

Buprenorphine is a semisynthetic derivative of thebaine, an alkaloid present in the poppy Papaver somniferum. The chemical structure of buprenorphine contains the general morphine skeleton but has its own specific pharmacology due to some structural differences. Buprenorphine is suitable for transdermal delivery as it is highly soluble in both water and lipids (Budd 2002), has a low molecular weight and high analgesic potency. The pKa is 8.5.

**Comment:** The PI describes buprenorphine as ‘poorly soluble’ in water. It is elsewhere described as ‘soluble’ and ‘highly soluble’ in water. The 2002 review by Budd, frequently referred to in the clinical overview, describes it as highly soluble.

4.2.1.1. **Patch characteristics**

Comment: The specific characteristics of a transdermal drug delivery system are not discussed in the clinical overview. In the same way that tablet size, interaction with food and effects on the GIT mucosa are important to absorption of orally administered drugs, patch size and the patch skin interface are important to trans-dermally administered drugs. The EMA Guideline on quality of transdermal patches advises that applications for transdermal preparations should discuss: ‘Local tolerance, the means of administration (including occlusion, if relevant), administration site, posology, patient compliance in medication taking’. Given this importance some of the issues unique to this route of administration are discussed below. The information is sourced from different locations within the dossier, in particular the Appendix of PSUR8 (July 2005) which includes an ‘evaluation of the effect of Transtec on human skin’ together with a number of articles on transdermal drug delivery systems. These documents are not referred to in the clinical overview.

4.2.1.1.1. **Patch wearability**

Patch wearability is an important aspect of patch use and absorption. Firm adhesion of the patch to the skin is essential for absorption to occur. The CMI advises that: preferable sites are on the upper body, on the back or on the chest below the collar-bone and that the wearer should ‘press the sticky edge of the patch to the skin, then peel off the remaining foil and press the patch firmly onto the skin with the palm of the hand for 30 seconds. Make sure the whole patch is in contact with the skin especially around the edges.’ The patches have a large physical size (up to 7 by 12 cm) and it may be physically difficult for the patch to be successfully applied, especially in the elderly or those with limited flexibility. The application characteristics of the patches were assessed in the open follow-up study WIS-BUP-LTS and the non-interventional studies Gru-BUP2002/01 and the Cohort study. The follow-up study found that 22.6% of patients were unable to apply the patch by themselves, with most of these needing the help of another person. The Study Gru-BUP 2002/01 of 1,223 patients found that changing of the buprenorphine transdermal patch was done by the patient 65.4% of the time, by family members 30.2% of the time, by health care staff 3.8%. The Cohort study asked that patients complete a questionnaire with every patch change. It found that in 39.3% of patch changes, the patient needed the help of another person to apply the patch. The Cohort study also found that patch adhesion remained good after bathing and showering. The free text comments provided

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10 Guideline on quality of transdermal patches, EMA/CHMP/QWP/911254/2011
by patients, and included in the study report, show numerous instances when patients were concerned by poor adhesion and buckling of the patch due to size, movement and sweating. It may be helpful for the CMI to explicitly indicate that the help of another person may be required for successful patch application and to suggest an application schedule.

4.2.1.2.  Local tolerability of the patch and sensitisation

This issue was not discussed in the clinical overview. The information below is sourced from different locations within the dossier.

The use of transdermal systems for the administration of drugs may be associated with two types of skin reactions: irritant reactions or allergic skin reactions. Patient populations at risk for skin reactions include patients with very dry skin, the elderly, those who suffer from coexisting allergic conditions and patients on long-term treatment. The mechanisms for irritant reactions include the effects of skin stripping and occlusion.

4.2.1.2.1.  Skin stripping

The stratum corneum provides the first barrier to the percutaneous absorption of drugs. The removal of a patch can cause stripping of the upper stratum corneum layers and result in visible damage or irritation, ranging from mild erythema to a superficial burn with blistering, depending on the fragility of the skin. Skin from which layers of the stratum corneum have been stripped is more permeable than intact skin. It takes some time for skin regeneration to occur. If a patch is applied to the same site before this has occurred, an increased rate of absorption of buprenorphine may be seen, as described below.

4.2.1.2.2.  Occlusion

Occlusion of the skin causes sweat and water vapour to accumulate on the skin's surface and increases epidermal hydration. If occlusion continues for some days, skin irritation can result from sweat accumulation, sweat duct and hair follicle occlusion, with or without bacterial or yeast overgrowth. This cutaneous irritation may also facilitate sensitisation to constituents of the patch. An allergic contact dermatitis may then present as irritation, swelling and blistering that is usually localised to the patch site. Time to onset of contact dermatitis is variable and may be months. The presence of contact dermatitis may alter absorption of the drug from the patch.

Skin reactions of the irritant type were reported frequently in the clinical studies (up to 49% of patients). Reactions consistent with hypersensitivity were infrequent.

4.2.1.2.  Absorption

4.2.1.2.1.  Sites, mechanisms and rates of absorption

Comment: The specific characteristics of drug absorption from a transdermal drug delivery system are not substantially discussed in the clinical overview. The information below is sourced from different locations within the dossier.

This submission is for a transdermal delivery system for buprenorphine. The transdermal patch consists of a polymer matrix in which the active substance, buprenorphine, is dispersed in a 10% solution. When the patch is applied to the skin, buprenorphine diffuses from the matrix into the skin and subcutaneous tissues. A depot forms there from which buprenorphine is subsequently absorbed into the systemic circulation. Absorption of the drug into the systemic circulation occurs passively and is proportional to the area in contact with the subject’s skin. Higher strength patches have more drug matrix and a greater area of contact.

Absorption is subject to intra as well as inter individual variability. In principle, the rate and/or extent of release into the systemic circulation may be altered by the temperature, state of hydration, thickness of the stratum corneum or presence of scarring, thickness of the subcutaneous fat layer, hairiness of the skin and integrity of the skin at the application site. In addition, it may also depend on blood flow in the area of administration, which may increase or
decrease with the subject's level of activity, body temperature and locally applied heat. Small upward ticks in plasma concentration seen in the first hour after patch removal in the pharmacokinetic Study HP5303/01 were attributed to an increase in local blood supply due to the irritation of physical patch removal. The skin sites tested in the clinical studies were in the mid-clavicular line directly under the clavicle and the supra-scapular region of the back; no comparison of absorption from these sites was provided. Subjects with particular body traits that may affect absorption (excessive hair at the skin sites or obese with BMI > 30) were excluded from the pharmacokinetic studies. The potential for inter individual variation in absorption to result in wide variations in plasma concentrations is discussed below.

The potential for different absorption under different conditions, especially heat, was not investigated according to the materials provided in the dossier. The draft CMI advises: ‘Do not expose the patch to heat sources such as saunas, infrared heat lamps, heating pads, hot water bottles, electric blankets, hot tubs or heated water beds etcetera. Avoid intensive sunbathing. Heat may cause more medicine than normal to be absorbed, lead to increased side effects or prevent the patch from sticking properly’. The draft PI also addresses this issue, although less specifically, with ‘Fever and the presence of heat may increase the permeability of the skin. Theoretically in such situations buprenorphine serum concentrations may be raised during Transtec treatment’. The Australian PI for the sponsor’s product Norspan, a buprenorphine patch that is structurally identical to Transtec (although worn for 7 days not 4) states that: ‘In a study of healthy subjects, application of a heating pad directly on the Butrans 10 µg/hour system caused a 26% to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. For this reason, instruct patients not to apply heating pads directly to the Butrans system during system wear’.2; this study was not provided in the dossier and was not evaluated. A more strongly worded warning of the effect of local heat in the draft PI would be appropriate and would also provide greater consistency between the CMI and PI.

The rate of absorption may also be affected by the length of time between the recycling of a skin site. The original protocol for Study HP5303/02, in which three patches were worn sequentially, required that the third patch be placed on the same site as the first patch (a 3 day break only). This protocol was followed for the first group of 18 patients. A pronounced increase of plasma concentrations was observed throughout application of the third patch and was considered to be due to too rapid recycling of the patch skin site such that there was insufficient time allowed for the skin to regenerate after removal of the first patch. Three separate skin sites were used for sequential patch wearing for the subsequent groups in the study.

The issue of the appropriate time to allow between recycling of skin sites was not discussed in the dossier. A recommendation of at least one week between the use and re-use of a skin site is made in the draft PI although no rationale for this timeframe is provided. The PI for the 7 day patch Norspan states that: ‘In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events’ and that ‘A new patch should not be applied to the same skin site for 3 to 4 weeks’.2 The study referred to was not provided in the dossier and so the rationale for the recommendation of 3 to 4 weeks cannot be evaluated.

4.2.1.2.2. Time dependent plasma concentration; single dose

Comment: The following sections are based on the clinical overview and cited studies unless otherwise specified.

Study HP5303/01 was an open label, cross over study with three treatment arms (20 mg patch, 40 mg patch and 0.3mg intravenous administration of buprenorphine) that compared the plasma concentration achieved with a single 72 h wearing of the 20 mg and 40 mg patches and single intravenous administration of 0.3 mg of buprenorphine. With transdermal administration there was a progressive increase in plasma concentrations, reaching minimum therapeutic concentration for analgesia (> 100pg/mL) after 24 and 12 hours and plateau levels reached
after 36 and 60 hours for the 20 mg and 40 mg patches respectively. $C_{\text{max}}$ (mean ± SD) was 305 ± 117 pg/mL for the 20 mg patch, 624 ± 185 pg/mL for the 40 mg patch and 3,625 ± 1,315 pg/mL for the intravenous dose of 0.3mg. On removing the transdermal system, after a transient increase during the first hour, there was steady decrease in plasma concentrations with, in most of the subjects, plasma concentration declining more than 80% by 72 h.

**Figure 4: Study HP5303/01; Mean Plasma Buprenorphine concentration from 20 mg TD administration (TTS 50) and 40 mg TD administration (TTS 100)**

![Figure 4: Study HP5303/01; Mean Plasma Buprenorphine concentration from 20 mg TD administration (TTS 50) and 40 mg TD administration (TTS 100)](image)

Comparison of the intravenous (IV) to the transdermal dose shows considerably higher $C_{\text{max}}$ for the IV dose and a much lower terminal half-life ($t_{\frac{1}{2}}$) with intravenous administration (8.5 h compared to 25.3 h and 27.4 h for the 20 mg and 40 mg patch respectively). It was postulated that the prolonged half-life is due to continued absorption of buprenorphine from a depot in the skin into the systemic circulation.

**Comment:** the estimate of minimum therapeutic concentration (> 100 pg/mL) is based on the expert statement of [information redacted] of the Pharmacology and Toxicology Department of the University Hospital of Geneva given in a 2004 letter to [information redacted], the developers of the transdermal delivery system for buprenorphine.11

### 4.2.1.3. Bioavailability

Buprenorphine is subject to extensive first pass metabolism such that oral administration is ineffective. Currently used routes are: intravenous and intramuscular (100% bioavailability), sublingual (estimated 50 to 60% bioavailability) and transdermal (estimated 50% bioavailability).

#### 4.2.1.3.1. Absolute bioavailability of the transdermal preparation

A stated objective of Study HP5303/01 was to determine the absolute bioavailability of the transdermal delivery system (against intravenous administration). However, this was unable to be determined due to deficiencies in study conduct. An estimate of the absolute bioavailability of about 50% for the patch was calculated with this only based on the mean AUC values normalized to the released doses over 72 hours.

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**Comment:** The estimate of absolute bioavailability of 50% is as described in the clinical overview. The precise method of deriving it was not evident in the cited study HP5303/01.

4.2.1.3.2. Bioavailability relative to an oral solution or micronised suspension

Not applicable.

4.2.1.3.3. Bioequivalence of clinical trial and market formulations

Not applicable. Apart from the early pharmacokinetic Study, LAB91206, which is not essential to a description of the pharmacokinetics of the patch, the dose form proposed for marketing is identical to that used in the clinical pharmacokinetic studies.

4.2.1.3.4. Bioequivalence of different patch wearing times

The clinical studies presented were based on a 72 hour wearing time for the buprenorphine patch. Anecdotal experience indicated that a 96 h wearing time could also provide effective analgesia. Study HP5303/04, an open, randomized, single centre, single application, 2 treatment, 2 sequence, 2 period crossover trial in 30 healthy male volunteers compared the pharmacokinetics of a 72 hour and a 96 hour application of the 20 mg buprenorphine patch. Each subject randomly received a buprenorphine 20 mg patch twice, once for 72 hours and once for 96 hours with a 10 day washout time between each patch. The plasma concentration time curves of buprenorphine after application for 96 hours and 72 hours overlapped up to and including Day 3. During the fourth day of patch application (72 hours to 96 hours), the concentrations of buprenorphine showed an additional slight increase, consistent with ongoing release of the drug from the patch. The decline of buprenorphine concentrations following patch removal was nearly identical after both treatments. The 90% CIs for the ratio of a 96 hour application and 72 hour application with respect to the pharmacokinetic parameters Cmax, t½, z, and partial AUCs (AUC_{72-96} and AUC_{48-72}, for the respective last treatment days) were within the range (80% to 125%) and consistent with bioequivalence.

**Figure 5: Study HP5303/04. Concentration time profiles of buprenorphine following application of the two transdermal treatments with the 20 mg patch: A (application of patch for 96 h) and B (application for 72 h)**

The bioequivalence of the 72 h and 96 h wearing time was further assessed in the population pharmacokinetic Studies PK761 and PP0017P. Study PK761 used the data from Study HP5303/04 and the Wagner-Nelson model to determine the time dependent release of buprenorphine over 72 and 96 hours with the results showing a constant and linear release of buprenorphine from the patch over both time periods. Study PP0017P used the data from HP5303/04 to develop a model that was then tested over ten simulated steady state cross over bioequivalence studies with 16 subjects. These simulations showed that the point estimates of
AUC and C\textsubscript{max} for the 72 and the 96 hours application regimen were the same, again consistent with bioequivalence.

**Comment:** Bioequivalence of the 72 and 96 hour wearing times is demonstrated in healthy volunteers. A Phase III, randomized, open label, crossover study comparing 72 h and 96 h application times in the target population was published in 2007\textsuperscript{12}. This was briefly described in PSUR 12 from 2008 but was not included in the submission and could not be evaluated.

4.2.1.3.5. **Bioequivalence to relevant registered products**

Not demonstrated.

**Comment:** No comparison was made to the sponsor’s other product, the 7 day buprenorphine patch registered in Australia under the trade name, Norspan. This patch is identical to the Transtec patch apart from the duration of application. No comparison is made to other opioids used for the same indication, in particular fentanyl patches.

4.2.1.3.6. **Influence of food**

Not indicated. Administration is transdermal.

4.2.1.3.7. **Dose proportionality**

The submission proposes three strengths of the transdermal delivery system, with the patches containing 20 mg, 30 mg and 40 mg of buprenorphine respectively. Study HP5303/01 was described as showing dose proportionality between the 20 mg and 40 mg patch as, after dose normalization, the 90% CIs for the ratios of AUC and C\textsubscript{max} for the 20 mg and 40 mg patches were within the range (80% to 125%).

4.2.1.3.8. **Bioavailability during multiple dosing**

The prolonged terminal half-life seen after patch removal is thought to indicate ongoing absorption of buprenorphine from the depot in the skin. When a new patch is applied, continued absorption from the previous site prevents plasma concentrations from decreasing to sub therapeutic values while another depot is forming below the new application site. The pharmacokinetics with multiple dosing in healthy volunteers was examined in Study HP5303/02, an open, balanced, parallel group, randomized trial in which each patch strength was worn for 3 applications of 72 hours each.

During 3 consecutive patch applications, the mean concentration time profiles showed similar and parallel shapes for all 3 patch strengths and were within the estimated range for therapeutic concentrations of buprenorphine (> 100 pg/mL). After patch removal and application of a new patch, a small transient decrease in plasma concentrations was observed. This decrease did not fall below the estimated minimum effective concentration for analgesia. The ongoing increases in C_{max} and AUC with each patch indicate that the steady state of buprenorphine was not fully reached with the third patch. After removal of the third patch, the mean terminal phase half-life (t_{1/2, z}) was between about 33 hours and 37 hours for the three patch strengths. The pharmacokinetics of multiple dosing (up to 5 sequential patches) was also tested in the target population in WIS-BUP02 (see below) but with inconclusive results. The population pharmacokinetic Study PP017P, was used to demonstrate steady state after three 96 h sequential wearings of the patch or four 72 h sequential applications of the patch and that accumulation with multiple applications did not occur.

**Comment:** the estimate of minimum therapeutic concentration is based on the expert statement of [information redacted] of the Pharmacology and Toxicology Department of the University Hospital of Geneva given in a 2004 letter to [information redacted], the developers of the transdermal delivery system for buprenorphine.\(^{13}\)

Ongoing absorption from a skin depot that continues after patch removal is relevant to the management of overdose. It is commented on in the body of the PI but not reiterated in the section on the management of overdose.

### 4.2.1.3.9 Effect of administration timing

Administration is continued for 72 to 96 hours. Timing of patch application is unlikely to be of significance.

### 4.2.1.4 Distribution

**Comment:** The information on distribution is based on the information within the clinical overview unless otherwise stated.

4.2.1.4.1. **Volume of distribution**

Buprenorphine has a high volume of distribution 430 L.

4.2.1.4.2. **Plasma protein binding**

Based on the literature provided, buprenorphine is highly protein bound (96%), mainly to alpha- and beta-globulin fractions. Animal studies are reported to show that buprenorphine passes the blood brain and placental barriers.

4.2.1.4.3. **Erythrocyte distribution**

Not described.

4.2.1.4.4. **Tissue distribution**

Animal studies are reported to show that buprenorphine is widely distributed and that it crosses both the blood brain barrier and the placenta. The active metabolite, norbuprenorphine, is said to not cross the blood brain barrier although it is active at peripheral mu opioid receptors.

4.2.1.5. **Metabolism**

**Comment:** The information on metabolism is based on the information within the clinical overview unless otherwise stated.

4.2.1.5.1. **Interconversion between enantiomers**

Not applicable.

4.2.1.5.2. **Sites of metabolism and mechanisms / enzyme systems involved**

Buprenorphine primarily undergoes N-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by UGT-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3β-O-glucuronide. Norbuprenorphine, the major metabolite, is also glucuronidated (mainly UGT1A3) prior to excretion. Metabolism by the enzyme CYP3A4 accounts for about 30% of the total metabolism of buprenorphine.

Specific investigations of the metabolism of buprenorphine in the skin were not considered necessary as published data with analogously metabolized compounds such as morphine (metabolised by glucuronidation), fentanyl and sufentanil (metabolised by CYP3A4) do not show any relevant biotransformation in the skin.

4.2.1.5.3. **Non-renal clearance**

Buprenorphine and norbuprenorphine are predominately eliminated in the bile.

4.2.1.5.4. **Metabolites identified in humans**

4.2.1.5.4.1. **Active metabolites**

The metabolite norbuprenorphine is a mu-opioid receptor agonist and has a weak analgesic action. It is however a more powerful depressant of respiration (approximately 10 times) than the parent compound with this action thought to be via mu-opioid receptors in the lungs.14

4.2.1.5.4.2. **Other metabolites**

According to the information provided, other metabolites include the inactive glucuronide conjugates of buprenorphine and norbuprenorphine.

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4.2.1.5.5. Pharmacokinetics of metabolites

Norbuprenorphine is eliminated unchanged in the urine and in the bile following hepatic conjugation to glucuronide.

4.2.1.5.6. Consequences of genetic polymorphism

Not discussed.

4.2.1.6. Excretion

**Comment:** The information on excretion is based on the information within the clinical overview unless otherwise stated.

4.2.1.6.1. Routes and mechanisms of excretion

Animal studies indicate that excretion is mainly through the bile (90%). This is said to have been confirmed in humans: after intravenous administration of buprenorphine, only 10% to 27% of the administered drug was excreted in urine. The faeces contain mainly unchanged buprenorphine, while urinary excretory products were conjugates of the parent compound and norbuprenorphine.

**Comment:** The effect of reduced hepatic blood flow on elimination of buprenorphine was not discussed in the dossier. Given that metabolism and excretion of buprenorphine occurs mainly via hepatic elimination, reductions in hepatic blood flow resulting from conditions such as cardiac failure, and some drugs, may result in a decreased rate of hepatic elimination of the drug, leading to increased plasma concentrations. The draft PI refers to enterohepatic circulation. This is not described elsewhere.

4.2.1.6.2. Mass balance studies

Not described.

4.2.1.6.3. Renal clearance

Renal clearance is thought to account for less than 30% of the excretion of buprenorphine. In chronic therapy, comparison of buprenorphine levels in patients with and without renal failure is said to have shown no difference in buprenorphine levels, although the levels of metabolites was higher in the renal failure patients. It was suggested that this was indicative of the renal route of excretion being more important for the metabolite norbuprenorphine.

4.2.1.7. Intra- and inter-individual variability of pharmacokinetics

Inter patient variability was not discussed in the clinical overview. The following discussion is sourced from different locations in the dossier.

There is considerable inter patient variability in absorption rates and the plasma concentrations achieved. This is evident on close inspection in the results of all of the pharmacokinetic studies, although inter patient variability was not made a focus of any of these studies. This variability was not always readily apparent in the study reports, with only the mean and SEM provided for many parameters. Inspection of individual patient data revealed surprising variability: individual release rates in Study PK1599 varied up to 100 times; individual patient data in other studies, including HP5303 01, 02 and 04, showed up to 10 fold variations in plasma concentration.

Study PK1599 measured the residual buprenorphine in the used patches removed from volunteers in the clinical pharmacokinetic studies HP5303/01 and HP5303/02 after 72 hours of wear. An average hourly loss rate from each patch was calculated. These were averaged in turn to determine the ‘release rate’ for each patch strength. From this the 20 mg patch has an estimated average release rate of 35 µg/h and the 40 mg patch an estimated average rate of 70 µg/h. The 30 mg patch was not used in Study HP5303/01 but, on the basis of dose proportionality, the estimated average rate for the 30 mg patch was 52.5 µg/h. The rates for
individual patients determined from the amount of buprenorphine lost from each patch, showed over 100 fold inter patient variability with the rates for the 20 mg patch ranging from 2.0 µg/h to 80.2 µg/h and for the 40 mg patch ranging from 1.5 µg/h to 208.6 µg/h.

The potential for individual variability in absorption to result in wide variations in plasma concentrations of buprenorphine is shown in the pharmacokinetic studies. In the studies on healthy volunteers, HP5303/01 (single application) and HP5303/02 (multiple sequential applications), individual buprenorphine plasma concentrations at different time-points showed variation ranging from three fold to over 100 fold. In the crossover Study HP5303/04, 20 mg patches were worn by volunteers for 72 h or 96 h and buprenorphine levels measured. The SD of the mean buprenorphine level at each time point demonstrates wide inter-individual variation in plasma concentration.

Figure 7: Study HP5303/04. Concentration time for buprenorphine plasma levels during 96 h application showing standard deviation for each data point

This degree of inter individual variability is not substantially discussed in the dossier and not made explicit in the PI. A statement advising of individual variation in absorption would be clinically useful.

4.2.2. Pharmacokinetics in the target population

The dossier included one study of pharmacokinetics in the target population. This provided limited information regarding the time dependent plasma concentrations with multiple doses. No further information regarding the pharmacokinetics in the target population was available.

4.2.2.1. Absorption

4.2.2.1.1. Time dependent plasma concentration; multiple dose

The clinical efficacy Study WIS-BUP02 included a pharmacokinetic investigation, reported as WIS-BUP02PK. A subset of 46 patients from WIS-BUP02 provided blood samples for the determination of buprenorphine plasma concentrations during 5 sequential applications of buprenorphine patches, each worn for 72 hours. Patients were randomised to one of the three strength patches or to a placebo patch. Blood specimens were to be collected prior to the first patch and then just before the removal of each patch. Sublingual buprenorphine tablets (0.2 mg) were used for breakthrough pain.

According to the study report: the general profile of the plasma concentrations was similar for all three patch strengths, with concentrations slightly increased after the second patch and then remaining constant for the rest of the study period; all the observed values were within the range of known therapeutic concentrations for buprenorphine and correspond to those in the
healthy volunteer studies; the course of the plasma concentrations in the placebo group was
less stable and constant due to the intake of different quantities of sublingual tablets at different
time points.

**Comment:** This study was problematic with regard to both design and conduct. Small
recruitment numbers, multiple arms for analysis and frequent protocol violations
(involving missed specimen collection) resulted in very small numbers at each data
point for example, in the analysis of patients receiving the 40 mg patch and none or
one sublingual tablet, there were only 2 or 3 specimens available for analysis at
each of the 5 time points. This, together with the wide inter-patient variability in
plasma levels, makes the results difficult to interpret.

These issues are acknowledged in the clinical overview with: ‘It should be noted that
due to the difficult clinical situation when treating patients with cancer pain and to
the confounding factor of sublingual buprenorphine tablets used as rescue medication,
only a small number of patients could be analysed statistically so that the data is to be
considered of explorative nature only’

### 4.2.3. Pharmacokinetics in other special populations

**Comment:** The clinical overview states that: ‘Pharmacokinetic trials in special populations with
buprenorphine transdermal patch application were not been conducted with the
rationale that information on the pharmacokinetics of buprenorphine in these
populations is available from the literature.’ Of note is that the review of the
literature provided has not been updated since 2005. The information below is
derived from the clinical overview and literature provided. Direct reference is made
to this literature where appropriate.

#### 4.2.3.1. Pharmacokinetics in subjects with impaired hepatic function

Metabolism and excretion of buprenorphine is largely through glucuronide conjugation in the
liver with subsequent biliary excretion and, to a lesser extent, by de-alkylation to
norbuprenorphine. On this basis, it is postulated that metabolism may be affected in liver
disease, potentially leading to higher plasma buprenorphine levels.

**Comment:** The cited publication\(^\text{15}\) provides no evidence regarding pharmacokinetics in liver
disease but speculates that it may be affected. The PI warns that patients with liver
disease should be carefully monitored during transdermal buprenorphine
administration. No specific recommendation is made regarding occlusive biliary
disease, although based on the pharmacokinetics, buprenorphine would be contra
indicated in these patients.

#### 4.2.3.2. Pharmacokinetics in subjects with impaired renal function

Clearance of buprenorphine was shown to be relatively independent of the renal system and is
not altered in patients with renal impairment. Intravenous administration of 0.3 mg of
buprenorphine to 15 patients during elective surgery (6 healthy controls and 9 patients with
dialysis dependent renal failure) found no significant differences in pharmacokinetic variables
between the two groups and no detectable levels of metabolites.\(^\text{16}\) Continuous infusion of
buprenorphine was administered to 20 Intensive Care patients (8 with renal failure as shown
by creatinine clearance < 9 mL/min and all with normal hepatic function) for duration of 2
hours to 560 hours and total dose range of 0.4 to 58 mg. Plasma buprenorphine measurement
showed no accumulation of buprenorphine in the patients with renal failure although
accumulation of the metabolites, norbuprenorphine and buprenorphine-3-glucuronide did

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\(^{16}\) Hand CW, et al. Buprenorphine disposition in patients with renal impairment: single and continuous
occur: this was not to levels that were thought to be clinically significant. Ten patients with dialysis dependent renal failure and requiring a strong opioid for pain control were treated with buprenorphine patches, titrated to effective pain relief. Blood specimens for plasma buprenorphine (LLOQ 0.05ng/mL) and norbuprenorphine levels were collected after a minimum of 7 days treatment both before and after dialysis. Plasma buprenorphine levels were within the range reported in healthy volunteers and a significant correlation was found between administered buprenorphine dose and buprenorphine plasma concentrations. Buprenorphine levels and pain control were not affected by haemodialysis. Seven patients had un-recordable norbuprenorphine levels; the other 3 had low levels only.

Comment: The PI notes that use in patients with renal insufficiency, including dialysis patients, is possible.

4.2.3.3. Pharmacokinetics according to age

The dossier states that no relevant age or gender dependent differences in the drug’s absorption, metabolism, or excretion were observed when buprenorphine was administered intravenously or sublingually but that no clinical trials in children have been performed.

Comment: The PI advises against the use of the product in children aged less than 18 years and advises that no dosage adjustment is required for elderly patients.

4.2.3.4. Pharmacokinetics related to genetic factors

Not discussed.

Comment: The reported pharmacokinetic studies were all performed in Caucasians. On this basis, altered pharmacokinetics in other genetic backgrounds cannot be excluded.

4.2.3.5. Pharmacokinetics in pregnancy and lactation

According to the information provided, there are no adequate data from the use of buprenorphine transdermal patch in pregnant women. Animal studies have shown that buprenorphine passes placental barriers and may be associated with reproductive toxicity. There is very little data available to determine the potential risk for humans although infants born to opioid addicted mothers substituted with buprenorphine did not show teratogenic effects. It was also noted that long-term administration of buprenorphine during the last 3 months of pregnancy may cause a withdrawal syndrome in the neonate. Buprenorphine is said to be excreted in human milk and that, in rats, buprenorphine has been found to inhibit lactation.

Comment: The PI contains an appropriate warning and advises that buprenorphine is contraindicated in pregnancy and should not be used during lactation.

4.2.3.6. Pharmacokinetics in inter-current disorders

Not discussed.

Comment: Accumulation of buprenorphine could be expected in biliary occlusive disorders and higher plasma levels may be expected in conditions with reduced hepatic blood flow. These are not specifically covered in the PI.

4.2.4. Pharmacokinetic interactions

4.2.4.1. Pharmacokinetic interactions demonstrated in in vitro and in vivo studies

Pharmacokinetic interactions were not investigated in the clinical trials presented in the dossier and reliance was placed on in vitro investigations in the existing literature.

4.2.4.1.1. Interactions with Cytochrome P450 3A4

Metabolism of buprenorphine to norbuprenorphine by Cytochrome P450 3A4 (CYP3A4), accounts for about 30% of the total metabolism of buprenorphine. Buprenorphine and its main metabolite norbuprenorphine have been reported to have in vitro inhibitory effects on CYP3A4, although this only occurred at concentrations that were 2,000 fold above clinically relevant concentrations.

The inhibitory potential of other medications administered concurrently with buprenorphine have been reported to have been investigated, including the selective serotonin reuptake inhibitors (fluoxetine and fluvoxamine) and HIV-1 protease inhibitors (ritonavir, indinavir, and saquinavir). Of the selective serotonin reuptake inhibitors, fluvoxamine was found to inhibit the N-dealkylation of buprenorphine to some extent whereas fluoxetine did not. The HIV-1 protease inhibitors were considered to have the potential for inhibition of buprenorphine metabolism via CYP3A4.

Since the elimination of buprenorphine in-vivo is only partly by CYP3A4, with the main route of excretion as unchanged via the biliary system and faeces and to a lesser extent by glucuronide conjugation followed by biliary excretion, it is not thought that in vivo inhibition of CYP3A4 is likely to be of any significance.

The dossier demonstrates only limited testing of this proposition. The effect of the CYP3A4 inducer, efavirenz, on the steady state pharmacokinetics of sublingually applied buprenorphine for the treatment of opioid dependence was investigated in 10 buprenorphine maintained HIV-infected subjects. After two weeks on a stable dose of buprenorphine (dose not described in the publication), blood specimens were collected for plasma buprenorphine levels. Efavirenz was commenced (600 mg once daily) and blood specimens collected 15 days later. The results showed that efavirenz administration was associated with a significant decrease in buprenorphine AUC by about 50%. Despite this, none of the 10 patients experienced symptoms of opioid withdrawal. This interaction has not been tested in the patient population receiving the much lower dose of buprenorphine used to treat pain.

Comment: The National Library of Medicine in its monograph for the 7 day buprenorphine patch provides additional information regarding drug interactions: ‘However, certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine and naloxone were administered sublingually. Cmax and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and Cmax and AUC for norbuprenorphine increased by up to 1.6 and 2.0 fold respectively, when sublingual norbuprenorphine was administered with these PIs. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. As such, the drug-drug interaction potential for buprenorphine with CYP3A4 inhibitors is likely to be dependent on the route of administration as well as the specificity of enzyme inhibition.’ It would be helpful if these studies, and any others identified through a current review of the literature, were included in the submission.

The PI describes the potential for inhibitors or inducers of CYP 3A4 to intensify or weaken the efficacy of transdermal buprenorphine.


4.2.4.1.2. **Other drug interactions**

Other mechanisms for drug interactions such as displacement from plasma proteins are postulated but not considered likely.

4.2.4.2. **Clinical implications of in vitro findings**

**Comment:** The limited drug interaction information available cannot provide a guide to the possible effects that may occur in vivo. It is appropriate that the PI advise caution with the concomitant use of any drug recognised to change the activity of CYP3A4.

4.3. **Evaluator’s overall conclusions on pharmacokinetics**

A limited description of the PK of buprenorphine and the specific PK of the transdermal delivery system is provided. No review of the unique characteristics of transdermal drug delivery systems and factors affecting absorption is provided. Individual patient data in the pharmacokinetic studies reveals considerable inter-patient variability in absorption that is not discussed in the clinical overview.

Some specific issues related to the patches were not tested:

- Patch application to the infra clavicular region and upper back was described in the studies. No comparison of absorption from these sites was provided nor was there any investigation of the effects on activity on adhesion and absorption.

- The dossier describes the possibility of increased absorption with increased heat (local and systemic). The draft CMI notes that the patch should not be exposed to excessive heat (for example, sauna, infrared radiation). The dossier, however, does not include any testing of the effect of heat on the patch, although this information is apparently available for the sponsor’s product Norspan.20

- Increased absorption from the patch was noted when there was only a three days gap before re-using a skin site in Study HP5303/02. The draft PI recommends that ‘At least one week should elapse before a new transdermal patch is applied to the same area of skin’. The dossier does not provide any evidence to support this as an adequate interval. The Australian PI for Norspan states that ‘In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events’ and that ‘A new patch should not be applied to the same skin site for 3 to 4 weeks’.

The clinical pharmacokinetic studies performed by the developers of the transdermal delivery system provided adequate data regarding the time dependent plasma concentration changes seen with single and multiple dose patch application, although there is a reliance on population pharmacokinetic studies to determine when steady state occurs with multiple dosing, that accumulation does not occur and to support the equivalence of 72 h and 96 h application times. Dose proportionality of the different patch strengths is to some extent established, as is the bioequivalence of 72 h and 96 h patch wearing times in healthy volunteers. These clinical studies are limited in that there is considerable inter-patient variability in absorption rates from the patches and subsequent plasma levels achieved. Caution must therefore be taken when recommendations are based on averaged results, and this should be explicit in the PI.

The pharmacokinetics of buprenorphine after absorption is heavily dependent on existing literature regarding buprenorphine administered by other routes. Many of the studies on which the pharmacokinetic information is based were performed in the 1980’s and 1990’s and

20 Clarification: The original dossier, however, did not include any testing of the effect of heat on the patch, although this information was subsequently supplied in full in response to questions (as previously provided for the sponsor’s product Norspan).
involved small numbers of patients. Information regarding use in special populations and drug interactions is extremely limited and there is no evidence of consideration of the literature since 2006.\textsuperscript{21} There is scanty information provided regarding pharmacokinetic drug interactions and dependence appears to be on post-marketing surveillance over the 30 to 40 years of use to have revealed any major interactions or issues. There are also inconsistencies between the documents provided. For example, the Transtec PI states ‘There is evidence of enterohepatic recirculation’. This pharmacokinetic property is not discussed in the nonclinical overview or the clinical overview of pharmacokinetic properties of buprenorphine.

A more recent review and summary of the available literature and inclusion of studies performed during the development of the 7 day version of this same patch (Norspan) would enable a more complete description of the PKs of the transdermal formulation of buprenorphine.\textsuperscript{22}

5. PHARMACODYNAMICS

5.1. Studies providing pharmacodynamic data

Two of the clinical pharmacokinetic studies, HP5303/01 and HP5303/02, also provided data on pharmacodynamics but only for the variable of pupil size. Table 5 shows the 2 studies. Neither of these studies had deficiencies that excluded their results from consideration.

A thorough QT study was performed by the sponsor of the 7 day buprenorphine patch during its development for registration in the USA. This study was not included in the dossier,\textsuperscript{23} except in the appendix of the PSURs. It is discussed below and in the clinical safety section of this evaluation (see Attachment 1), and a summary provided, due to its importance.

Table 5: Submitted pharmacodynamic studies

<table>
<thead>
<tr>
<th>PD Topic</th>
<th>Subtopic</th>
<th>Study ID</th>
<th>*Primary Aim</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Pharmacology</td>
<td>Effect on pupil size and reactivity</td>
<td>HP5303/01</td>
<td>Pharmacokinetics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HP5303/02</td>
<td>Pharmacokinetics</td>
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<tr>
<td>Secondary pharmacology</td>
<td>QT prolongation</td>
<td>BUP101**</td>
<td>Evaluate QT prolongation</td>
</tr>
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</table>

* Indicates the primary aim of the study. ** BUP101\textsuperscript{11} was not submitted in the dossier but was included in an appendix to a PSUR. It is included here due to its importance.

5.2. Summary of pharmacodynamics

The information in the following pharmacodynamics summary is derived from the information provided in the clinical overview, with this largely based on existing literature for buprenorphine administered by other routes, unless otherwise stated.

\textsuperscript{21} Clarification; regular review of the literature has not revealed any new relevant publications on Transtec since 2006.

\textsuperscript{22} Data from the 7 day patch was made available where it was relevant in response to TGA questions.

\textsuperscript{23} This study was subsequently provided, together with expert overviews, in response to the TGA’s questions.
5.2.1. Mechanism of action

Human studies show that buprenorphine behaviour is typical of mu-opioid receptor agonists, with respect to its intended effect (potent and long-lasting analgesia) and side effects (including sedation, nausea, delayed gastric emptying, constipation and respiratory depression). Buprenorphine also acts at the delta-opioid (agonist) and kappa-opioid (antagonist) receptors although little clinical action is thought to result from this.

Buprenorphine binds competitively to the mu-opioid receptor and has been shown to have a high affinity and to dissociate slowly, such that it has been described as ‘sticky’. This is thought to account for a duration of effect, that is longer than other opioid analgesics. It is also thought to account for buprenorphine not being easily displaced by opioid antagonists.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

Buprenorphine has been characterised as a partial agonist at the mu-opioid receptor, with a bell shaped dose response curve that is not seen with other standard opioid analgesics. This has raised concerns that there may be a ceiling effect to its analgesic efficacy. It is reported that clinical trials have not shown a ceiling dose for analgesia and that full pain relief was achieved, although other drug effects, including respiratory depression, were demonstrated to reach a plateau. It is speculated that the absence of ceiling effect for analgesia is because the decreasing part of the buprenorphine dose response curve is seen at very high dosages that is, considerably higher than the normal analgesic dose range.

5.2.2.2. Secondary pharmacodynamic effects

The side effect profile of buprenorphine includes CNS effects, respiratory depression, cardiovascular effects, euphoria, sedation and gastrointestinal inhibition. There is said to be a ceiling effect with respect to respiratory depression, such that increasing doses of buprenorphine do not cause increasing respiratory depression. The secondary pharmacodynamics effects of buprenorphine were not further discussed in the clinical overview.

Two possible cardiac effects are identified in the Risk Management Plan that are not discussed in the clinical overview. Only one of these is addressed in the Summary of Clinical Safety.

5.2.2.2.1. QT Prolongation

According to the nonclinical overview, various opioids including buprenorphine have been reported to inhibit the Human Ether-a-Go-Go-Related Gene (HERG) potassium channel in animal studies. Inhibition of cardiac repolarizing potassium currents through HERG channels may alter myocardial repolarisation, prolonging the QT interval and potentially lead to life threatening arrhythmias of the torsade de pointes (TdP) type. The concentration of buprenorphine required to inhibit the HERG channels was estimated to be more than 90 times that of therapeutic plasma concentrations for buprenorphine.

This issue was not discussed in the clinical overview. It is briefly discussed in the Summary of Clinical Safety and the Risk Management Plan. It is apparent from these documents that a ‘thorough QT study’ was performed by the sponsor of the 7 day patch (Purdue Pharma LP) during its development for the USA. This study is not included in the dossier and is not referred to in the clinical overview. A copy of the study can, however, be found in the appendices of several of the PSURs.

The NLM monograph on transdermal buprenorphine provides this summary of the study: The effect of Butrans 10 µg/hour and 2 x Butrans 20 µg/hour on QTc interval was evaluated in a double blind (Butrans versus placebo), randomized, placebo and active controlled (moxifloxacin 400 mg, open label), parallel group, dose escalating, single dose study in 132 healthy male and female subjects aged 18 to 55 years. The dose escalation sequence for Butrans during the
titration period was: Butrans 5 µg/hour for 3 days, then Butrans 10 µg/hour for 3 days, then Butrans 20 µg/hour for 3 days, then 2 x Butrans 20 µg/hour for 4 days. The QTc evaluation was performed during the third day of Butrans 10 µg/hour and the fourth day of 2 x Butrans 20 µg/hour when the plasma levels of buprenorphine were at steady state for the corresponding doses. There was no clinically meaningful effect on mean QTc with a Butrans dose of 10 µg/hour. A Butrans dose of 40 µg/hour (given as two 20 µg/hour Butrans Transdermal Systems) prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2 to 13.3) msec across the 13 assessment time points.24

A scientific evaluation of myocardial repolarisation and Buprenorphine was performed by [information redacted] and is included in the PSUR appendices. This evaluation came to the conclusion that the risk of buprenorphine being proarrhythmogenic was unlikely. This issue is discussed in greater detail under the heading of Cardiac Safety in the Clinical Safety section of this evaluation.

5.2.2.2. Coronary vasospasm

This issue is only addressed in the Risk Management Plan. According to this, two well documented individual case reports were received during post marketing surveillance that were suggestive of vasospastic angina induced by buprenorphine. Both cases were reported as serious, requiring hospitalisation, and both recovered. No further information could be located regarding this possible effect in the dossier.

5.2.3. Time course of pharmacodynamic effects

A description of the time course of analgesic effect is provided as: ‘Compared to other analgesics, the onset of agonistic effects is slower and the duration of action is longer.’ The time taken to reach the purported minimum effective concentration for analgesia in healthy volunteers is described in the clinical pharmacokinetic studies but this has not been correlated with pharmacodynamics effects, except for miosis (HP5303/01 and HP5303/02). In these studies, pupil size was observed to decrease by 10 hours after patch application and to plateau at 36 hours. After patch removal, pupil size took some hours to return to normal (approximately 40 hours). There was no correlation provided between measured plasma concentrations and analgesic effect in the target population.

5.2.4. Relationship between drug concentration and pharmacodynamic effects

Potency and the minimum effective plasma concentration of buprenorphine have been difficult to determine.

In a study of 27 patients with moderate to severe chronic cancer pain, 0.3mg of buprenorphine was compared to 10 mg of morphine, both administered intramuscularly.25 This study found similar efficacy, with a longer duration of effect seen with buprenorphine, suggesting a relative analgesic potency of intramuscular buprenorphine to intramuscular morphine of around 30 times. The dossier states a relative potency of 25 to 50 times higher than that of morphine.

The advice of an expert was sought ([information redacted] of the Pharmacology and Toxicology Department of the University Hospital of Geneva) regarding the relationship between plasma concentration and analgesia. His advice is given in a 2004 letter26 to [information redacted], the developers of the transdermal delivery system for buprenorphine. He comments that the ‘use of analgesics is based on the empirical application of varying doses to obtain meaningful analgesic effects. The opioids concentration range in the plasma required to obtain an analgesic effect

remains a question for debate’. His conclusion, after reviewing the relevant literature available at the time was that these ‘data are consistent with a roughly estimated BUP minimal effective plasma concentration above 0.1 to 0.2 ng/mL.’

**Comment:** The study by Kjaer et al\(^25\) was incorrectly described in the dossier as being performed in post-operative patients. The clinical overview cites a review document\(^27\) as the source of the estimate of relative potency of 25 to 50 times that of morphine: the estimate found in this review was ‘at least thirty times that of morphine’.

5.2.5. **Relative potency**

**Comment:** Switching from one opioid analgesic to another is not uncommon in the treatment of chronic pain and choosing the appropriate dose of the new opioid can be difficult. This issue is not specifically addressed in the pharmacodynamic section of the clinical overview, although a relative potency of intra-muscular buprenorphine to intramuscular morphine of 25 to 50 times higher is proposed (see above).

Switching, however, is usually from an oral agent to either another oral agent or a transdermal preparation. Earlier versions of the SPC provided the following table to assist with switching.

**Figure 8: Opioid switching advice from the company core data sheet included in the appendices of PSUR from 2002 to 2007**

![Opioid switching table](image)

In 2007 these guidelines were removed from the SPC and replaced by: ‘In general it is advisable to titrate the dose individually, starting with the lowest transdermal patch strength (<Trade Name> 35 micrograms/h). Clinical experience has shown that patients who were previously treated with higher daily dosages of a strong opioid (in the dimension of approximately 120 mg oral morphine) may start the therapy with the next higher transdermal patch strength.’ A rationale for this change was not provided in the PSUR but may have been due to the results of the following post-marketing surveillance studies.

In the post marketing surveillance Study AWB Transtec 2003/2, an analysis of the subset of patients previously receiving at least 120 mg oral morphine who then

switched to transdermal buprenorphine was performed. It showed that 29 out of 42 patients were commenced on the 30 mg (52.5 µg/h) patch resulting in improved pain control. Interpretation of this result is difficult given that, at the end of the 8 month observation period, 35 out of 42 patients were missing, 3 were using the 30 mg patch and 2 were using the 40 mg patch.

The 2005 post-marketing Study AWB Transtec Pro 2005/2 included a subgroup analysis of patients switching from fentanyl or morphine to transdermal buprenorphine. Initial patch strength choice was to be in accordance with the advice provided in the SPC. The results of this study showed that in 50% of patients the initial prescription was not in accordance with the recommendations (with both higher and lower patch strengths used used). In those patients who were commenced on a lower patch strength, 95% achieved an at least equi-analgesic effect to the previously administered fentanyl or morphine. Those patients who commenced on the recommended patch strength had a similar result (96%). The summary of the study made this conclusion: ‘the results therefore support both the current estimation of a higher analgesic potency of transdermal buprenorphine as well as the need to critically question standardised conversion or equianalgesia tables’. Interpretation of this study is, however, difficult given the high discontinuation rate.

Advice regarding equipotency of opioids can be found in a variety of sources. The current UK SmPC, provided in the dossier advises that the relative potency of oral morphine and transdermal buprenorphine has been described in the literature as: ‘Morphine p.o.: BUP TTS as 1 : 75 - 115 (multiple dose, chronic pain)’. There was no apparent reference to this literature in the dossier. A recent systematic review suggests that there is some evidence that the 20 mg patch (35 µg/h) is equivalent to 60 mg of oral morphine and 25 µg/h of transdermal fentanyl. The Australian Therapeutic Guidelines: Analgesic (version 6, 2012) advises that the 7 day 20 µg/h buprenorphine patch is approximately equipotent to 50 mg oral morphine per day.

5.2.6. Genetic, gender and age related differences in pharmacodynamic response

Not discussed.

Comment: It is increasingly recognised that opioids are ethnically sensitive and that genetic polymorphisms may account for some of the variability in clinical response to opioids. Some discussion of this would be appropriate.

5.2.7. Pharmacodynamic interactions

5.2.7.1. With other CNS or respiratory depressant agents

The pharmacodynamic interaction profile of buprenorphine is described as typical for an opioid analgesic. It is expected that the respiration and the central nervous system depressant effects of buprenorphine will be enhanced by other depressants of the central nervous system such as alcohol, anaesthetics, hypnotics, sedatives, tricyclic depressants and phenothiazines.

5.2.7.2. With monoamine oxidase inhibitors (MAOI)

Interactions between opioids (pethidine and dextromethorphan) and monoamine oxidase inhibitors (MAOI) have resulted in a life threatening serotonergic syndrome and the combination of morphine and MAOI been resulted in potentiation of the depressant effects of morphine. As a consequence, the PI lists use of buprenorphine with MAOI as a contra indication.

5.2.7.3. With other opioids

As buprenorphine is a partial agonist and demonstrates high affinity for the mu-opioid receptor, concerns have been raised that other opioids would be ineffective in the presence of buprenorphine. Animal studies are reported to show that the combination of buprenorphine
with morphine in the submaximal analgesic dose range resulted in an additive type of interaction but that combination of high dose buprenorphine and high dose morphine decreases the morphine effect to the level of the administered buprenorphine dose.

**Comment:** The PI warns about the potential interaction with other CNS depressant agents that is common to all opioids: the CNS and respiratory depressant effect of buprenorphine may be intensified by co-administration of other opioids, anaesthetics, hypnotics, sedatives, antidepressants, neuroleptics, and alcohol. The PI states that the use of the product is contra-indicated in patients on MAOI (or who have taken them in the previous two weeks) due to the interaction that is reported to have occurred with pethidine. A retrospective chart analysis of patients who had analgesic titration of chronic pain with oral morphine followed by transfer buprenorphine patches with oral morphine continued as rescue medication was referred to elsewhere in the clinical overview. This study found no deterioration in pain control during the changeover and that oral morphine remained effective in the presence of buprenorphine. 28

5.2.7.4. **With naloxone**

As buprenorphine is a partial agonist and demonstrates high affinity for the mu-opioid receptor, concerns have been raised that the opioid antagonist would be unable to reverse the actions of buprenorphine, particularly respiratory depression. This issue is discussed in the RMP in the dossier which states that ‘a clinically meaningful reversal of respiratory depression induced by buprenorphine can be achieved by the administration of naloxone’. 29

**Comment:** The publication cited in the RMP to support the reversibility of buprenorphine's respiratory depression by naloxone is a review article and not included in the dossier. One article that addresses the issue is included. Van Dorp et al29 performed a sequence of studies to determine the ability of the opioid antagonist naloxone to reverse respiratory depression produced by a therapeutic dose of parenterally administered buprenorphine (total 0.2 mg) in healthy volunteers and using sensitive measures of ventilation. The dose of naloxone recommended to partially reverse respiratory depression following a therapeutic dose of opioids such as morphine is 100 to 400 µg. 18 Van Dorp et al found that a dose of 800 µg was ineffective and that doses of 2 to 4 mg naloxone given over 30 min were required to produce full reversal of this buprenorphine effect. The authors recommend that respiratory depression due to a therapeutic dose of buprenorphine be managed by bolus naloxone of 2 to 4mg followed by an infusion of naloxone at 4 mg/h, continued for the likely duration of action of buprenorphine. Respiratory depression was seen to recur when naloxone infusions were ceased after 2 hours.

5.3. **Evaluator’s overall conclusions on pharmacodynamics**

Limited information regarding the specific pharmacodynamics of the buprenorphine transdermal delivery system is provided. Information regarding pharmacodynamics is largely based on the literature available regarding the administration of buprenorphine by other routes. This section of the clinical overview appeared to have been compiled in 2006 and not subsequently updated. This resulted in significant gaps in the discussion provided, for example

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there was no discussion of the effect of buprenorphine at the HERG potassium channel and the implication of this.30

A summary of the mechanism of action and primary pharmacodynamics effect is provided. The secondary pharmacodynamics effects are listed as typical mu-opioid receptor agonist effects and not further discussed, apart from the postulated ceiling effect to respiratory depression.

A question mark remains over the potential for the life threatening arrhythmia of polymorphic ventricular tachycardia (Torsades de Points, TdP). Of note is that the PI for the sponsor’s 7 day patch Norspan2 includes the following paragraph under Precautions:

In a study of the effect of Norspan patches on the QTc interval in 131 healthy males, therapeutic dosages (10 µg/h) had no effect on the QTci interval. Higher dosages (40 µg/h) and the active control (moxifloxacin 400 mg) each produced increases of 5.9 ms in the QTci interval. This observation should be considered when prescribing Norspan patches for patients with congenital QT prolongation and for patients taking antiarrhythmic medications in either Class 1A (for example quinidine, procainamide) or in Class III (for example amiodarone, sotalol) or any other medication which prolongs the QT interval.

This study was not provided in the dossier. It was however located in an appendix to a PSUR, together with the response of [information redacted]. The potential for QT prolongation (as a surrogate for the risk of TdP) was not discussed in the clinical overview but was addressed in the RMP. The conclusion reached in the RMP is that the relevant study was inconclusive, that the safety record of buprenorphine was reassuring and that there is insufficient evidence for proarrhythmogenic effects of buprenorphine. The studies cited in support of this were not included in the dossier and so were not evaluated. With regard to the safety record, the most likely consequence of TdP is sudden death. This may not be recognised as potentially attributed to buprenorphine, particularly in the patients with advanced malignancies, and may not be reported as an adverse effect. Greater importance needs to be placed on this risk, both in the dossier and in the draft PI. It is very concerning that this major safety risk was not discussed in the clinical overview and that the Study, BUP1011 together with the [information redacted] response, was not included in the body of the dossier. Consistency would also seem to require that if it is appropriate to include the risk of QT prolongation as a Precaution in the PI for Norspan, then it should be similarly included in the PI for the higher dose formulation, Transtec.

There is another question mark remains over the potential for life threatening coronary vasospasm. Too little information has been provided to enable evaluation of this effect.

The only information provided regarding equipotent doses of buprenorphine and other opioid analgesics is the estimate of intramuscular buprenorphine being 25 to 50 times more potent than intra muscular morphine. Information regarding equipotent doses of buprenorphine and the formations of other opioids used in the management of chronic pain (for example oral morphine) would be helpful with respect to advice regarding switching. The draft PI advises that ‘Clinical experience has shown that patients who were previously treated with higher daily dosages of a strong opioid (in the dimension of approximately 120 mg oral morphine) may start the therapy with the next higher transdermal patch strength’. The source of this information is not provided in the PI and the issue is not discussed in the clinical overview.

Opioids are generally accepted as being ethnically sensitive, with genetic polymorphisms resulting in different responses in different ethnic populations. This was not discussed in the dossier.

The discussion of pharmacodynamic drug interactions provided is limited and the publications referred to date from 1991 to 1993.31 Given the frequency with which new drugs and new

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30 Clarification: buprenorphine’s potential to cause QT prolongation has been discussed in the RMP
Therapeutic Goods Administration

classes of drugs are developed, it is concerning that there is no evidence of a recent evaluation of pharmacodynamic drug interactions, for example potential interaction with other drugs known to prolong the QT interval.

The potential for naloxone to reverse the unwanted effects of buprenorphine, especially in overdose, also remains problematic. The draft PI recommends an initial bolus of 1 to 2 mg intravenously with this followed by an infusion. This initial dose may be inadequate and an initial bolus dose of 2 to 4 mg more appropriate, with a similarly high dose infusion rate (4 mg/h) to follow. The Naloxone PI that is referred to in the Transtec PI section on overdose does not allow for this high infusion rate, except at inordinately high intravenous fluid rate of 1 L/h given the recommendation: For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9% or glucose 5% injection to produce a solution containing 4 micrograms/mL.

It would be helpful if more appropriate advice could be provided in the Transtec PI regarding the management of overdoses and the safety of a more concentrated solution of naloxone.

A more recent review and summary of the available literature, particularly with respect to drug interactions, and inclusion of studies performed during the development of the 7 day version of this patch (Norspan) is needed to provide a more complete description of the pharmacodynamics of the transdermal formulation of buprenorphine.

6. Dosage selection for the pivotal studies

The dossier provides the following information regarding the choice of application time and doses:

- Three buprenorphine patch strengths are proposed, 20 mg, 30 mg and 40 mg. These are said to provide an average release rate of 35 µg/h, 52.5 µg/h and 70 µg/h on the basis of the findings in the 2004 Study PK1599. Prior to this study, the average release rates had been estimated to be 50 µg/h, 75 µg/h and 100 µg/h

- The application period was 72 hours (three days) for each patch. This interval results from the patch technology, pharmaceutical and pharmacokinetic properties of the transdermal therapeutic system and from the skin physiology

- The dose provided over 24 hours by the range of three strength buprenorphine patches was estimated to correspond to 0.8 to 1.6 mg daily buprenorphine, as calculated from the average release rates determined in PK1599. A dose of 0.8 to 1.6 mg buprenorphine sublingually was said to be the daily dose in common practice (at the time and place of the trials; Europe in the late 1990’s) in the treatment of moderate to severe chronic pain. This range was also said to represent the overlapping zone of WHO step II to III and can be understood as an entrance dose range into step III

- Tramadol was selected as the active control in two studies in patients with moderate to severe pain due to osteoarthritis because it was in standard use in Europe as an analgesic therapy for patients with chronic benign pain. The standard daily tramadol dose of 200 mg was based upon current prescribing practice at the time.

Comment:

- According to the original estimates of release rates from the three strength buprenorphine patches, the daily dose provided would have been 1.2 mg.
1.8 mg and 2.4 mg respectively. The rationale for this dose selection in the development of the patches was not provided in the dossier.\(^3\)

- The average release rates calculated in the PK Study PK1599, reported in 2004, were 35 µg/h, 52.5 µg/h and 70 µg/h, equating to an average daily dose of 0.84 mg, 1.26 mg and 1.68 mg for the 20 mg, 30 mg and 40 mg patch respectively. There was considerable inter patient variability in absorption from the buprenorphine patches shown in Study PK1599. Minimum and maximum daily doses can be calculated using the ranges measured for individual patients. This shows that the daily dose delivered from a 20 mg patch could range from 0.048 mg to 1.9 mg and the range for a 40 mg patch could be 0.036 mg to 3.10 mg.

- The proposed duration of application was changed from 72 h to 96 h after anecdotal experience prompted further research into the application time; the efficacy studies all used a duration of application of 72 h. Only one study, the post-marketing surveillance Study AWB Transtec Pro 2005/2, used a patch application time of 96 hours.

- It was not established in the dossier that a dose of 0.8 to 1.6 mg is routinely absorbed from the patch (see possible range above). Nor was it established that the dose absorbed from the buprenorphine patch was equivalent to a dose of 0.8 to 1.6 mg per day of sublingual buprenorphine. An estimate of 50% bioavailability is provided for both routes.

- The dose of 0.8 to 1.6 mg of sublingual buprenorphine was said to be the daily dose in common practice (at the time and place of the trials) in the treatment of moderate to severe chronic pain. No references were provided and this was not otherwise established in the dossier.

- Tramadol is generally classed as a ‘weak opioid’, fitting in Level 2 of the WHO analgesic ladder (mild to moderate pain). The dossier seeks to position the buprenorphine patches as suitable for use in moderate to severe pain (WHO Level 3) or for patients transitioning from WHO Level 2 to WHO Level 3.\(^3\)

- The Use of prolonged release tramadol as an active comparator in two non-inferiority studies is not consistent with this. A more appropriate comparator would be oral morphine or transdermal fentanyl.

7. Clinical efficacy

Comment: The most recent clinical study provided in the dossier is from 2004. The most recent post marketing surveillance study discussed in the clinical overview is from 2004. It is apparent from the listings of new studies provided in the PSURs that more recent studies have been conducted (including 9 post-marketing surveillance studies from 2008 to 2013). Relevant clinical studies including ones sponsored by [information redacted], dating from after 2004 have not been included in the dossier.\(^3\)

\(^3\) The sponsor subsequently submitted literature to demonstrate that at the time of development of this product, total daily doses of buprenorphine were consistent with the doses proposed.

\(^3\) This was addressed during TGA’s evaluation of the company’s response.

\(^3\) Clarification; The sponsor subsequently submitted additional studies in the PSURs. No interventional studies have been performed by the company since 2005.
**Table 6: Efficacy studies**

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Type of trial</th>
<th>Description provided below</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIS-BUP01</td>
<td>Placebo-controlled, double blind, parallel group trial with run-in phase – three strength patches, tumour and non-tumour. Duration 15 days</td>
<td>Detailed</td>
</tr>
<tr>
<td>WIS-BUP02</td>
<td>Placebo-controlled, double blind, parallel group trial – three strength patches, tumour and non-tumour. Duration 15 days</td>
<td>Detailed</td>
</tr>
<tr>
<td>WIS-BUP03</td>
<td>Placebo-controlled, double blind, parallel group trial – 20 mg patch only, tumour and non-tumour. Duration 16 days</td>
<td>Detailed</td>
</tr>
<tr>
<td>PB-TTC-02</td>
<td>Placebo-controlled, double blind parallel group trial with run-in phase - 40 mg patch only, tumour patients. Duration 30 days</td>
<td>Detailed</td>
</tr>
<tr>
<td>PB-TTC-01</td>
<td>Active-controlled (Tramadol SR), double blind trial in patients with non-tumour pain. Duration 4 weeks.</td>
<td>Detailed</td>
</tr>
<tr>
<td>BUP4201</td>
<td>Active-controlled (Tramadol SR), double blind trial in patients with osteoarthritis. Duration 5-8 weeks</td>
<td>Detailed</td>
</tr>
<tr>
<td>WIS-BUP-LTS</td>
<td>Uncontrolled follow-up</td>
<td>Summary</td>
</tr>
<tr>
<td>PB-TTC-01 follow-up</td>
<td>6-month uncontrolled follow-up</td>
<td>Summary</td>
</tr>
<tr>
<td>AWB Transtec 2001/1*</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
<tr>
<td>PM Transtec 2001/2</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
<tr>
<td>AWB Transtec 2003*</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
<tr>
<td>AWB Transtec onco 2003</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
<tr>
<td>AEB Transtec Pro 2005/2</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
<tr>
<td>GRU-BUP-2002-</td>
<td>Post marketing surveillance study</td>
<td>Summary</td>
</tr>
</tbody>
</table>
Study Identifier | Type of trial | Description provided below
--- | --- | ---
01* | Post marketing surveillance study | Summary
BIOC/11/03/04* | Cohort trial Transtec versus. Durogesic | Post marketing surveillance study – buprenorphine compared to fentanyl patch
TTC-MATRIX-AWB-2003* | Post marketing surveillance study | Summary
BUP4202 | Post marketing surveillance study | Summary
Report WIS-BUP123 | Combined efficacy analysis of WIS-BUP01, 02 and 03 | Brief

Post marketing surveillance studies discussed in the clinical overview

**Comment:** All of the post marketing studies that were provided in the dossier are described and discussed below, although not all of them were discussed in the clinical overview. The letter of application states: ‘the following 4 post-marketing studies are not referred to in the clinical overview as they do not describe the efficacy and safety of the product and are included for historical reference only: WIS-BUP-FU, AWB Transtec 2003/3, AWB Transtec ONCO 2003/2 and AWB Transtec Pro 2005/2’. This is not consistent with the contents of the dossier as it did not contain AWB Transtec 2003/3 and AWB Transtec onco 2003/2.

Indication: Management of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics.

**7.1.1. Pivotal efficacy studies**

**Comment:**

- The dossier describes the three placebo controlled studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03 as pivotal studies, despite the pre-defined primary variable analysis failing to demonstrate efficacy in all three trials. The primary outcome in each was the response rate, with this defined by a composite endpoint of patient assessed pain relief and some measure of sublingual buprenorphine tablets taken for breakthrough pain during patch wearing.

- The three pivotal studies were performed some time ago: WIS-BUP01- 1995 to 1998; WIS-BUP02 - 1996 to 1998; WIS-BUP03 - 1995 to 1997. This transdermal buprenorphine system was first registered in 2000. The regulatory environment fifteen years ago was different. The guideline CPMP/EWP/612/00 Note For Guidance On Clinical Investigation Of Medicinal Products For Treatment Of Nociceptive Pain came into operation in the EU in 2003 and was adopted by the TGA in 2005. The guideline CPMP/EWP/252/03 Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain was also adopted by the TGA in 2005. This latter guideline was replaced by a revision involving the paediatric section in 2009.
The studies share similar efficacy variables, randomisation and blinding methods and statistical analysis. However, the design of each study is different, as are some of the outcome measures, so they are each described separately below.

Comments that are relevant to the three studies are grouped together in the section Evaluator’s conclusions on clinical efficacy.

Buprenorphine is a controlled drug and subject to narcotic drug regulations. Each study report states that all proceedings with regard to the dispatch and return of the study medication were carried out according to national legislation and that the CRO was not involved in the distribution or collection of the study medication.

### 7.1.2. Study nomenclature

The dossier describes 3 dose strength buprenorphine patches containing 20 mg, 30 mg, or 40 mg buprenorphine per patch. Absorption rates were initially estimated to be 50 µg/h, 75 µg/h and 100 µg/h respectively, when applied over 72 hours, so that each patch strength was referred to as transdermal therapeutic system (TTS) TTS50, TTS75, and TTS100 in the study reports. This is apparent in the tables and figures taken from these reports. The in vivo absorption rates were subsequently found to roughly average 35 µg/h for TTS50, 52.5 µg/h for TTS75, and 70 µg/h for TTS100 (Pharmacokinetic Study PK1599).

#### Table 7: Patch synonyms

<table>
<thead>
<tr>
<th>Synonyms</th>
<th>Buprenorphine amount</th>
<th>Average in vivo absorption rate (72 to 96 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTS 50</td>
<td>BUP-TD35 µg/h</td>
<td>20 mg</td>
</tr>
<tr>
<td>TTS75</td>
<td>BUP-TD 52.5 µg/h</td>
<td>30 mg</td>
</tr>
<tr>
<td>TTS100</td>
<td>BUP-TD 70 µg/h</td>
<td>40 mg</td>
</tr>
</tbody>
</table>

### 7.1.2.1. Study WIS-BUP01

Study Title: Determination of the analgesic efficacy of three buprenorphine dosages versus placebo in a transdermal therapeutic system (TTS) in patients with cancer pain and patients with chronic pain of non-cancer origin.

#### 7.1.2.1.1. Study design, objectives, locations and dates

Design: Randomised, double blind, placebo controlled, multicentre Phase III study with 4 parallel groups (total 144 patients) to investigate three dosages 20 mg (TTS 50), 30 mg (TTS 75) and 40 mg (TTS 100) over 15 days (run-in phase: 6 days; double blind phase: 9 days).

Location: 18 European sites; 15 in Germany, 2 in Hungary, 1 in Austria.


Objectives: To determine the analgesic efficacy and safety of three buprenorphine patch dosages compared to patch placebo in chronic pain patients who have demonstrated acceptable pain control on buprenorphine sublingual tablets.

Additional objectives were to investigate the number of buprenorphine sublingual tablets taken, to determine skin status after removal of the patch and to investigate adverse events.
7.1.2.2. Inclusion and exclusion criteria

7.1.2.2.1. Inclusion criteria
Adult hospital in-patients and out-patients with age over 18 years, male or female, with persistent severe to very severe chronic pain In addition, at the end of the initial 5 day open run-in phase the patients had to fulfil the following randomisation criteria:

- At least satisfactory pain relief with a daily dose of 0.8 to 1.2 mg buprenorphine according to the patient's retrograde assessment of pain relief (VRS) at the end of the run-in phase.

7.1.2.2.2. Exclusion criteria

- Contra indications to the use of opioids in general and buprenorphine specifically, including known hypersensitivity towards opioids; pregnancy or lactation or women with inadequate contraceptive measures; administration of MAO inhibitors or withdrawal of MAO inhibitors within the last 2 weeks before the start of the study; clinically relevant limitation of the respiratory function (for example obstructive pulmonary diseases, pulmonary heart disease, existing respiratory depression)
- Simultaneous administration of other opioids.

7.1.2.3. Study treatments
The study extended over 15 days and was divided into two phase, run-in and double blind. Throughout the fifteen days of the trial, the patient kept a diary and recorded pain intensity morning and evening, duration of uninterrupted sleep each morning and any adverse events.

Initial Run-In phase (6 days): During this phase all patients took regular sublingual 0.2 mg buprenorphine tablets for pain, according to the investigator's assessment of the patient's needs, with total dose between 0.8 and 1.2 mg per day. Additional 0.2 mg tablets were to be taken for breakthrough pain. This dose range was chosen as it was said to represent common practices in the treatment of moderate to severe chronic pain. On enrolment, a full history and physical examination, including vital parameters (blood pressure, pulse rate and temperature) was performed. All concomitant medications were documented in the case report form with details of preparation names, dose, period of administration and reason; any change in the concomitant medication during the study was documented.

Assessment for inclusion in the double blind phase: On the sixth day, the patient was assessed by the investigator for participation in the randomised component of the trial. If the inclusion criteria were met (main criteria being adequate pain control on the dose of 0.8 mg to 1.6 mg buprenorphine), the patient was randomised to one of four arms (the three strength patches and placebo patch) and the first patch was applied. Blood specimens for laboratory parameters (haematological parameters, sodium, potassium, SGOT, SGPT, creatinine, urea and prothrombin time) were collected at this visit.

Double blind phase (9 days): On the morning of the sixth day the patient took the usual sublingual buprenorphine tablets to cover the latency period of the first patch. From Day 7 on, sublingual buprenorphine tablets were only to be taken for breakthrough pain. Two patches were worn sequentially for 72 h each, starting on Day 6. The patients had an appointment with the investigator for removal of the first patch and placement of the second on Day 9 and for removal of the second patch on Day 12. Between Day 12 and Day 15, sublingual buprenorphine was taken for pain and a final examination occurred on Day 15. In the event of early withdrawal from the study, a final examination was performed at the time of withdrawal.

At each appointment with the investigator, the patient was asked to make a retrospective assessment of his/her pain relief over the previous few days, the investigator checked the patient’s diary for compliance, confirmed the number of buprenorphine sublingual tablet medications taken since the last appointment (by examining the packaging to count used and unused tablets) and assessed the skin site. An open question about adverse events was asked.
Patients, who had benefited from the patch application, were offered a further treatment with the 20 mg patch in an open label follow-up phase over six months (Study WIS-BUP-LTS).

7.1.2.4. Efficacy variables and outcomes

7.1.2.4.1. Main efficacy variables

- Retrograde assessment of pain relief: This subjective assessment of the patient’s pain relief was made by the patient at the Day 6, 9, 12 and 15 appointments. The pain was classified using a four point verbal rating scale (VRS) with the categories: unsatisfactory pain relief, satisfactory pain relief, good pain relief, complete pain relief.

- Assessment of pain intensity: This was assessed by the patient and recorded in the patient diary that was kept throughout the 15 days. The patient was asked to document the time and number of sublingual tablets taken, pain intensity overnight with this recorded at 08:00 h and pain intensity during the day at 20:00 h. Pain was classified using a five point VRS with the categories of: very severe pain, severe pain, moderate pain, slight pain, no pain.

- Assessment of duration of sleep: The patient recorded sleep duration in the patient diary at 08:00 h each morning. Sleep was classified into one of 4 categories: duration of sleep at least 6 hours uninterrupted by pain, duration of sleep 3 to 6 hours uninterrupted by pain, duration of sleep 2 to 3 hours uninterrupted by pain, duration of sleep less than 2 hours uninterrupted by pain. Only pain related interruptions to sleep were to be taken into account in the assessment.

7.1.2.4.2. Primary efficacy outcome measure

Response rate: the percentage of patients responding to the treatment where a patient was defined as a responder if his/her pain relief was classified as at least satisfactory at each investigator visit in the double blind phase (excluding final examination visit) and if he/she took in mean not more than 1 additional SL buprenorphine tablet per day from the second day of buprenorphine patch application to the last day of patch wearing (Day 7 to Day 12; total 5 days).

Comment: This definition of a responder changed to the above prior to unblinding. The original definition of a responder was that no additional buprenorphine sublingual was taken. No rationale was given for this change. The decision was also made to analyse the data separately for tumour and non-tumour patients with the stated aim of being able to detect possible differences concerning efficacy and safety data.

The aim of ‘at least satisfactory’ pain relief on the four point scale used may not be considered adequate from a patient perspective. An aim of ‘good’ or ‘complete’ may be more in keeping with their expectations.

7.1.2.4.3. Other measures included

- Safety: Adverse events (AEs) were differentiated as at patch site or not and were defined as any adverse, harmful or pathological change in a patient indicated by signs, symptoms and/or laboratory value changes, which appears in connection with the use of a drug, regardless of whether it is thought to be related to the drug or not (differentiated by at patch or not). AEs were categorised as mild, moderate or severe and as definite, probable, possible and improbable causal relationship with the study drug.

- Skin status after each patch change (swelling, erythema, pruritus, signs of infection, other; all as yes/no items). The skin site was to be assessed at least 15 minutes after patch removal so that irritations relating to the removal of the patch would not be regarded as adverse event.

- Variables to describe the patient group were recorded. These included previous and concomitant diseases (according to body systems), ethnic group, age, height, weight, sex, heart rate, blood pressure, body temperature, cause of pain (diagnosis), medication which
was stopped prior to study entry or taken continuously during the study were given, laboratory parameters taken at entry to the double blind phase.

7.1.2.4.4. Randomisation and blinding methods

The study medication was to be supplied to the investigator by [information redacted] and was to be labelled and packed individually for each patient. According to the randomisation list, eligible patients were to be entered in the study in ascending order within each centre and were to receive the corresponding medication packages containing the patches. All patches, regardless of dose, were the same physical size: total size of 76 cm², and consisted of 3 sections (one of 25 cm², containing 20 mg buprenorphine base, two of 12.5 cm², containing 10 mg buprenorphine base) plus corresponding peripheral area. The sections contained drug containing matrix or placebo matrix according to dose strength.

Two computer generated randomisation lists were prepared in the Biometry Department at [information redacted] by a person not involved in the conduct or data management of the study. The lists were sealed in envelopes directly after generation with one envelope sent to the pharmaceutical development department which was responsible for the preparation of the study medication packages and the other envelope kept in the biometry department and not opened until 95% of the data concerning the primary endpoint had been completed and corrected.

As the study was performed in a double blind manner, the investigators, the scientific study coordinator and the drug safety department of [information redacted] received a sealed envelope for each individual patient. The outside of the envelope was marked with the patient number and contained the description of the respective study medication. This envelope was only to be opened in an emergency when an identification of the study medication was necessary. Envelopes were collected at study end to determine if any had been opened; none had been.

7.1.2.4.5. Analysis populations

The statistical evaluation of the primary outcome measure was carried out according to the intention to treat principle. Patients, who received no medication and patients who were not entered in the double blind phase were excluded from the evaluation. All violations of the study protocol, which had no effect on the assessment of efficacy, were included in the evaluation. If a patient withdrew prematurely from the study in the course of the double blind phase because of AEs or unsatisfactory pain relief and any patient for whom there was no clear information, he/she was evaluated as a non-responder.

The analysis plan was changed prior to unblinding with a change in the definition of a responder with 'No additional buprenorphine sublingual' replace by with 'in mean not more than 1 additional buprenorphine sublingual per day'. It was also decided to analyse the data separately for tumour and non-tumour patients to be able to detect possible differences concerning efficacy and safety data.

The safety analysis was of AEs only and the run-in and double blind phases were analysed separately. Only those patients participating in the run-in or double blind phase were included.

7.1.2.4.6. Sample size

A sample size calculation was performed using the following definitions or assumptions:

- Response rate with buprenorphine 20 mg patch 55%
- Response rate with placebo patch 20%
- \( \alpha = 0.05, \beta = 0.2 \)
- two sided hypothesis.
Higher response rates were expected for 30 mg and 40 mg. On this basis, 35 patients were needed in each treatment group. The planned number of patients to be randomised into the double blind phase of the study was 144, with another 20 to 30 patients expected to be required for the run-in phase.

**Comment:** no explanation was provided for the assumptions that the response rates for buprenorphine transdermal patch 20 mg (35 µg/h) would be 55% and 20% for the placebo patch. The response rates chosen in WIS-BUP02 and WIS-BUP03 for the sample size calculations were 40% for the active patch and 15% for placebo. Both placebo rates (20% and 15%) seem low for a clinical analgesia study. A placebo response rate of 30% seems more likely.

### 7.1.2.4.7. Statistical methods

**Missing data:**

- In the case of premature termination the last available value up to the end of the observation period was assessed. If a value was missing in the course of the observation period, the previous value was used.

- Sublingual buprenorphine tablet number: any inconsistencies concerning tablets taken between the data recorded in the CRF and in the diary were not corrected. The investigator counted the remaining sublingual tablets in the boxes and documented the number in the CRF. If inconsistencies were found, it was to be assumed that the entries in the diary were not correct.

Summary statistics for continuous data include mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum value. For the categorical data tables with absolute and relative frequencies were produced.

**Comparability of treatment groups:** Socio demographical data, medical history including risk factors, current health status, ethnic group, age, height, weight, sex, cause of pain and the baseline values of the efficacy and safety parameters were evaluated by the following tests:

- The normally distributed continuous variables (age, height, weight, body temperature, blood pressure and heart rate) were compared by a general linear model for treatment and centre effects and their interactions

- The categorical data (sex, pain intensity before medication) were compared by a Cochran-Mantel-Haenszel test and a Breslow Day test.

**Primary outcome measure:** This primary endpoint was examined in a confirmatory manner with ordered hypothesis based on increasing patch strength (buprenorphine transdermal patch 40 mg ≥ 30 mg/h ≥ 20 mg) in order to avoid adjusting the p values or α inflation, respectively.

As a test of the hypothesis of equal rates at the level α = 0.05 a Cochran-Mantel-Haenszel test was carried out. If the hypothesis was rejected, then as a test of the hypothesis of equal rates of TTS 100 and placebo a Cochran-Mantel-Haenszel test at the level α = 0.05 was carried out. If, in turn, this hypothesis was rejected, then as a test of the hypothesis of equal rates of TTS 75 and placebo a Cochran-Mantel-Haenszel test at the level α = 0.05 was carried out. If this hypothesis was rejected then as a test of the hypothesis of equal rates of TTS 50 and placebo a Cochran-Mantel-Haenszel test at the level α = 0.05 was carried out. The hypothesis of no interactions between the centres and treatments was carried out with the Breslow-Day test at the level α = 0.05.

**Secondary outcome measures:** Exploratory tests were performed for consumption of SL buprenorphine (ANOVA with factors centre, treatment), and pain relief (maximum likelihood estimates and CMH). Pain intensity and duration of sleep were described but not tested statistically.
7.1.2.4.8. **Participant flow**

189 patients were screened. 38 patients were not randomised into the double blind phase. These patients are not included in the intention to treat analysis for primary outcome.

- 12 patients were not randomised due to refractory adverse events during the run-in phase
  - The adverse events were mainly symptoms of the central nervous and the gastrointestinal system. In two patients a serious adverse event occurred. One patient died at the end of the run-in phase and the other patient was admitted to hospital with adynamic ileus.

- 21 patients were not randomised as either pain relief was not satisfactory or the mean daily buprenorphine dose was outside the range of 0.8 to 1.2 mg

- 5 patients were not randomised due to other reasons:
  - One patient terminated the run-in phase prematurely due to psychological reasons
  - For two patients no reason was given. For one, there were no adverse events and pain relief was good. In the other, pain relief was assessed as good and sedation was stated as an adverse event
  - One patient terminated the run-in phase prematurely, because she suspected that the study medication was less effective
  - One in-patient was discharged home and it was too far to return for appointments.

151 patients were randomised into the double blind phase with outcome as shown in Table 8.

**Table 8: WIS-BUP01 Participant flow (of the 151 patients in the double blind phase)**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 mg patch</th>
<th>30 mg patch</th>
<th>40 mg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BUP-TDP 35</td>
<td>TTS 50</td>
<td>BUP-TDP 52.5</td>
<td>TTS 75</td>
</tr>
<tr>
<td>Planned</td>
<td>36</td>
<td>36</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Randomised</td>
<td>37</td>
<td>35</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Treated</td>
<td>37</td>
<td>35</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>ITT</td>
<td>35*</td>
<td>35</td>
<td>41</td>
<td>38</td>
</tr>
<tr>
<td>Completed Study</td>
<td>34</td>
<td>33</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Number withdrawn</td>
<td>3</td>
<td>2</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reasons for withdrawal</th>
<th>Placebo</th>
<th>20 mg patch</th>
<th>30 mg patch</th>
<th>40 mg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE (2)</td>
<td>AE (1)</td>
<td>AE (3)</td>
<td>AE (1)</td>
<td></td>
</tr>
<tr>
<td>Unsatisfactory response (1)</td>
<td>Unsatisfactory response (1)</td>
<td>Unsatisfactory response (2)</td>
<td>Other reason 1</td>
<td></td>
</tr>
<tr>
<td>Unsatisfactory response (1)</td>
<td></td>
<td></td>
<td>AE (1)</td>
<td></td>
</tr>
</tbody>
</table>

* 2 patients considered as not evaluable: one because the patches fell off and one died within 24 h of the first patch application.
Thirteen out of 151 patients (8.6%) withdrew from the study prematurely.

- Seven of these patients (2 patients treated with placebo, 1 patient treated with 20 mg patch, 3 patients treated with 30 mg patch and 1 patient treated with 40 mg patch) withdrew due to adverse events
- five patients (1 patient treated with placebo, 1 patient treated with 20 mg patch, 2 patients treated with 30 mg patch and 1 patient treated with 40 mg patch) withdrew due to inadequate pain control
- one patient treated with 30 mg patch due to other reasons; this patient was transferred to the oncologic department where the analgesic medication was changed without consultation.

Recruitment at the 18 centres was highly variable (ranging from 1 patient to 31). Before unblinding it was decided to analyse all centres with at least one complete block separately and the remaining centres together as one amalgamated centre with 38 patients. This amalgamated centre was checked concerning misrepresentation of results.

7.1.2.4.9. Major protocol violations/deviations

In most of the patients (64.2%) the skin status was assessed less than 15 minutes after removal of the patch, although the protocol specified after 15 minutes. In all of the patients either no reaction was observed or the skin reaction lasted for more than 30 minutes.

In nearly a quarter of the patients (26.5%) the patch was not changed as described in the protocol. Most of them changed the side of the body (infra clavicular to upper back) instead of the region (right to left). In single cases the patch was applied to the same site were the previous patch was applied.

18 patients received buprenorphine doses outside the range 0.8 to 1.2 mg before randomisation:

- 10 patients received dose < 0.8 mg: two patients each in the placebo and 20 mg (TTS 50) groups, three patients each in the 30 mg (TTS 75) and 40 mg (TTS 100) groups.
- 8 patients received dose > 1.2 mg: two patients each in the placebo and 40 mg (TTS 100) groups, three patients in the 20 mg (TTS 50) group and four patients in the 40 mg (TTS 100) group.

A total of four patients received concomitant opioids or strong analgesics:

- One patient on 30 mg patch (TTS 75) received 50 mg intramuscular tramadol (Day 7) from his physician for his pain.
- One patient on 30 mg patch (TTS 75) took 225 mg tramadol daily during the run-in phase. On entry into the double blind phase tramadol was changed to the non-opioid analgesic metamizole.
- One patient on 20 mg patch (TTS 50) received 20 mg morphine intravenously during the run-in phase
- One patient on 40 mg patch (TTS 100) took 100 mg tramadol once during the run-in phase.

Comment: These protocol deviations are unlikely to have affected the study outcomes. Of note, however, is that 38 patients (26%) did not meet all criteria for randomisation and that in 21 out of 38 this was due to lack of efficacy; this was not discussed in the study report.
### Baseline data

All patients were Caucasians, 70 male and 81 female patients in the age of 26 to 83 years. There were no relevant differences between the treatment groups regarding height, weight and sex distribution, laboratory parameters although there was regarding age distribution; the patients of the placebo group were younger than those of the other groups: mean age placebo group 54.9, 20 mg patch group 60.6 years, 30 mg patch group 60.5 years, 40 mg patch group 62.7 years.

#### Table 9: WIS-BUP01 Baseline characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n = 37)</th>
<th>Buprenorphine TDS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>35 μg/h (n = 35)</td>
</tr>
<tr>
<td><strong>Mean (± SD)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>54.9 (11.5)</td>
<td>60.6 (12.2)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>172.6 (9.7)</td>
<td>168.9 (7.2)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>69.0 (12.6)</td>
<td>68.5 (16.0)</td>
</tr>
<tr>
<td><strong>No. (%) of patients</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female/male</td>
<td>18/49 (51)</td>
<td>18/51 (49)</td>
</tr>
<tr>
<td>Malignant/ non-malignant origin of pain</td>
<td>20/54 (46)</td>
<td>22/63 (37)</td>
</tr>
</tbody>
</table>

Percentages were rounded up to the nearest integer.

The underlying pathology of the chronic pain was malignant in 55% of patients and of non-malignant origin in 45% of patients. No single type of malignancy or source of benign pain was predominant in any treatment group.

#### Figure 9: WIS-BUP01 Diagnoses causing pain

**Tumour diagnoses included (number):**
- mouth/tongue/larynx (7)
- oesophagus/stomach (4)
- duodenum/colon/rectum (12)
- liver/gall bladder/pancreas (5)
- bronchus/lung/pleura (13)
- female breast (14)
- uterus/ovary/vulva (16)
- prostate/kidney/bladder (12)
- others (10)
- secondary (metastasis) (51)

**Types of non-tumour pain included (number):**
- others (7)
- post-herpetic neuralgia (2)
- polyneuropathy (2)
- phantom limb pain/deafferentation p./nerve lesion (12)
- condition after trauma/endoprosthesis operation (5)
- post-laminectomy syndrome/intervertebral disc disorders (19)
- osteoporosis (9)
- degenerative spinal pain (11)
- Arthrosis/rheumatic (2)
- Vascular pain (11)
- Enthesopathy/muscle/soft tissue affect (5)
- Other diseases of locomotor system (6)
- Gastro-intestinal pain (1)

**Comment:** Despite randomisation there were some imbalances:

1. The number of tumour and non-tumour patients is not evenly spread across all treatment groups. The 20 mg patch group has 22 tumour patients and 13 non-tumour patients.
2. In the patients with pain due to tumour, patients in the placebo group had more advanced disease, as shown by the presence of metastases. 80.0% of the patients in the placebo group had metastases, compared with 63.6% in the 20 mg patch group, 59.1% in the 30 mg patch group and only 42.1% in the 40 mg patch group.
3. The diagnoses of the non-tumour pain patients were not evenly distributed amongst the treatment groups. This was inevitable given the number of diagnostic categories used (13) and the number of enrolled patients.

7.1.2.4.10.1. Concomitant diseases:

Multiple diseases per patient were observed. The incidence of previous or concomitant diseases or surgery in the placebo and TTS 50 groups tended to be lower than in the 30 mg (TTS 75) and 40 mg (TTS 100) groups. The non-tumour patients in the placebo and 40 mg (TTS 100) groups were more often affected.

7.1.2.4.10.2. Previous pain and use of opioids

No measure of pain prior to entry into the run-in phase is provided. Strong opioids (step III of the WHO analgesic ladder) had been prescribed in almost all patients (90 to 93% of patients in each treatment arm). The most commonly used strong opioid used was buprenorphine (84.2 to 91.9% of patients in each treatment arm). Use of weak opioids (WHO step II) was much less frequent (0 to 8% of patients in each of the treatment groups) and this was most commonly tramadol. The administration of other opioids, such as morphine, tilidate/naloxone and codeine/DHC, was comparatively seldom.

7.1.2.4.10.3. Concomitant analgesics during the trial

The use of concomitant medications for pain was common (118 of 151 patients) with this fairly evenly spread across the groups. The most common single agent was metamizole (47 of 118 patients) although the most common class was NSAIDs (112 of 118 patients, including metamizole). In addition, during the study 6 patients received radiotherapy; two patients each in the placebo and 20 mg (TTS 50) groups (10.0% and 9.1%, respectively) and four patients in 30 mg (TTS 75) and 40 mg (TTS 100) groups (18.2% and 21.1%, respectively). Chemotherapy was administered during the study to 8 patients during the study; 2 in the placebo, 1 in the 20 mg (TTS 50), 3 in the 30 mg (TTS 75) and 2 in the 40 mg (TTS 100) groups.

Comment: The tumour population in the study is probably generalisable to the Australian population. It is difficult to say if this is the case for the non-tumour group as some of the diagnoses used are not those used in Australia and diagnosis definitions were not provided. The previous exposure to buprenorphine will be different in the Australian population as this analgesic is infrequently prescribed, with codeine, oxycodone and tramadol the most commonly prescribed (in order of frequency of prescriptions).36 The use of concomitant analgesics and other therapies that may reduce pain (radiotherapy and chemotherapy) seem roughly evenly spread. Metamizole is a non-steroidal anti-inflammatory drug (NSAID) that is not registered for use in Australia.

7.1.2.5. Results for the primary efficacy outcome

The primary outcome measure was the response rate with a responder defined by pain relief at least satisfactory at all assessment points and on average not more than 1 additional SL buprenorphine tablet per day. The response rate according to the patch strength was 31.4% with placebo, 34.3% with the 20 mg patch, 36.6% with the 30 mg patch and 50.0% with the 40 mg patch. The primary endpoint was not reached (p = 0.374, overlapping confidence intervals). This was attributed to the higher than expected placebo effect (31.4% compared to 20% expected).

Table 10: WIS-BUP01 Response rates

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI lower limit</th>
<th>95% CI upper limit</th>
<th>difference vs. placebo</th>
<th>95% CI lower limit</th>
<th>95% CI upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td>19</td>
<td>9</td>
<td>47.4</td>
<td>24.4</td>
<td>71.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>non-tumour pain</td>
<td>16</td>
<td>2</td>
<td>12.5</td>
<td>1.6</td>
<td>30.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>all patients</td>
<td>35</td>
<td>11</td>
<td>31.4</td>
<td>16.9</td>
<td>49.3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TTS 50</td>
<td>22</td>
<td>7</td>
<td>31.8</td>
<td>13.9</td>
<td>54.9</td>
<td>-15.6</td>
<td>-50.2</td>
<td>19.1</td>
</tr>
<tr>
<td>non-tumour pain</td>
<td>13</td>
<td>5</td>
<td>38.5</td>
<td>13.9</td>
<td>68.4</td>
<td>26.0</td>
<td>-12.0</td>
<td>63.9</td>
</tr>
<tr>
<td>all patients</td>
<td>35</td>
<td>12</td>
<td>34.3</td>
<td>19.1</td>
<td>52.2</td>
<td>2.9</td>
<td>-22.0</td>
<td>27.7</td>
</tr>
<tr>
<td>TTS 75</td>
<td>22</td>
<td>8</td>
<td>36.4</td>
<td>17.2</td>
<td>59.3</td>
<td>-11.0</td>
<td>-46.0</td>
<td>24.0</td>
</tr>
<tr>
<td>non-tumour pain</td>
<td>19</td>
<td>7</td>
<td>36.8</td>
<td>16.3</td>
<td>61.6</td>
<td>24.3</td>
<td>-8.5</td>
<td>57.2</td>
</tr>
<tr>
<td>all patients</td>
<td>41</td>
<td>15</td>
<td>36.6</td>
<td>22.1</td>
<td>53.1</td>
<td>5.2</td>
<td>-18.8</td>
<td>29.1</td>
</tr>
<tr>
<td>TTS 100</td>
<td>22</td>
<td>8</td>
<td>42.1</td>
<td>20.3</td>
<td>66.5</td>
<td>-5.3</td>
<td>-42.1</td>
<td>31.6</td>
</tr>
<tr>
<td>non-tumour pain</td>
<td>19</td>
<td>11</td>
<td>57.9</td>
<td>33.5</td>
<td>79.7</td>
<td>45.4</td>
<td>12.2</td>
<td>78.6</td>
</tr>
<tr>
<td>all patients</td>
<td>38</td>
<td>19</td>
<td>50.0</td>
<td>33.4</td>
<td>66.6</td>
<td>18.6</td>
<td>-6.3</td>
<td>43.4</td>
</tr>
</tbody>
</table>

There were no apparent differences in the number of responders in the tumour patients compared to the non-tumour patients.

Comment:

- Note that all groups used sublingual buprenorphine as required for breakthrough pain; this enabled the placebo patients to self-titrate to desired effect and may partially account for the high placebo response rate
- The wide confidence intervals suggest that this study is likely to be underpowered to show a treatment effect, with this resulting from the small sample size. The assumptions in the sample size calculation overestimated the treatment effect and under estimated the placebo effect.

7.1.2.6. Results for other efficacy outcomes

Small positive changes were seen in the other efficacy variables. No tests of significance were reported.

7.1.2.6.1. Consumption of rescue medication (SL buprenorphine tablets 0.2 mg)

During the run-in phase, patients controlled pain by consuming a mean of 0.9 to 1.0 mg/day sublingual buprenorphine tablets. This intake was reduced in the double blind phase by 0.6 mg/day for active treatment groups, and 0.5 mg/day for the placebo group. The mean daily consumption of sublingual buprenorphine increased after removal of the second patch in all groups.
7.1.2.6.2. Retrograde assessment of pain relief (VRS, 4 categories)

The percentage of patients with good or complete pain relief decreased in the placebo group during the double blind phase. There were increases of around 8% for patients in the 20 mg and 30 mg patch groups (equating to 3 patients) but a decrease in the 40 mg patch group.

Table 11: WIS-BUP01. Changes in retrospective assessment of pain relief

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Patients with ‘good’ + ‘complete’ pain relief</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>End of Run-in Phase (Day 6)</td>
</tr>
<tr>
<td></td>
<td>Number (%)</td>
</tr>
<tr>
<td>Placebo</td>
<td>20 (57.1)</td>
</tr>
<tr>
<td>20 mg patch</td>
<td>19 (54.3)</td>
</tr>
<tr>
<td>30 mg patch</td>
<td>18 (43.9)</td>
</tr>
<tr>
<td>40 mg patch</td>
<td>20 (52.6)</td>
</tr>
</tbody>
</table>

7.1.2.6.3. Pain intensity as assessed by the patient (VRS, 5 categories)

Pain intensity was recorded by the patient twice a day. The mean percentages of all values for pain intensity (VRS) as recorded in the patient’s diary are given in the table below. In the placebo group, the proportion of patients with mild or no pain decreased during patch wearing and increased after removal of the second patch. In all three buprenorphine patch groups, the proportion of patients with mild or no pain increased during patch wearing but there were inconsistent changes after patch removal, with virtually no change in the 30 mg patch group, a small decrease in the 20 mg patch group and a large decrease in the 40 mg patch group.
7.1.2.6.4. Duration of sleep (4 categories)

Every morning the patients recorded the duration of sleep uninterrupted by pain in the previous night in their diary. The percentage of patients averaging more than 6 h uninterrupted sleep decreased in the placebo group and increased in the buprenorphine patch groups.

Table 13: WIS-BUP01 Changes in sleep

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Placebo</th>
<th>20 mg patch</th>
<th>30 mg patch</th>
<th>40 mg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 to 6 (Run-in Phase)</td>
<td>49.1</td>
<td>46.9</td>
<td>37.7</td>
<td>42.9</td>
</tr>
<tr>
<td>Day 6 to 12 (Double-blind phase)</td>
<td>33.8</td>
<td>55.2</td>
<td>40.2</td>
<td>54.8</td>
</tr>
<tr>
<td>Day 12 to 15 (no patch)</td>
<td>39</td>
<td>40.0</td>
<td>33.3</td>
<td>55.3</td>
</tr>
</tbody>
</table>

Comment: The changes seen with patch wearing in regard to the secondary efficacy outcome measures were small and inconsistent as would be expected from an under-powered study. The question as to whether buprenorphine patches provide effective analgesia in this patient population is not answered by this study.

An article based on this study was published in 2003.37 This article reported the primary outcome measure as described in the study and attributed the failure to demonstrate efficacy to the unexpectedly high placebo rate.

7.1.3. Study WIS-BUP02

Study Title: Determination of the analgesic efficacy of three buprenorphine dosages versus placebo in a transdermal therapeutic system (TTS) in patients with tumour pain and patients with chronic non-tumour related pain.

7.1.3.1. Study design, objectives, locations and dates

Study Design: Randomised, multicentre, double blind, placebo controlled parallel study for the investigation of three buprenorphine patch dosages; 20 mg (TTS 50) patch, 30 mg (TTS 75) patch and 40 mg (TTS 100) patch. The study was conducted over 15 days with no run-in/washout period.

Locations: 16 centres, 12 in Germany, 2 in Austria, 2 in the Netherlands.


Objectives: To determine the analgesic efficacy of three buprenorphine dosages compared to placebo by ascertaining the number and percentage of responders where responders are defined as those patients who take in mean not more than one additional buprenorphine sublingual tablet per day from the second day of treatment and indicate at least satisfactory pain relief at each patch change.

7.1.3.2. Inclusion and exclusion criteria

Main criteria for inclusion: In-patients and out-patients aged over 18 years and with continuous severe tumour and non-tumour related pain that cannot be adequately managed with regular weak opioids according to WHO step II of tumour pain drug treatment.

Main criteria for exclusion: Patients previously treated with moderate doses of a potent opioid, such as morphine with a daily dose of more than 30 mg orally or 10 mg parenterally or the equivalent dose of another opioid. Treatment with a daily dose of 30 mg morphine orally (or 10 mg morphine parenterally) was regarded as equivalent to a daily dose of 100 to 150 mg tramadol.

Full inclusion and exclusion criteria were provided.

7.1.3.3. Study treatments

The study extended over 15 days. Suitable patients were randomised to one of four arms (the three strength patches and placebo patch) with the first patch applied at randomisation. During the first day after patch application, the patient was allowed to administer the analgesic medication of the previous day (even if this involved another opioid) to cover the latency period of the patch. From Day 2 to Day 15, sublingual 0.2 mg buprenorphine tablets were available for all patients (including the placebo arm) for breakthrough pain. Five patches were worn sequentially, for 72 h each, with the patch replaced on Day 3, Day 6, Day 9 and Day 12. The patch was applied either to non-irritated normal skin in the infra-clavicular region or upper back. An application sequence was to be followed to ensure an adequate time has elapsed before a site is re-used (9 days according to the schedule). The last patch was removed on Day 15 and the final examination occurred on Day 16.

A patient diary was kept throughout the 15 days to record the patient's assessment of pain, sleep, sublingual buprenorphine tablets taken for breakthrough pain and occurrence of adverse events. The patient was reviewed at each patch change; vital signs were taken, the quality of pain treatment (retrograde assessment of pain relief by the patient) was documented and the skin status of the patch site assessed. Laboratory parameters were determined at the initial examination for use in baseline comparison of the groups. Adverse events were recorded throughout the whole study.

If a patient was withdrawn from the trial prematurely, the planned final examination was carried out at the time of the withdrawal. If a patient’s pain was inadequately controlled, the patient was withdrawn from the trial.

Any previous concomitant medication/treatment was documented in the case report form with details of preparation, dose and period of administration. Apart from the study medication (buprenorphine patch, buprenorphine sublingual tablets) the simultaneous administration of
other centrally acting analgesics was not allowed during the study with the exception of the first day of treatment. The administration of peripherally acting analgesics (NSAIDs) and the administration of co-analgesics such as neuroleptics, antidepressants or anticonvulsants were allowed without change during the study. Radiotherapy, chemotherapy and the administration of corticosteroids could be continued during the study but should not be commenced during the study, unless from clinical necessity.

Patients, who had benefited from the TTS application, were offered further treatment with the 20 mg (TTS 50) patch in an open label follow-up phase over six months, WIS-BUP-LTS.

Comment: As adequate analgesia has to be ensured in patients with chronic pain, it is appropriate that an analgesic for breakthrough pain be provided. The choice of sublingual buprenorphine was not explained but may be consistent with usual practice in Germany at the time.

7.1.3.4. Efficacy variables and outcomes

7.1.3.4.1. Main efficacy variables

The main efficacy variables were:

7.1.3.4.1.1. Consumption of sublingual 0.2 mg buprenorphine tablets for breakthrough pain

This was recorded in the patient’s diary and verified by the investigator at the regular appointments by checking the packaging and remaining tablet numbers. If there were discrepancies, the number recorded by the investigator was used and the number recorded in the diary was regarded as incorrect.

7.1.3.4.1.2. Retrograde assessment of pain relief

This subjective assessment of pain relief was made by the patient at the Day 2 and Day 3, and at each patch change, using a four point VRS: unsatisfactory pain relief, satisfactory pain relief, good pain relief, complete pain relief.

7.1.3.4.1.3. Assessment of pain intensity

This was assessed by the patient and recorded in the patient diary that was kept throughout the 15 days. The patient was asked to document the time and number of sublingual tablets taken, pain intensity overnight with this recorded at 08:00 h and pain intensity during the day at 20:00 h. Pain was classified using a five point VRS: very severe pain, severe pain, moderate pain, slight pain, no pain.

7.1.3.4.1.4. Assessment of duration of sleep

The patient also recorded sleep duration in the patient diary with this entry being made at 08:00 h. Sleep was classified into one of 4 categories: duration of sleep at least 6 hours uninterrupted by pain, duration of sleep 3 to 6 hours uninterrupted by pain, duration of sleep 2 to 3 hours uninterrupted by pain, duration of sleep less than 2 hours uninterrupted by pain. Only pain related interruptions to sleep were to be taken into account in the assessment.

7.1.3.5. The primary efficacy outcome

The primary efficacy outcome was:

Response rate for each group was the primary efficacy outcome measure where responders were defined as patients who took in mean not more than one additional buprenorphine sublingual tablet per day from the second day of TTS application and who indicated retrospectively at least satisfactory pain relief at each patch change.

Comment: This definition was the result of a change prior to unblinding. The original definition of a responder was that no additional buprenorphine sublingual was taken. No rationale was given for this change. The decision was also made to analyse the data
separately for tumour and non-tumour patients with the stated aim of being able to detect possible differences concerning efficacy and safety data.

The aim of 'at least satisfactory' pain relief on the four point scale used may not be considered adequate from a patient perspective. An aim of 'good' or 'complete' may be more in keeping with their expectation.

7.1.3.6. Other variables

7.1.3.6.1. Safety

- Adverse events (AEs) were differentiated as at patch site or not and were defined as any adverse, harmful or pathological change in a patient indicated by signs, symptoms and/or laboratory value changes, which appears in connection with the use of a drug, regardless of whether it is thought to be related to the drug or not (differentiated by at patch or not). AEs were categorised as mild, moderate or severe and as definite, probable, possible and improbable causal relationship with the study drug

- Skin status at each patch change: Skin status (presence of swelling, erythema, pruritus, signs of infection, other; all as yes/no items) was recorded by the investigator prior to each patch application (on Day 1, 4, 7, 10 and 13) and after each patch removal (on Day 4, 7, 10, 13 and 16). Skin abnormalities were also differentiated by at patch or not.

Variables to describe the patient group were recorded. These included previous and concomitant diseases (according to body systems), ethnic group, age, height, weight, sex, heart rate, blood pressure, body temperature, cause of pain (diagnosis), medication which was stopped prior to study entry or taken continuously during the study were given.

7.1.3.7. Randomisation and blinding methods

The study medication was supplied to the investigator by [information redacted] and was labelled and packed individually for each patient. According to the randomisation list patients who met inclusion and exclusion criteria were to be entered in the study in ascending order within each centre and were to receive the corresponding medication packages containing the patches. All patches regardless of dose were the same physical size: total size of 76.32 cm², which consists of 3 sections (one of 25 cm², containing 20 mg buprenorphine base, two of 12.5 cm², containing 10 mg buprenorphine base, plus corresponding peripheral area. According to dose strength corresponding sections contain placebo matrices).

The randomisation was performed using the procedure of 'permuted block randomisation' at the biometry department of [information redacted]. A single block was generated according to the urn model (taking the order into account without putting back). Two randomisation lists were prepared in the Biometry Department at [information redacted] by a person not involved in the conduct or data management of the study. Both lists were sealed in envelopes directly after generation so that all persons involved in the study, including biostatisticians, did not know the code. Documentation concerning hard and software was kept in the Biometry Department.

All code envelopes were checked at study end to confirm that they were still closed. One envelope had been opened; after premature withdrawal of the patient from the study due to intolerable constipation and unsatisfactory pain relief. All other envelopes were closed.

7.1.3.8. Analysis populations

The primary analysis was of the intention to treat (ITT) set. Patients in whom no patch was applied were excluded from the evaluation. If a patient withdrew prematurely from the study because of AEs or unsatisfactory pain relief, he/she was evaluated as a non-responder. All other cases of premature termination of the study had to be assessed individually prior to unblinding. All patients in whom a patch was applied were included in the safety analysis.
7.1.3.9. **Sample size**

Sample size calculation was carried out and based on the following definitions or assumptions:

- $\alpha = 0.05$, $\beta = 0.2$
- response with buprenorphine 20 mg (TTS50) patch 40%
- response with placebo 15%
- two sided hypothesis.

The 30 mg (TTS 75) patch and 40 mg (TTS 100) patch were assumed to show higher response rates. No $\alpha$ adjustment was made, as ordered hypotheses were to be tested. On the basis of the assumptions made, $n = 38$ per treatment group.

**Comment:** No explanation was provided for the assumptions of a response rate of 40% for buprenorphine transdermal patch 20 mg (35 µg/h) and 15% for placebo. The concurrently run study WIS-BUP01 assumed a response rate of 55% for the 20 mg patch and 20% for placebo. Both placebo rates (20% and 15%) seem low for a short clinical analgesia study. A placebo response rate of 30% seems more likely.

7.1.3.10. **Statistical methods**

7.1.3.10.1. **Missing data**

- In the case of premature termination the last available value up to the end of the observation period was assessed. If a value was missing in the course of the observation period, the previous value was used
- Sublingual buprenorphine tablet number: any inconsistencies concerning tablets taken between the data recorded by the investigator in the CRF and in the diary were not corrected. The CRF was assumed to be correct and this data was used in the analysis.

7.1.3.10.2. **Summary statistics**

Summary statistics for continuous data include mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum value. For the categorical data tables with absolute and relative frequencies were produced.

7.1.3.10.3. **Comparability of treatment groups**

Socio demographical data, medical history including risk factors, current health status, ethnic group, age, height, weight, sex, cause of pain and the baseline values of the efficacy and safety parameters were evaluated by the following tests:

- The normally distributed continuous variables (age, height, weight, body temperature, blood pressure and heart rate) were compared by a general linear model for treatment and centre effects and their interactions
- The categorical data (sex, pain intensity before medication) were compared by a Cochran-Mantel-Haenszel test and a Breslow Day test.

7.1.3.10.4. **Primary outcome measure**

This primary endpoint was examined in a confirmatory manner with ordered hypothesis based on increasing patch strength (buprenorphine transdermal patch 40 mg $\geq$ 30 mg/h $\geq$ 20 mg) in order to avoid adjusting the $p$ values or $\alpha$ inflation, respectively.

As a test of the hypothesis of equal rates at the level $\alpha = 0.05$ a Cochran-Mantel-Haenszel test was carried out. If the hypothesis was rejected, then as a test of the hypothesis of equal rates of TTS 100 and placebo a Cochran-Mantel-Haenszel test at the level $\alpha = 0.05$ was carried out. If, in turn, this hypothesis was rejected, then as a test of the hypothesis of equal rates of TTS 75 and placebo a Cochran-Mantel-Haenszel test at the level $\alpha = 0.05$ was carried out.
was carried out. If this hypothesis was rejected then as a test of the hypothesis of equal rates of TTS 50 and placebo a Cochran-Mantel-Haenszel test at the level \(\alpha = 0.05\) was carried out. The hypothesis of no interactions between the centres and treatments was carried out with the Breslow-Day test at the level \(\alpha = 0.05\).

In addition the trend in relation to dosage and effect will be examined secondarily using the Cochran-Armittage trend test.

7.1.3.10.5. Secondary outcome measures

The tests for the secondary end points were described as explorative.

- The consumption of sublingual tablets was evaluated with a twofold variance analysis. The interactions between centres and treatment were examined at the level \(\alpha = 0.05\). Then an LSD test was carried out using ordered hypotheses as per the primary end point for the comparison versus placebo at the level \(\alpha = 0.05\).

- The retrograde assessment of pain relief was investigated with a logistic regression for ordinal categorical data.

- The course of the pain intensity was evaluated separately for the entries in the morning and in the evening. In addition the mean of both entries was examined. These values and the duration of sleep were evaluated by variance analysis. The interactions between time and treatment as well as the effects resulting from a multicentre study were examined. For the comparison versus placebo the difference of the last value to the baseline value was calculated. The latter was examined by means of an LSD test at the level \(\alpha = 0.05\) with ordered hypotheses as per the primary end point.

7.1.3.10.6. Safety analysis

Only adverse events (AE) were evaluated, which appeared after the application of the study medication, or, if already present before application, became more intense after application. For each treatment and centre incidence distributions were prepared which represent the number of patients with and without AEs irrespective of the number of AEs occurring, and which take the individual AEs into account. As a test of the hypothesis of equal incidence rates at the level \(\alpha = 0.05\) a Cochran-Mantel-Haenszel test was carried out.

Comment: The statistical plan is acceptable and was followed in the analysis of results. Some extra analyses that were not included in the statistical plan were performed:

- A comparison of the 20 mg and 30 mg patches to placebo as separate analyses and not as part of an ordered analysis.

- A more complicated analysis of the secondary outcome measure of sublingual buprenorphine in terms of 'buprenorphine equivalents.'

7.1.3.11. Participant flow

According to the study report, only one patient was screened and not entered into the trial; 'the patient refused to give her consent, because she was hospitalised only for three days and the distance from home to the hospital was too long for the patient.'

158 patients were screened, 157 patients were randomised, 157 patients received double blind medication and 154 patients were included in the efficacy analysis. Before unblinding, it was decided to exclude 3 patients as in each of them the 1st patch was removed within the first 24 hours and no further patches were worn. The circumstance for each patient was:

- In one patient the patch was removed after 16.5 h due to coma and the patient died the following day.

- In one patient the patch was removed after 20 h and the patient withdrew his consent.
• In one patient the patch was removed after 23.2 h due to a serious adverse event.

**Table 14: Study WIS-BUP02 participant flow**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 mg patch</th>
<th>30 mg patch</th>
<th>40 mg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>BUP-TDP 35</td>
<td>BUP-TDP 52.5</td>
<td>BUP-TDP 70</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TTS50</td>
<td>TTS75</td>
<td>TTS100</td>
</tr>
<tr>
<td>Planned</td>
<td>38</td>
<td>38</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Randomised</td>
<td>38</td>
<td>41</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>Treated</td>
<td>38</td>
<td>41</td>
<td>41</td>
<td>37</td>
</tr>
<tr>
<td>ITT*</td>
<td>37</td>
<td>41</td>
<td>40</td>
<td>36</td>
</tr>
<tr>
<td>Completed Study</td>
<td>22</td>
<td>29</td>
<td>30</td>
<td>32</td>
</tr>
<tr>
<td>Number withdrawn</td>
<td>16</td>
<td>12</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Reasons for withdrawal (number)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AE (6)</td>
<td>AE (3)</td>
<td>AE (5)</td>
<td>AE (3)</td>
</tr>
<tr>
<td></td>
<td>Unsatisfactory response (8)</td>
<td>Unsatisfactory response (3)</td>
<td>Unsatisfactory response (4)</td>
<td>Unsatisfactory response (0)</td>
</tr>
<tr>
<td></td>
<td>Informed consent withdrawal (1)</td>
<td>Informed consent withdrawal (6)</td>
<td>Informed consent withdrawal (1)</td>
<td>Informed consent withdrawal (1)</td>
</tr>
<tr>
<td></td>
<td>Other (1)</td>
<td>Other (0)</td>
<td>Other (1)</td>
<td>Other (1)</td>
</tr>
</tbody>
</table>

* 3 patients were excluded from analysis as the total duration of patch wearing was less than 24 hours.

44 of the 157 patients were withdrawn prematurely from the study:

• 17 withdrew due to adverse events (AE)
• 15 withdrew due to unsatisfactory response with inadequate pain control
• 3 withdrew due to other reasons
  – One patient treated with placebo developed a painful abscess in the right side of the neck. The patch did not provide sufficient pain relief for this and the patient refused to apply the next patch
  – One patient treated with the 30 mg (TTS 75) patch withdrew prematurely due to unforeseeable tumour progression
  – One patient treated with 40 mg (TTS 100) patch was withdrawn as the last patch was not available

• 9 patients (1 patient treated with placebo, 6 patients treated with 20 mg (TTS 50), 1 patient treated with 30 mg (TTS 75) and 1 patient treated with 40 mg (TTS 100) withdrew their consent. In six of the 9 patients the most probable reason for this was said to be adverse events.

The number recruited at each centre ranged from 1 to 32. Before unblinding it was decided to analyse all centres with at least one complete block separately and the remaining centres together as one amalgamated centre with 38 patients with the intention that this amalgamated centre be checked carefully concerning misrepresentation of results.

**Comment:** More patients were randomised (157) than planned (152) resulting in some small differences in the numbers in each treatment group. The numbers of withdrawals
are unevenly spread across the groups ranging from 16 in the placebo group to 5 in the highest dose patch group. The withdrawals from the placebo group were mainly due to adverse events (6) and inadequate pain control (8). The reason for the largest number of withdrawals from the TTS100 group was AEs (3), with none withdrawing due to inadequate response. As patients withdrawing early from the study were classified as non-responders, the uneven spread could positively influence the outcome of the trial.

7.1.3.12. Major protocol violations/deviations

- In 5 centres, the patients were not entered in the study in ascending order
- There were discrepancies in the recording of pain on patient admission to the study with some investigators documenting pain as it was in the presence of analgesics and some documenting an estimate of how the pain would be if analgesics were not being taken. As a result, pain on admission to the study was not included in the analysis
- In some of the patients (12.7%) the skin status was assessed less than 15 minutes after removal of the patch despite the protocol requirement of more than 15 minutes. These patients were checked for skin reactions. In all of the patients ‘either no reaction was observed or the skin reaction lasted for longer than 30 minutes’; no further information provided
- 6 patients received concomitant opioids during the study;
  - Two patients of the placebo group; one patient received 50 mg pethidine during endoscopy and one patient received piritramide from another physician for his pain. In both patients this medication was administered one day before premature withdrawal from the study
  - One patient in the 20 mg (TTS 50) group had tramadol continued during the study. This patient was withdrawn from the study on Day 2
  - Two patients of the 30 mg (TTS 75) group received tramadol. One patient received tramadol on the fourth day for his pain; this patient was prematurely withdrawn from the study on Day 7. The other patient had tramadol continued throughout the study
  - One patient in the 40 mg (TTS 100) group had dihydrocodeine prescribed on Day 4 due to unsatisfactory pain relief
- The protocol required that every randomised patient undergo 6 assessments (at Days 2, 3, 6, 9, 12 and 15). The retrospective assessment of pain relief was performed at these assessments. On 27 occasions, planned assessments were not performed:
  - 4 times in the placebo group
  - 11 times in the TTS50 group
  - 11 times in the TTS75 group
  - 1 time in the TTS100 group.

Comment: The missing assessments were not discussed in the study report. They represent a very small percentage of the total assessments for each group but may represent a major number of assessments for an individual patient (for example the 11 missing assessments in the TTS 50 group could have occurred in two patients ) so it is hard to comment on the possible effect. The other protocol breaches as described in the report are unlikely to have any effect on the outcome of the study.
7.1.3.13. **Baseline data**

With the exception of one patient ('Negroid') all patients were Caucasians, 71 male and 86 female patients with age range of 28 to 88 years. There were no relevant differences between the treatment groups regarding height, weight and sex distribution but regarding age distribution. The patients of the TTS 75 group were older than those of the other groups (mean 64 years compared to 55 to 58 years).

**Table 15: WIS-BUP02 Baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buprenorphine TDS</th>
<th>Placebo (n = 38)</th>
<th>All Patients (N = 157)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>35.0 µg/h (n = 41)</td>
<td>52.5 µg/h (n = 41)</td>
<td>70.0 µg/h (n = 37)</td>
</tr>
<tr>
<td><strong>Sex, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>20 (48.8)</td>
<td>23 (56.1)</td>
<td>22 (59.5)</td>
</tr>
<tr>
<td>Men</td>
<td>21 (51.2)</td>
<td>18 (43.9)</td>
<td>15 (40.5)</td>
</tr>
<tr>
<td><strong>Mean (SD) age, y</strong></td>
<td>57.4 (10.3)</td>
<td>63.7 (11.3)*</td>
<td>54.9 (12.5)</td>
</tr>
<tr>
<td><strong>Mean (SD) height, cm</strong></td>
<td>168.3 (6.9)</td>
<td>167.9 (10.4)</td>
<td>168.9 (9.1)</td>
</tr>
<tr>
<td><strong>Mean (SD) body weight, kg</strong></td>
<td>71.5 (12.3)</td>
<td>70.1 (14.6)</td>
<td>72.1 (15.7)</td>
</tr>
<tr>
<td><strong>Type of pain, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer related¹</td>
<td>32 (78.0)</td>
<td>31 (75.6)</td>
<td>29 (78.4)</td>
</tr>
<tr>
<td>Non-cancer related¹</td>
<td>9 (22.0)</td>
<td>10 (24.4)</td>
<td>8 (21.6)</td>
</tr>
<tr>
<td><strong>Prior opioid analgesic therapy, no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>18 (43.9)</td>
<td>24 (58.5)</td>
<td>18 (48.6)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>6 (14.6)</td>
<td>5 (12.2)</td>
<td>9 (24.3)</td>
</tr>
<tr>
<td>Codeine</td>
<td>6 (14.6)</td>
<td>2 (4.9)</td>
<td>4 (10.8)</td>
</tr>
<tr>
<td>Morphine</td>
<td>6 (14.6)</td>
<td>6 (14.6)</td>
<td>3 (8.1)</td>
</tr>
<tr>
<td>Pantopramide</td>
<td>0 (0.0)</td>
<td>3 (7.3)</td>
<td>1 (2.7)</td>
</tr>
<tr>
<td>Tridione</td>
<td>2 (4.9)</td>
<td>3 (7.3)</td>
<td>4 (10.8)</td>
</tr>
</tbody>
</table>

TDS = transdermal delivery system.
¹P < 0.05 versus all other groups.
²Primary cancer (oesophagus/stomach; duodenum/nucleus; liver/gall bladder/pancreas; lung; breast/uterus/ovary/vulva (female); prostate/urinary bladder).
³Locomotor system, neuropathic pain, or pain of other cause.

The main cause of patients' chronic pain was related to cancer in 77.1% of patients with this evenly distributed between treatment groups. The remaining 22.9% of patients had chronic pain from a variety of causes.
**Figure 11: WIS-BUP02 Tumour and non-tumour sources of pain**

<table>
<thead>
<tr>
<th>Tumour diagnoses included (number):</th>
<th>Types of non-tumour pain included (number):</th>
</tr>
</thead>
<tbody>
<tr>
<td>- mouth/tongue/larynx (8)</td>
<td>- others (4)</td>
</tr>
<tr>
<td>- oesophagus/stomach (7)</td>
<td>- post-herpetic neuralgia (3)</td>
</tr>
<tr>
<td>- duodenum/colon/rectum (18)</td>
<td>- polyneuropathy (3)</td>
</tr>
<tr>
<td>- liver/gall bladder/pancreas (12)</td>
<td>- phantom limb pain/afferent p. nerve lesion (4)</td>
</tr>
<tr>
<td>- bronchus/lung/pleura (24)</td>
<td>- condition after trauma/endoprostheses/operation (2)</td>
</tr>
<tr>
<td>- female breast (20)</td>
<td>- post-laminectomy syndrome/intervertebral disc disorders (5)</td>
</tr>
<tr>
<td>- uterus/ovary/vulva (16)</td>
<td>- osteoporosis (2)</td>
</tr>
<tr>
<td>- prostate/kidney/bladder (13)</td>
<td>- degenerative spinal pain (3)</td>
</tr>
<tr>
<td>- others (8)</td>
<td>- Arthrosis/rheumatic (2)</td>
</tr>
<tr>
<td>- secondary (metastasis) (64)</td>
<td>- Vascular pain (3)</td>
</tr>
<tr>
<td></td>
<td>- Enthesopathy/muscle/soft tissue affect (3)</td>
</tr>
<tr>
<td></td>
<td>- Other diseases of locomotor system (3)</td>
</tr>
<tr>
<td></td>
<td>- Gastro-intestinal pain (2)</td>
</tr>
</tbody>
</table>

**Comment:** The distribution of tumour pain diagnoses was fairly evenly spread across the groups. Non-tumour pain diagnoses were not evenly spread across the groups but this was inevitable given the number of diagnoses (13) and the number of patients (8 to 10 in each non-tumour group).

7.1.3.13.1. **Concomitant diseases**

Multiple concomitant diseases per patient were observed. These were classified into 11 categories according to organ system. There were no major variations in the spread of these across the groups.

7.1.3.13.2. **Previous pain and use of opioids**

No measure of pain prior to study inclusion is provided, apart from previous analgesic therapy. The study sought to position the buprenorphine patch as suitable for patients transitioning from WHO Level 2 to WHO Level 3 pain relief. As such, patients who had previously used a weak opioid or low dose of a strong opioid were eligible for the trial. Many of the patients (94 of 157, 60%) had previously used opioids (see Table 15 above). Tramadol was the most commonly used opioid medication prior to the study (86 out of 157, 54.8%). Other opioids included buprenorphine, codeine, morphine, pethidine, hydrocodone, piritramide and tilidine (the last two are synthetic opioids not available in Australia). Many patients also took NSAIDs, with this unevenly spread across the groups: placebo group (19 out of 38 patients), 20 mg patch group (7 out of 41 patients), 30 mg patch group (12 out of 41 patients), 40 mg patch group (12 out of 37 patients). Opioids and tramadol were ceased after entering the study (after the first day) except for the few protocol breaches described above. NSAIDs and paracetamol were continued.

The study report provides an estimate of the amount of opioids (as an average daily dose of ‘buprenorphine equivalent’) being taken by the patients prior to entry into the study. A daily dose range of 0.8 to 1.6 mg buprenorphine sublingually was described as common practice in the treatment of moderate to severe chronic pain in Germany at the time.
Table 16: Study WIS-BUP02 Average daily opioid intake

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Number of patients taking this range of average daily dose of opioid in 'Buprenorphine equivalents'</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to &lt; 0.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>8</td>
</tr>
<tr>
<td>20 mg patch</td>
<td>9</td>
</tr>
<tr>
<td>30 mg patch</td>
<td>9</td>
</tr>
<tr>
<td>40 mg patch*</td>
<td>4</td>
</tr>
</tbody>
</table>

*Information not available for one patient in this group.

**Comment:** The analysis in terms of 'buprenorphine equivalents' was not part of the statistical plan and no detail is provided regarding how the buprenorphine equivalent doses were determined. The cited reference (a German publication from 1990) was not included in the dossier. Note that 80% of the patients were taking opioids.

7.1.3.13.3. Other therapies that could affect pain

During the study, 17 patients received radiotherapy, with a disproportionate number in the 40 mg patch group to 5 patients each in the placebo, 2 in the 20 mg (TTS 50) group, 3 patients in 30 mg (TTS 75) and 7 in the 40 mg (TTS 100) groups.

Chemotherapy was administered during the study to 18 patients; 4 in the placebo, 3 in the TTS 50, 5 in the TTS 75 and 6 in the TTS 100 groups.

There were no clinically relevant differences between the treatment groups regarding laboratory parameters.

**Comment:** Baseline characteristics and factors that could impact on pain during the trial seem fairly evenly spread except for the slight excess of radiotherapy and chemotherapy in the 40 mg (TTS 100) group. Radiotherapy and chemotherapy may result in a decrease in pain and have a positive effect on the response rate in this group. The tumour population in the study is probably generalisable to the Australian population. It is difficult to say if this is the case for the non-tumour group as some of the diagnoses used are not those used in Australia and diagnosis definitions were not provided in the main section of the study report.

7.1.3.14. Results for the primary efficacy outcome

The response rates in the buprenorphine patch groups were higher than the placebo group:

- 16.2% in the placebo group
- 36.6% in the 20 mg (TTS 50) group
- 47.5% in the 30 mg (TTS 75) group
- 33.3% in the 40 mg (TTS 100) group

However, this difference in an ordered analysis was not statistically significant (p > 0.05) and the primary endpoint was not reached. The study report attributed this to the test being performed with basically ordered hypotheses and the comparison of the 40 mg (TTS 100) and placebo was not significant (p = 0.121).
Table 17: Study WIS-BUP02 response rates (TTS50 = 20 mg patch, TTS75 = 30 mg patch, TTS100 = 40 mg patch)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>N</th>
<th>n</th>
<th>%</th>
<th>95% CI lower limit</th>
<th>95% CI upper limit</th>
<th>difference vs. placebo</th>
<th>95% CI lower limit</th>
<th>95% CI upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumour pain</td>
<td>28</td>
<td>5</td>
<td>17.9</td>
<td>6.1</td>
<td>36.9</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
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<td>6.2</td>
<td>32.0</td>
<td>-</td>
<td>-</td>
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<td>29</td>
<td>11</td>
<td>37.9</td>
<td>20.7</td>
<td>57.7</td>
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<td>1</td>
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<td>0.4</td>
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<td>3.2</td>
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<td>12</td>
<td>33.3</td>
<td>18.6</td>
<td>51.0</td>
<td>17.1</td>
<td>-5.1</td>
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</table>

An exploratory comparison, that was not part of the pre-specified statistical analysis and that did not include basically ordered hypotheses, was also performed. For the 20 mg patch (35 µg/h) and the 30 mg patch (52.5 µg/h), the difference versus placebo reached statistical significance (p = 0.032 and p = 0.003, respectively). A trend analysis also showed significant results provided the 40 mg patch (70 µg/h) data were not included.

**Comment:** The basically ordered hypothesis was specified in the statistical plan and reflects the presumed dose proportionality of effect. However, given the inconsistencies in the response rates and the wide confidence intervals, this probably represents an underpowered study.

### 7.1.3.15. Results for other efficacy outcomes

#### 7.1.3.15.1. Consumption of additional buprenorphine sublingual tablets

Six patients were excluded from this analysis: three patients had not filled in their diaries; three patients withdrew prematurely from the study on Day 2. Patients in the placebo group were found to take, on average, more sublingual buprenorphine tablets:

- Placebo patch; average daily dose 0.7 mg
- Buprenorphine patches, all strengths; average daily dose of 0.3 mg

(p 0.0016; the comparison versus placebo by means of an LSD test resulted in p values below 0.05 for all patches).
An additional analysis was performed to assess the ‘analgesic effect’ of the patch. Thirty seven patients were excluded from this analysis: the 6 described above; 30 patients who were not taking opioids or a dose less than 0.4 mg buprenorphine equivalent; one patient whose opioid dose was unknown. The dose of additional buprenorphine sublingual tablets from the second day of treatment with the patch was compared with the average daily dose of previous opioid converted to buprenorphine equivalents. The first day of patch wearing was not included due to the latency period. Analysis was by treatment group, tumour or non-tumour pain and by the 3 levels of buprenorphine equivalent daily dose. It showed that on average the amount of sublingual buprenorphine tablets taken was less than the dose of opioid the patient had been taking prior to patch wearing. The tablet reduction with placebo was 8%, with the 20 mg (TTS50) group it was 56.9%, with the 30 mg (TTS75) group it was 61.6% and for the 40 mg (TTS100) group it was 51.6%. This was interpreted as the patches having some efficacy with respect to pain and substituting for the previous opioid.
7.1.3.15.2. **Retrograde assessment of pain relief**

This was assessed on Day two and three and then after each patch change (7 assessments per patient) using a four point scale. Around 45% of the patients wearing the buprenorphine patches reported good or complete pain relief (20 mg (TTS 50) patch; 44.3%, 30 mg (TTS 75) patch; 44.6% and 40 mg (TTS 100) patch; 45.6%) compared to 30.1% for patients wearing the placebo patch.

7.1.3.15.3. **Course of day and night pain intensity (twice daily assessment)**

The number of patients with ‘no’ or ‘mild’ pain increased in a dose dependent fashion: placebo patch; 40.3%, 20 mg patch (TTS 50); 47.3%, 30 mg patch (TTS 75); 58.7% and 40 mg patch (TTS100); 62.2%). This difference persisted across the duration of the study.

**Figure 13: WIS-BUP02. Pain intensity. Mean percentages for pain intensity (VRS) according to patient’s diary in all patients**
Figure 14: WIS-BUP02 Pain intensity across the trial duration for morning and evening assessments

7.1.3.15.4. **Duration of sleep uninterrupted by pain throughout the study**

There were inconsistent differences in the percentage of patients with 6 or more hours of uninterrupted sleep between the patients wearing the placebo patch and patients wearing the active buprenorphine patches: placebo; 36.6%, 20 mg patch; 44.1%, 30 mg patch; 47.1%, 40 mg patch; 40.6%. Poor sleep was common to all groups across the 15 nights of the trial.
Figure 15: Study WIS-BUP02 Sleep duration. Mean duration of sleep according to patient’s diary in all patients.

Comment: The pre-specified primary outcome measure of efficacy as determined by response rate did not show the buprenorphine patches to be efficacious. The exploratory analysis for the two lower strength patches and the secondary efficacy variables were suggestive that the buprenorphine patches have some efficacy. The 40 mg (TTS100) group seems to perform worse that the other buprenorphine patches with this seeming to be partly due to a poor response in the non-tumour subgroup. This inconsistent performance of the 40 mg patch was also observed in WIS-BUP01. An article using the data from this study was published in 2003. This article used the exploratory comparison of the two lower strength patches versus placebo rather than using the pre-specified basically ordered hypotheses to demonstrate efficacy. The discussion section of the article comments:

‘The limitations of this study in terms of the number of patients enrolled and duration of treatment, as well as confounding factors, such as interpatient variability in response to opioids, meant that it was unlikely to demonstrate a clear and statistically significant dose dependent increase in response rates with the 3 dosages of buprenorphine TDS investigated. Nevertheless, buprenorphine TDS did demonstrate superiority to the placebo patch according to the composite definition of response.’

7.1.4. Study WIS-BUP03

Study title: Comparison of the analgesic efficacy and safety of buprenorphine in the form of a sublingual tablet and a transdermal therapeutic system (TTS 50) in chronic pain.

7.1.4.1. Study design, objectives, locations and dates

7.1.4.1.1. Design

Randomised, multicentre, double blind, placebo controlled parallel study with a run-in phase with buprenorphine sublingual tablets over 6 days followed by a double blind phase with 3 sequential patches for 3 days each (9 days).

Location: 17 centres, predominately in Germany but including 2 in Poland.


7.1.4.1.2. Objectives

To compare the analgesic efficacy of buprenorphine in the form of a sublingual tablet and a transdermal therapeutic system 20 mg (TTS 50) patch in chronic pain and to prove the superior efficacy of the 20 mg (TTS 50) patch compared to placebo patch by determining the response rate in percent. The safety of buprenorphine 20 mg patch will be assessed by determining adverse events.

Comment: This study partly overlaps the Studies WIS-BUP01 and WIS-BUP02 on dates.

7.1.4.2. Inclusion and exclusion criteria

See the table in section 18.2.3 for the full list of inclusion and exclusion criteria.

7.1.4.2.1. Main inclusion criteria

Adult hospital in or out-patients with severe or very severe pain of benign or malignant origin, requiring the administration of a strong opioid such as buprenorphine.

7.1.4.2.2. Criteria for randomisation

At the end of the 6 day run-in phase the patient had to meet the additional criteria of:

- At least satisfactory pain relief with a mean daily dose of 0.8 to 1.6 mg buprenorphine according to the retrograde assessment of pain relief (VRS) at the end of the run-in phase.
- Consistency between the retrograde assessment of least satisfactory pain relief according to the retrograde assessment of pain relief and the entries made in the diary regarding pain intensity during the run-in phase.
- No refractory adverse events during the run-in phase.

7.1.4.2.3. Main exclusion criteria

These were all generic and as expected for a trial involving opioids. Use of opioids at the time of recruitment was not an exclusion criterion.

7.1.4.3. Study treatments

The study was designed in three study phases, with efficacy to be assessed during the steady state phase:

1. Run-in; during this phase of 6 days the patient took regular sublingual buprenorphine tablets to control pain, as prescribed by an investigator after an individual assessment of requirements. Additional 0.2 mg tablets were to be taken for breakthrough pain. If pain control was adequate on 0.8 to 1.2 mg dose at the end of 6 days, the patient was eligible to enter the double blind component of the study. This dose range was chosen as it was said to represent common practices in the treatment of moderate to severe chronic pain.

The double blind phase was composed of the influx and steady state phases. At the end of the run-in phase, eligible patients were randomised to wear one of two patch types, the 20 mg buprenorphine patch or placebo patch. The patients and investigator were blinded to the type of patch.

2. Influx: This phase commenced with application of the first patch. On the morning of the first day of the influx phase (Day 7) the patient was to take that amount of sublingual tablets which she/he had normally taken in the run-in phase (to ensure adequate analgesia during the patch’s latency period). The patch was to be applied either to normal skin in the infra-clavicular region or upper back.

3. Steady state: This phase commenced 3 days later with the application of the second patch. This patch was applied by the investigator to the opposite side of the body from the first.
Three days later, this patch was changed to the third and final patch, by the investigator if an in-patient, by the patient if an out-patient. The final patch was removed after 3 days of wear by the investigator at the final examination.

Throughout all phases of the trial and in both groups (active and placebo), breakthrough pain was to be managed using sublingual 0.2 mg buprenorphine tablets.

A patient diary was kept throughout the 15 days. During the entire study the patient was to document in his/her diary the times of administration and the number of buprenorphine sublingual tablets taken. The patient’s diary was to be checked by the investigator at each visit and a count made of the used and unused sublingual tablets from the packaging material that the patient brought in. If there was a discrepancy between the number of tablets taken (diary record versus tablet count), the diary was presumed to be in error. The patient also recorded their pain intensity three times a day (08:00, 14:00 and 20:00h) and the duration of sleep uninterrupted by pain each morning. AEs were also to be recorded.

Each patient had an investigator appointment several times during the study:

- Day 1 at which a full history and examination, including vital sign, was performed and the dose of regular buprenorphine was determined
- Day 7 at which the patient was assessed for entry into the double blind phase and the first patch applied, after a skin site assessment. A blood specimen for laboratory parameters was collected, a tablet count was made and the patient was asked to make a retrograde assessment of pain relief during the previous 6 days. An open question was put to the patient to identify AEs
- Day 10 at which the first patch was removed and the second applied. A skin site assessment and tablet count was made and the patient was asked to make a retrograde assessment of pain relief during the previous 3 days. An open question was put to the patient to identify AEs
- (Day 13; hospital in-patients were seen by the investigator and the patch was changed. An open question was put to the patient to identify AEs. Out-patients changed their own patch)
- Day 16; the third patch was removed. A skin site assessment and tablet count was made and the patient was asked to make a retrograde assessment of pain relief during the previous 3 days. An open question was put to the patient to identify AEs.

Concomitant administration of other opioid analgesics was not allowed during the study. Concomitant administration of other analgesic substances (non-opioid analgesics, NSAIDs, antispasmodics etcetera) was allowed and documented in the CRF. Throughout the study period this analgesic concomitant medication was not to be changed unless urgently required for clinical reasons, with this also documented in the CRF.

Patients, who had benefited from the patch application, were offered a further treatment with the 20 mg patch in an open label follow-up phase over three months.

### 7.1.4.4. Efficacy variables and outcomes

The main efficacy variables were:

#### 7.1.4.4.1. Retrograde assessment of pain relief

Subjective pain relief was to be assessed by the patient before randomisation of the patient and entry into the double blind phase of the study, at the end of the influx phase and the end of the steady state phase using a four point VRS: unsatisfactory pain relief, satisfactory pain relief, good pain relief or complete pain relief.
7.1.4.4.2. **Assessment of pain intensity**

For daily assessment of the pain intensity the patient was to record his/her pain intensity relating to the previous night in the morning, at lunch time and in the evening relating to the previous daytime hours using a five point verbal rating scale (VRS): very severe pain, severe pain, moderate pain, slight pain, no pain.

7.1.4.4.3. **Assessment of duration of sleep**

For assessment of the duration of sleep in relation to the previous night the patient was to give a classification every day in the morning according to one of the following four categories:

- Duration of sleep at least 6 hours uninterrupted by pain
- Duration of sleep 3 to 6 hours uninterrupted by pain
- Duration of sleep 2 to 3 hours uninterrupted by pain
- Duration of sleep less than 2 hours uninterrupted by pain.

7.1.4.5. **Primary efficacy outcome measure**

The primary efficacy outcome was the response rate with ‘responders’ defined as those patients who, during the steady state phase:

- required at least 40% fewer buprenorphine sublingual tablets than in the run-in phase and
- who stated that the pain relief was at least satisfactory during the steady state phase.

**Comment:** Before unblinding the primary endpoint was modified. The original definition of responders were those patients who within the steady state phase require at least 40% fewer buprenorphine sublingual tablets than in the run-in phase. The additional requirement of the patient’s assessment of pain as ‘at least satisfactory’ was added. The aim of ‘at least satisfactory’ pain relief on the four point scale used may not be considered adequate from a patient perspective. An aim of ‘good’ or ‘complete’ may be more in keeping with a patient’s expectation.

7.1.4.6. **Other measures included**

7.1.4.6.1. **Safety**

- Adverse events (AEs) were differentiated as at patch site or not and were defined as any adverse, harmful or pathological change in a patient indicated by signs, symptoms and/or laboratory value changes, which appears in connection with the use of a drug, regardless of whether it is thought to be related to the drug or not (differentiated by at patch or not). AEs were categorised as mild, moderate or severe and as definite, probable, possible and improbable causal relationship with the study drug.

- Skin status at each patch change: Skin status (presence of swelling, erythema, pruritus, signs of infection, other; all as yes/no items) was recorded by the investigator prior to the first and second patch application (on Day 7 and 10) and after removal of the first and third patches (on Day 10, and 16). Skin abnormalities were also differentiated by at patch or not.

Variables to describe the patient group were recorded. These included previous and concomitant diseases (according to body systems), ethnic group, age, height, weight, sex, heart rate, blood pressure, body temperature, laboratory parameters, cause of pain (diagnosis), medication which was stopped prior to study entry or taken continuously during the study were given.
7.1.4.7. Randomisation and blinding methods

According to the randomisation list patients were to be entered in the double blind phase in ascending order within each centre and were to receive the corresponding medication packages. The randomisation was performed using the procedure of ‘permuted block randomisation’ at the biometry department of [information redacted]. A single block was generated according to the urn model (taking the order into account without putting back).

Randomisation was carried out in blocks and in the ratio 2:1 (active substance: placebo). The size of the blocks was given in the randomisation list and was not imparted to the investigators. Both types of patches were identical in size and appearance.

The scientific study coordinator and the drug safety department of [information redacted] received a sealed envelope for each individual patient. The outside of the envelope was marked with the patient number and contained the description of the respective study medication. This envelope was only to be opened in an emergency when an identification of the study medication was necessary. The code envelopes were checked at study end to confirm their integrity. One envelope of patient [information redacted] was opened due to a serious adverse event. All other envelopes were still closed.

7.1.4.8. Analysis populations

Patients, who were not entered in the double blind phase, were excluded from analysis. All deviations from the study protocol which did not influence the assessment of efficacy were included in the analysis. All other cases were discussed individually and a decision was made before unblinding.

The statistical evaluation of the primary efficacy outcome was carried out according to the intention-to-treat principle. Patients, who did not enter in the double blind phase, were excluded from the evaluation. If a patient withdrew prematurely from the study during the double blind phase because of AEs or unsatisfactory pain relief, he/she was evaluated as a non-responder. All other cases of premature termination of the study had to be assessed individually prior to unblinding.

7.1.4.9. Sample size

The sample size calculation was based on the following definitions or assumptions:

- $\alpha = 0.05$, $\beta = 0.2$
- response rate of 40% with buprenorphine patch
- response rate of 15% with placebo patch
- two sided hypothesis.

On the basis of the assumptions made, $n = 57$ per treatment group.

As the study was to be randomised in the ratio 2:1 (active substance: placebo) the number of cases was adjusted. The study was to be carried out in 11 centres, so that a total of 132 patients were to be included in the study, who will be randomised in the ratio 2:1 (active substance: placebo). This gives $n = 88$ for patients with buprenorphine patch treatment and $n = 44$ for patients with TTS placebo treatment. No interim analysis was to be performed.

Comment: As with WIS-BUP01 and WIS-BUP02, no explanation was provided for the specific estimates of response rates for buprenorphine transdermal patch (40%) and the placebo patch (15%). Nor was any explanation provided for the different estimates across the three studies. A placebo rate of 15% seems low for a clinical analgesia study, particularly when the rescue medication is essentially the same as the active treatment.
7.1.4.10. **Statistical methods**

7.1.4.10.1. **Summary statistics**

Summary statistics for continuous data include mean, standard deviation, minimum, 1st quartile, median, 3rd quartile and maximum value. For the categorical data tables with absolute and relative frequencies were produced.

7.1.4.10.2. **Comparability of treatment groups**

Comparability of treatment groups regarding socio demographical data, medical history including risk factors, current health status, laboratory parameters and the baseline values of the efficacy and safety parameters was evaluated by the performance of different tests:

- The normally distributed continuous variables (age, height, weight, body temperature, blood pressure and heart rate) were compared by a general linear model for treatment and centre effects and their interactions.
- The categorical data (sex, pain intensity before medication) were compared by a Cochran-Mantel-Haenszel test and a Breslow Day test.

7.1.4.10.3. **Analysis of efficacy**

Analysis of efficacy was carried out according to the intention to treat principle. For the primary end point as a test of the hypothesis of equal rates at the level $\alpha = 0.05$ a Cochran-Mantel-Haenszel test was carried out. The hypothesis of no interactions between the centres and treatments was carried out with the Breslow-Day test at the level $\alpha = 0.05$. The 95% confidence intervals for the respective frequencies per treatment and for the difference of the respective frequencies per centre and overall were calculated.

The mean daily dose of buprenorphine (mg) during run-in and steady state phase was computed by multiplying the number of tablets taken in $6 \times 24$ hours with 0.2 and dividing by six. The reduction of tablets (%) was computed as follows $(100; (\text{tablets in steady state phase/\text{tablets in run-in phase}}) \times 100)$.

7.1.4.10.4. **Analysis of the secondary efficacy measures**

Analysis of the secondary efficacy measures was explorative:

- The course of the pain intensity was assessed separately for the entries at 08:00, 14:00 and 20:00. In addition, the mean value of the entries of 14:00 and 20:00 was investigated.
- The retrograde assessment of pain relief at the end of the different phases was investigated with a logistic regression for ordinally scaled data. In addition the frequencies of positive changes compared to the run-in phase were examined using the Cochran-Mantel-Haenszel test.
- The parameters pain intensity and duration of sleep were evaluated by variance analysis. The interactions between time and treatment and the effects resulting from a multicentre study were examined. Furthermore, the influence of the mean daily dosage on pain intensity and on duration of sleep was examined.
- The difference in consumption of sublingual tablets in the steady state phase compared to the run-in phase was evaluated with a twofold variance analysis. The interactions between centres and treatment were examined.

7.1.4.10.5. **Examination of subgroups**

All parameters were analysed separately for tumour and non-tumour pain.

7.1.4.10.6. **Changes in planned analysis (before unblinding)**

- The change in the responder definition in the primary outcome measure described above
- 17 centres instead of 11 recruited patients. Before unblinding it was decided to amalgamate low recruiting centres into 3, so that in total 14 centres were analysed
- The data was to be analysed separately for tumour and non-tumour patients
- An additional analysis was done regarding the amount of sublingual buprenorphine taken with this to include Day 8 to 13 (that is the last two days of the influx phase together with the steady state phase). The rational for this was to facilitate a comparison the three clinical studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03.

**Comment:** The statistical plan was followed in the analysis of results. Additional analyses (not described in the statistical plan) were also performed of the response rates with the patients groups divided according to the average amount of buprenorphine taken during the run-in phase.

### 7.1.4.11. Participant flow

174 patients entered the run-in phase. 37 of the 174 patients did not progress to the double blind phase:
- 13 patients were not randomised due to refractory adverse events during the run-in phase
  - The adverse events were mainly symptoms of the central nervous and the gastrointestinal system. In one patient a serious adverse event occurred. The patient did not mention a cerebral convulsion in the medical history (exclusion criterion) and suffered a convulsion during the run-in phase
- 23 patients either had pain relief was not satisfactory or the mean daily buprenorphine dose was outside the range 0.8 to 1.6 mg
- ‘One patient was afraid of the patch, because he did not know the amount of buprenorphine being in the body’

137 patients were randomised in 17 centres, with 2 to 16 patients recruited at each centre.

90 patients were allocated to the active group and 47 patients to the placebo group.

**Table 18: WIS-BUP03 Participant flow**

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<td>Randomised</td>
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</tr>
<tr>
<td>Number withdrawn</td>
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<td>2</td>
</tr>
<tr>
<td>Reasons for withdrawal (number)</td>
<td>AE (4) Unsatisfactory response (2)</td>
<td>AE (1) Unsatisfactory response (1)</td>
</tr>
</tbody>
</table>

*unable to locate reasons for exclusion of missing patients.

### 7.1.4.12. Major protocol violations/deviations

Major protocol deviations described included:
• Inclusion criteria not met:
  – In the buprenorphine patch group
    ▪ six patients took daily doses of buprenorphine below 0.8 mg or above 1.6 mg during
      the run-in phase
    ▪ one patient had a retrograde assessment of poor pain relief after the run-in phase
    ▪ one patient did not complete the diary during the run-in phase
  – In the placebo group
    ▪ five patients took daily doses of buprenorphine below 0.8 mg during the run-in
      phase
    ▪ one patient had a retrograde assessment of poor pain relief after the run-in phase
    ▪ one patient had therapy resistant adverse events occur in the run-in phase
• In nearly half of the patients (48.2%) the skin status was assessed after less than 15
  minutes after removal of the patch (the protocol specified that assessment was to occur 15
  minutes after patch removal). These patients were checked for skin reactions. In all of the
  patients either no reaction was observed or the skin reaction lasted for more than 30 minutes
• In some of the patients (18.2%) the patch was not changed as described in the protocol.
  Most of them changed the side of the body (sub-clavicular/dorsal) instead of the region
  (right/left). In single cases the patch was applied to the same site were the previous patch
  was applied.

Comment: The protocol deviations described in the report are unlikely to have any impact on
the outcome of the trial.

7.1.4.13. Baseline data

All patients were Caucasians, 70 male and 67 female patients in the age of 27 to 86 years. There
were no relevant differences between the treatment groups regarding age, height, weight and
sex distribution. Multiple diseases per patient were observed, with no major differences
between the treatment groups.

Table 19: WIS-BUP03 Baseline characteristics

| Table 1. Baseline characteristics of patients participating in the double-blind phase.* |
|---------------------------------|---------------------------------|---------------------------------|-------------------------------|
| Characteristic                 | Buprenorphine TDS (n = 90)     | Placebo (n = 47)                |
| Sex, no. (%)                   | (male 47 (52.2), female 43 (47.8)) | (male 23 (48.9), female 24 (51.1)) |
| Age, mean (SD), y              | 56.0 (12.1)                     | 55.7 (12.9)                     |
| Height, mean (SD), cm          | 169.8 (9.2)                     | 170.5 (7.9)                     |
| Body weight, mean (SD), kg     | 71.1 (13.5)                     | 72.8 (12.3)                     |

TDS = transdermal delivery system.
*All patients were white. There were no significant differences between treatment groups.
7.1.4.13.1. **Use of buprenorphine prior to the study**

There were no relevant differences in prior buprenorphine treatment between the treatment groups: almost half of all patients received buprenorphine for management of pain prior to screening, with more non-tumour than tumour patients in both treatment groups.

7.1.4.13.2. **Use of opioids prior to the study**

No measure of pain prior to study entry was provided, apart from the analgesics taken. In keeping with the inclusion criteria, most patients had been taking opioids prior to the study (85.6% of the buprenorphine patch group and 87.2% of the placebo group). Tramadol was the most commonly prescribed opioid (33.6%), followed by tilidine (14.0%), codeine (9.5%), morphine (8.0%), and others (for example, fentanyl, piripramide, pethidine). Using a classification of opioids according to the three step WHO analgesic ladder and comparing across treatment groups and according to cause of pain showed some uneven distribution:

- Strong opioids (Step III) were previously used in 54.4% of the 20 mg (TTS 50) patch patients and 59.6% of the placebo patients
- Strong opioids (Step III) were used more frequently in non-tumour patients than in tumour patients in both treatment groups (59.4% versus 42.3% in the 20 mg (TTS 50) patch group and 64.3% versus 52.6% in the placebo group)
- Weak opioids (Step II) were previously used in 31.1% of the buprenorphine patch group and 27.7% of the placebo group
- The use of the weak opioid tramadol was not consistent across the treatment groups in the tumour patients. In the buprenorphine patch group 53.8% of the tumour patients previously received tramadol compared to 26.3% of tumour patients in the placebo group.

7.1.4.13.3. **Use of other analgesics during the study**

The frequency of additional analgesics, such as NSAIDs and paracetamol, administered during the study was roughly equal in the patients with tumour diagnosis in the two treatment groups. However, more non-tumour patients in the buprenorphine patch group (27 out of 64) took additional analgesics during the trial compared to the placebo group (8 out of 28).

During the study one patient in each treatment group (5.3% and 3.8% respectively) received radiotherapy. Four patients in the buprenorphine patch group received chemotherapy during the study, and 2 in the placebo group.

7.1.4.13.4. **Vital signs and laboratory parameters**

There were no clinically relevant differences between the two treatment groups as regards vital signs and laboratory parameters.

7.1.4.13.5. **Differences between the treatment groups**

7.1.4.13.5.1. Diagnoses

Despite randomisation, there were some differences between the two treatment groups with respect to diagnoses. In total, there were 45 patients with tumour pain and 92 patients with non-tumour pain. This was not evenly distributed across the two treatment groups:

- 20 mg buprenorphine patch group; 26 patients (28.9%) had tumour pain and 64 patients (71.1%) non-tumour related pain
- Placebo patch group; 19 patients (40.4%) had tumour pain and 28 patients (59.6%) non-tumour related pain.

Diagnoses were also not evenly distributed. Tumour patients in the placebo group were in a more advanced stage of their disease, as defined by the presence of metastases; 9 out of 19 patients in the placebo group had secondary tumours, compared with 9 out of 26 patients in the
buprenorphine patch group. In the non-tumour patients of the buprenorphine patch group, 17 out of 64 patients had the diagnosis of phantom limb/deafferent pain/nerve lesions but there were no patients with this diagnosis in the placebo group.

Table 20: WIS-BUP03 Causes of pain

<table>
<thead>
<tr>
<th>Origin of Pain*</th>
<th>Buprenorphine TDS</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer pain</td>
<td>(n = 26)</td>
<td>(n = 19)</td>
</tr>
<tr>
<td>Duodenum/colon/rectum</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Uterus/ovary/vulva</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Female breast</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Mouth/tongue/arynx</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Bronchus/Ang/pleura</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Esophagus/stomach</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Prostate/kidney/bladder</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Liver/gallbladder/pancreas</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Secondary (metastases)</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Non-cancer pain</td>
<td>(n = 64)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Postamputee syndrome/intervertebral/disc disorders</td>
<td>26</td>
<td>12</td>
</tr>
<tr>
<td>Phantom limb pain/deafferent pain/nerve lesion pain</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Degenerative spinal pain</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Posttraumatic pain/arthrosis/surgery</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Arthritis/rheumatic pain</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal pain</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Enthesopathy/muscle/soft-tissue effects</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Vascular pain</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Postherpetic neuralgia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Other diseases of musculoskeletal system</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>

TDS = transdermal delivery system

7.1.4.13.6. Buprenorphine dose during the run-in phase

The mean daily dose of buprenorphine in the run-in phase was 0.9 mg for the placebo group and 1.1 mg for the buprenorphine patch group equating to a the difference between the two groups of one sublingual tablet (equivalent to 0.2 mg) per day (p = 0.0015). Consequently, when entering the double blind phase the initial level of the required daily dose of sublingual buprenorphine in the buprenorphine patch group was higher than in the placebo group.

Comment: Despite an appropriate method of randomisation, there were substantial differences between the two groups that could have an impact on outcome: the placebo group had both more tumour patients and more with advanced disease. Despite this, the placebo group seemed to have lower analgesic requirements in the run-in phase.
The study participants are representative of the patients who will receive the drug if the submission is approved on the basis of diagnoses and other variables except for ethnic background (no non Caucasians included in the trial).

7.1.4.14. Results for the primary efficacy outcome

Overall, 50 (57.5%) of the buprenorphine patch group and 21 (46.7%) of the placebo group were considered to be responders. Patients with tumour related pain were found to have a higher response rate compared to placebo, (69.2% compared to 44.4%); non-tumour patients showed a marginal difference in the response rate in the two treatment groups (52.5 and 48.1% respectively). However, the results did not show a significant difference overall or for the tumour and non-tumour sub-groups.

Table 21: WIS-BUP03 Response rates

<table>
<thead>
<tr>
<th></th>
<th>TTS 50</th>
<th>Placebo</th>
<th>difference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>total</td>
</tr>
<tr>
<td>tumour pain</td>
<td>18</td>
<td>69.2</td>
<td>26</td>
</tr>
<tr>
<td>non-tumour pain</td>
<td>32</td>
<td>52.5</td>
<td>61</td>
</tr>
<tr>
<td>all patients</td>
<td>50</td>
<td>57.5</td>
<td>87</td>
</tr>
</tbody>
</table>

Cochran-Mantel-Haenszel test p = 0.265  
Breslow-Day test p = 0.381

Additional analyses (not described in the statistical plan) were performed on the response rates with the patients groups divided according to the average amount of buprenorphine taken during the run-in phase. This found an inverse relationship between the response rate of the buprenorphine patch group and average buprenorphine dose with higher response rates in patients who required a lower average dose of buprenorphine, suggestive of a dose relationship. This relationship was not found in the placebo group.

Comment: The study is under powered, given the low estimate of placebo response used in the sample size calculation (46.7% compared to 15%) and the wide confidence intervals in the results. Demonstrating a difference between the tumour and non-tumour groups was unlikely given that the decision to analyse with the patients stratified in this way was made after the sample size calculation.

7.1.4.15. Results for other efficacy outcomes

7.1.4.15.1. Secondary endpoints were

7.1.4.15.1.1. Consumption of sublingual tablets in the run-in, influx and steady state phases

The average daily doses of sublingual buprenorphine in run-in and steady state phase were compared. In the buprenorphine patch group, there was a reduction of 0.6 mg (from 1.1 mg to 0.5 mg) equating to three sublingual tablets. In the placebo group, there was also a reduction although this was smaller at 0.4 mg, that is two sublingual tablets (from 0.9 mg to 0.5 mg) (p = 0.0288).
Additional analyses was performed.

1. With the patients stratified according to the average amount of buprenorphine taken during the run-in phase against the average percentage of reduction in tablets. An inverse relationship was again seen with the buprenorphine patches and no relationship with the placebo. This was said to be suggestive of a dose relationship.

2. The average amount of buprenorphine taken during the run-in phase was compared to average amount of buprenorphine taken as sublingual tablets from the second day of the influx phase to the end of steady state. The rational for this was that it enabled comparison with the other placebo controlled trials (WIS-BUP01 and WIS-BUP02). This showed a relationship between the average daily run-in dose and the average daily sublingual dose taken from Day 7 to 13 for the patients in the buprenorphine patch group with patients requiring a lower dose in the run-in phase taking fewer tablets during the double blind phase. This relationship was said not to be present in the placebo group.

Figure 17: WIS-BUP03 Average dose of sublingual buprenorphine in the double blind phase stratified according to the average run-in dose of sublingual buprenorphine for the buprenorphine patch group (TTS50)
Figure 18: WIS-BUP03 Average dose of sublingual buprenorphine in the double blind phase stratified according to the average run-in dose of sublingual buprenorphine for the placebo group (no patients in this group took more than 1.6 mg in the run-in phase)

7.1.4.15.2. Retrograde assessment of pain relief at the end of the run-in and influx phase and at the end of the study

A retrograde assessment of pain relief was made by the patients at the end of the run-in phase (Day 7), at the end of the influx phase (Day 10) and at the end of the steady state phase (Day 16) and documented in the diary. Patients in the placebo group assessed pain relief in the run-in phase to be better than the patients in the buprenorphine patch group with 51.1% of the placebo group rating the pain relief as good or complete compared to 25.3% of the buprenorphine patch group. The proportion of patients reporting good or complete pain relief in the placebo group decreased in the double blind phase, with an increase in the proportion reporting poor pain relief. The proportion reporting complete or good pain relief in the double blind phase increased slightly in the active group. The proportion reporting poor pain relief increased in both groups in the double blind phase.

Figure 19: WIS-BUP03 Retrograde pain relief in all patients
Inconsistent and small differences were seen when the patients were subdivided into tumour and non-tumour groups.

7.1.4.15.3. Pain intensity throughout the study (three times daily assessment)

Pain intensity was recorded three times daily: mornings (08:00), afternoons (14:00) and evenings (20:00). Days 7 to 10 (influx period) were not included in the analysis.

In the patients in the active group, there was a small increase in the proportion experiencing mild (3.7%) or moderate (2.1%) pain and a reduction in severe (-1.1%) and very severe (-3.0%) pain comparing the run-in period to the steady state phase. In the patients in the placebo group, there was a decrease in the proportion experiencing no pain (-7.2%), a smaller decrease in the proportion experiencing mild pain (-2.3%), a small increase in those experiencing moderate (4.7%) or severe (5.3%) pain.

Figure 20: WIS-BUP03 Mean pain intensity (%) (mean percentages for pain intensity (VRS) according to patient’s diary in all patients

![Chart showing pain intensity percentages]

Inconsistent differences were seen when the patients were subdivided into tumour and non-tumour groups.

7.1.4.15.4. Duration of sleep uninterrupted by pain throughout the study (daily assessment)

Every morning the patients recorded the duration of sleep uninterrupted by pain during the previous night in their diary. The results show that poor sleep was common. Sleep slightly improved in the active group, comparing the run-in and double blind phases, and was worse in the placebo group, although this group started off with much better sleep in the run-in phase.
Similar results were seen in the tumour group. In the non-tumour group, sleep for both the active and the placebo arms increased in the double blind phase.

**Comment:** The primary outcome measure of efficacy as determined by response rate did not show the buprenorphine patches to be efficacious. The secondary efficacy variables and analysis of the two components of the primary efficacy outcome separately, were suggestive of efficacy. Analysis of tumour versus non-tumour patients showed inconsistent results.

An article based on this study was published in 2004. This article used different primary outcome measures: the use of rescue medication and pain intensity as recorded in the patient’s diary. It found a statistically significant difference between treatment groups (P = 0.01) for the reduction in buprenorphine SL consumption between the run-in and double blind phases. The difference in pain intensity between the active group and placebo group was also found to be statistically significant.

### 7.1.5. Study PB-TTC 02

Study title: A randomised, multicentre, double blind, placebo controlled, parallel group study assessing the analgesic efficacy and safety of buprenorphine TDS 70 µg/h in patients with severe chronic tumour related pain

#### 7.1.5.1. Study design, objectives, locations and dates

**Design**

Randomized withdrawal parallel group design with a 15 day open label run-in period followed by a 15 day placebo controlled double blind period. Rescue medication was allowed throughout the study

**Locations**

Twenty six centres in 6 European countries including Belgium, Netherlands, France, Croatia.

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7.1.5.1.3. Dates
February 2004 to January 2005

7.1.5.1.4. Objectives
To investigate the analgesic efficacy and safety of buprenorphine 40 mg (TDS 70 µg/h) buprenorphine patch with an average release rate of 70 µg/h in patients with severe chronic tumour related pain.

7.1.5.2. Inclusion and exclusion criteria
7.1.5.2.1. Main inclusion criteria
Male or female in and out-patients aged more than 18 years at enrolment with malignant tumours requiring treatment with opioids at an equianalgesic dose range equivalent to 90 to 150 mg morphine orally per day.

7.1.5.2.2. Randomisation criteria for entry into the double blind phase
In the period of four days preceding the Randomisation Visit there were;
- At least 6 (of a possible 8 assessments) pain assessments in the patient’s diary
- The pain score was less than 5.0 on average on an 11 point numeric rating scale (NRS). A level of 5 or more was said to be regarded by pain experts as indicative of a need to review the patient's pain management
- The consumption of rescue medication was ≤ 8 tablets (≤ 2.0 tablets on average per day) buprenorphine SL.

7.1.5.2.3. Main exclusion criteria
Patients with predominant neuropathic pain were excluded.

Comment: The study report and protocol did not indicate how the morphine equivalent doses in the inclusion criteria were determined. Patients who were found to be non-compliant with elements of the study at the weekly visits, for example entries in the patient diary, could be removed from the study by the investigator.

7.1.5.3. Study treatments
The study was in two phases. Patients in the run-in phase who had acceptable pain control using the 40 mg patch and who were compliant with the study requirements were randomised into the double blind phase.

- Run-in phase (15 days): all patients were treated with buprenorphine 40 mg (70 µg/h) transdermal patches. Six patches were to be worn sequentially for 72 h each
- Double blind phase (15 days): patients were randomised to buprenorphine 40 mg (70 µg/h) transdermal patches or matching placebo patches. Five patches were to be sequentially for 72 hours each.

Patients were free to take as much rescue medication (buprenorphine sublingual tablets, 0.2 mg) as needed to control pain across both phases. A patient diary was kept throughout the study with twice daily entries regarding pain and a record made of all rescue medication taken.

The patient was seen by the investigator at enrolment, 7 days into the run-in phase, at randomisation on Day 16, 7 days into the double blind phase, at the final visit on Day 30 when study medication was ceased and at a follow-up visit 5 to 10 days later. A full history and examination, including vital signs, was performed at the first visit. At subsequent visits, vital signs were taken, the patient was asked for his/her assessment of the medication, the patient diary was checked for compliance with entries, recorded medications were checked against
packaging and occurrence of adverse events checked. A second physical examination was performed at the final visit.

Patients could continue to use the following concomitant medication (dose to remain constant):

- Medication for concomitant diseases and adjuvant analgesics (for example tricyclic antidepressants (TCA), anticonvulsants, serotonin reuptake inhibitors (SSRI) and muscle relaxants) if on a stable dose prior to and during randomisation. For benzodiazepines used as minor tranquillisers or hypnotics the same rule applied as for adjuvant analgesics
- Medication for induction or continuation of chemotherapy or radiotherapy
- Acetylsalicylic acid up to 325 mg daily for cardiovascular reasons.

Patients could not continue or commence the following concomitant medication:

- Any analgesics (including NSAIDs, COX-II-inhibitors, and paracetamol) other than the investigational product(s) or rescue medication.

7.1.5.4. **Efficacy variables and outcomes**

The main efficacy variables were:

- Twice daily assessment of the pain intensity using 11 point NRS.
  - Pain was assessed using an 11 point Numeric Rating Scale (NRS) and recorded by the patient in a diary daily at 08:00 and 20:00. The patient rated his pain intensity at the moment of assessment, using a scale from 0 to 10, where 0 was ‘No Pain’ and 10 was ‘Pain as bad as you can imagine’.
- Patient’s global evaluation using 5 point VRS on Day 7, 16, 23 and 30
  - The patient was asked to answer the following question: ‘How would you rate the study medication you received for pain?’ using the 5 categories; Excellent, Very Good, Good, Fair, Poor with the result recorded by the investigator
- Incidence and time to withdrawal due to adverse events or lack of efficacy
- Amount and frequency of intake of rescue medication
  - Consumption of rescue medication was documented by the patient in a diary. During the weekly visits the investigator checked and collected the patient diaries, used/unused patches and empty blisters of rescue medication.

7.1.5.4.1. **The primary efficacy outcome**

The proportion of patients classified as responders, where responders were defined as patients:

- who completed at least 12 days of the double blind period, and
- who had a pain intensity < 5.0 on average on an 11 point NRS during the last 6 days of treatment, and
- who did not use more than 2.0 tablets of rescue medication/day on average during the double blind period.

7.1.5.4.2. **Other efficacy outcomes included**

Safety: Adverse events, vital signs, physical examination. The study population was described by the following variables:

- Demographic data of the patient (sex, date of birth, weight, height, and ethnicity)
- Medical history of the patient, comprising: prior and concomitant diseases/interventions
- Prior and concomitant medication
• Physical examination and vital signs (pulse rate, supine blood pressure, respiratory rate).

7.1.5.5. Randomisation and blinding methods

Randomisation was in blocks and in the ratio 1:1 (buprenorphine 40 mg patch: placebo). The investigator was given a unique series of numbers which he assigned to each study patient in ascending numerical order. The placebo and active patches appeared identical.

A randomisation list was generated by a person in the biostatistical department not involved in the conduct or the data management of the study. After this list had been compiled it was printed and put into a sealed envelope, the electronic version was deleted.

7.1.5.6. Analysis populations

The primary analysis of the efficacy parameter was on the basis of the full analysis set (FAS)(patients with at least one post-randomization pain intensity assessment) Additional analyses were made of the per protocol set (patients who had no major protocol violation and at least finished Day 28 of treatment), and modified per protocol set (patients of the per protocol set and additionally, patients withdrawn in the double blind period to take into account the characteristics of a randomised withdrawal design). All analysis sets were pre-defined in the statistical analysis plan.

The safety population included all patients receiving any amount of investigational product, run-in and double blind phases.

7.1.5.7. Sample size

The sample size was calculated using Fisher’s exact test with the assumptions of:

• $\alpha = 0.05$ (two-sided) and 90% power ($\beta = 0.1$)
• Placebo responder rate of 30%
• Buprenorphine patch responder rate of 55%.

Comment: The response rate assumptions were based on the study WIS-BUP03, ‘where a difference of 25% in response rates between buprenorphine 20 mg (TDS 35 µg/h) patch and placebo was observed’. The reported response rates in WIS-BUP03 for patients with tumour pain were 69.2% for the active group and 44.4% for the placebo group.

Under these assumptions, $N = 88$ per treatment group (for the randomised period of the study, full analysis set) would be necessary to show the above mentioned difference in response rates between buprenorphine 40 mg (TDS 70 µg/h) and placebo.

Assuming a run-in failure (patients included in the run-in period who were not randomised) rate of around 30% during the run-in period, the number of patients to be enrolled was calculated to be 250.

7.1.5.8. Statistical methods

7.1.5.8.1. Missing values

Missing values concerning the pain intensity were replaced by carrying the last observation (no distinction between evening and morning assessments was made) forward with the exception of patients who discontinued the study due to intake of prohibited analgesic concomitant medication. For these patients the value documented before intake of prohibited analgesic concomitant medication was carried forward.

7.1.5.8.2. For the primary efficacy endpoint

For the primary efficacy endpoint, response rates were calculated and tabulated for each treatment group. Response rates for active treatment and placebo were compared with a
Cochran-Mantel-Haenszel (CMH) test adjusting for centre. The interaction of centre and treatment was checked by a Breslow-Day test for homogeneity. Differences in response rates with the respective two-sided 95% confidence intervals were also calculated.

7.1.5.8.3. **Pain assessments and use of rescue medication**

Pain assessments and use of rescue medication were analysed with descriptive statistics with 95% confidence intervals were calculated. In the global evaluation, absolute and relative frequencies were calculated, and groups compared with a CMH-test adjusting for centre.

7.1.5.8.4. **The incidence of withdrawal due to lack of efficacy**

The incidence of withdrawal due to lack of efficacy was presented with the respective two-sided 95% confidence limits according to Pearson-Clopper for each treatment group. The treatment groups were compared using a CMH test.

7.1.5.8.5. **The frequency of patients with any adverse event**

The frequency of patients with any adverse event during the study with the respective two-sided 95% confidence limits according to Pearson-Clopper was calculated for each treatment group. The frequency of patients with an event was compared between treatment groups using a CMH test. For each parameter of the vital signs (heart rate, supine blood pressure) descriptive statistics for the absolute values and the differences to baseline values were calculated at each assessment including the 95% confidence intervals for the mean.

7.1.5.9. **Changes in the statistical plan**

In 16 of the 26 centres, only a few patients were recruited to the double blind phase. These low recruiting centres were pooled, according to location, into 4 virtual centres of at least 8 randomised patients. The primary endpoint (response rate) was also analysed according to prior or concomitant radiotherapy or chemotherapy.

7.1.5.10. **Participant flow**

289 patients were enrolled into the run-in period with 227 finishing the run-in period. Sixty two patients (21.5%) withdrew prematurely from the run-in period for the following reasons:

- lack of efficacy (28 out of 62 patients, 45.2%)
- adverse events (21 out of 62 patients, 33.9%)
- withdrawal of informed consent (19 out of 62 patients, 30.6%)
- death (8 out of 62 patients)
- protocol violations (2 out of 62 patients)
- other (7 out of 62 patients).

38 were not randomized because they did not meet the randomization criteria in the following ways (multiple reasons possible):

- Rescue medication requirements more than 8 tablets (36)
- Average pain intensity score 5 or more (14)
- Fewer than 6 pain assessments completed (6)
- No diary (1).

189 were randomized into the double blind period. During this period, 7 patients withdrew from the buprenorphine group and 24 from the placebo group.
Table 22: Reasons for withdrawal from the double blind phase (more than one reason possible)

<table>
<thead>
<tr>
<th>Buprenorphine group:</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of efficacy: 4</td>
<td>Lack of efficacy: 14</td>
</tr>
<tr>
<td>Adverse event: 1</td>
<td>Withdrawal of Informed Consent: 3</td>
</tr>
<tr>
<td>Death: 1</td>
<td>Protocol violation: 4</td>
</tr>
<tr>
<td>Other: 2</td>
<td>Adverse event: 6</td>
</tr>
<tr>
<td></td>
<td>Death: 2</td>
</tr>
<tr>
<td></td>
<td>Other: 1</td>
</tr>
</tbody>
</table>

The full analysis set (FAS) of the double blind period comprised 188 patients (94 in both groups). One patient was excluded from the FAS as no pain assessments were available.

The per protocol analysis set of double blind period comprised 118 patients (64 in the active treatment group and 54 in the placebo group).

The modified per protocol analysis set of the double blind period comprised 137 patients (70 in the active treatment group and 67 in the placebo group).

**Comment:** 78 out of 100 patients did not progress to the double blind phase due to lack of efficacy (lack of efficacy 28 out of 100, excessive rescue medication 36 out of 100, too high pain score 14 out of 100). This would suggest that non-responders have been selected out and result in enrichment bias.

### 7.1.5.11. Major protocol violations /deviations

There were a number of protocol deviation with these resulting in one patient being excluded from the FAS (see above) and 71 being excluded from the per protocol group, 30 from the buprenorphine group and 41 from the placebo group.

Table 23: PB-TTC-02 Major protocol deviations (major protocol violations leading to exclusion from per protocol set during double blind period)

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine (N=94)</th>
<th>Placebo (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pain assessments in diaries</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Less than 4 patches were applied during DB-period(^1)</td>
<td>3 (1.6%)</td>
<td>20 (10.6%)</td>
</tr>
<tr>
<td>Less than 9 pain assessments during last 6 days of treatment(^1)</td>
<td>10 (5.3%)</td>
<td>23 (12.2%)</td>
</tr>
<tr>
<td>Less than 9 pain ass. during last 6 days of treatment and duration &gt;&gt; 12 days</td>
<td>5 (2.6%)</td>
<td>3 (1.6%)</td>
</tr>
<tr>
<td>Additional violation of incl.excl. criteria except No 1 and No 5</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Major violation of randomisation criteria</td>
<td>3 (1.6%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Intake of prohibited analgesic medication</td>
<td>15 (7.9%)</td>
<td>22 (11.6%)</td>
</tr>
<tr>
<td>Randonisation visit not between day 10 and day 17 of the run-in period</td>
<td>1 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Time difference between two successive patches &gt; 4 during the db-period</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

\(^1\)Because of the withdrawal design, these two exclusion criteria did not apply to the modified per-protocol set

Patients could have more than 1 reason for exclusion from the per protocol set. DB: double-blind
Comment: Protocol deviations were more common in the placebo group but did not result in the exclusion of patients from the FAS. The main deviations in the placebo group were not wearing the patch (20), not completing pain assessments (26) and taking other analgesics (22). 15 patients in the buprenorphine group took other analgesics.

7.1.5.12. Baseline data

57.1% of the patients in the run-in phase were male. In the double blind period, the sex distribution was similar for both treatment groups in all analysis sets. Most patients (> 90%) were of European Caucasian origin and mean age of enrolled patients and of patients in the various analysis sets were between 62 and 66 years. Mean BMI was similar across treatment and analysis groups. All patients had taken prior analgesic and anti-inflammatory drugs (prior defined as taken during the 28 days before enrolment).

Table 24: PB-TTC-02 Demographic and baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Double-blind period</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in N=289</td>
<td>Full analysis set N=188</td>
<td>Per-protocol set N=118</td>
<td>Modified per-protocol set N=137</td>
</tr>
<tr>
<td></td>
<td>Bup (n=64)</td>
<td>Pl (n=64)</td>
<td>Bup (n=64)</td>
<td>Pl (n=54)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>165 (57.1%)</td>
<td>54 (57.4%)</td>
<td>55 (59.6%)</td>
<td>30 (55.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>124 (42.9%)</td>
<td>40 (42.6%)</td>
<td>38 (40.4%)</td>
<td>29 (44.3%)</td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian, European</td>
<td>270 (93.4%)</td>
<td>89 (94.7%)</td>
<td>92 (97.9%)</td>
<td>62 (99.6%)</td>
</tr>
<tr>
<td>Caucasian, Non-European</td>
<td>6 (2.1%)</td>
<td>2 (2.1%)</td>
<td>2 (2.1%)</td>
<td>1 (1.7%)</td>
</tr>
<tr>
<td>Black</td>
<td>1 (0.3%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>12 (4.2%)</td>
<td>3 (3.2%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62±11.5</td>
<td>63±11.2</td>
<td>61±11.2</td>
<td>61±11.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.6±4.5</td>
<td>24.0±4.9</td>
<td>23.5±4.7</td>
<td>24.0±5.1</td>
</tr>
</tbody>
</table>

Prior radiotherapy had been administered to 21 out of 289 (7.3%) of the patients at enrolment, and was ongoing in 7 (2.4%). Twelve patients started radiotherapy during the run-in period, and 6 during the double blind period. Prior chemotherapy had been administered to 60 out of 289 (20.8%) of the patients at enrolment, and was ongoing in 11 (3.8%). Forty seven patients started radiotherapy during the run-in period, and 43 during the double blind period.

Table 25: PB-TTC-02 Tumour diagnoses. Summary of common types of neoplastic disease (> 5% of patients at enrolment)

<table>
<thead>
<tr>
<th></th>
<th>Double-blind period</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Run-in N=289</td>
<td>Full analysis set N=188</td>
<td>Per-protocol set N=118</td>
<td>Modified per-protocol set N=137</td>
</tr>
<tr>
<td></td>
<td>Bup (n=64)</td>
<td>Pl (n=64)</td>
<td>Bup (n=64)</td>
<td>Pl (n=54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with confirmed</td>
<td>280 (95.9%)</td>
<td>18 (10.9%)</td>
<td>19 (18.3%)</td>
<td>13 (20.3%)</td>
</tr>
<tr>
<td>neoplastic disease¹</td>
<td></td>
<td>39 (13.5%)</td>
<td>9 (9.6%)</td>
<td>5 (6.3%)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td></td>
<td>106 (38.7%)</td>
<td>38 (40.4%)</td>
<td>29 (30.9%)</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td></td>
<td>56 (19.4%)</td>
<td>22 (23.4%)</td>
<td>12 (12.8%)</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td></td>
<td>28 (9.7%)</td>
<td>6 (6.4%)</td>
<td>6 (6.4%)</td>
</tr>
<tr>
<td>Lung metastasis</td>
<td></td>
<td>21 (7.3%)</td>
<td>6 (6.4%)</td>
<td>6 (6.4%)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td>31 (10.7%)</td>
<td>10 (10.6%)</td>
<td>12 (12.8%)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td></td>
<td>8 (12.5%)</td>
<td>8 (14.8%)</td>
<td>8 (11.4%)</td>
</tr>
</tbody>
</table>

¹Multiple types of neoplastic disease possible
7.1.5.12.1. Prior pain and analgesics

No measure of pain prior to study entry was provided. Consistent with the inclusion criteria, all patients had been receiving analgesics prior to enrolment. Four drugs, and one class, had been taken by more than 10% of the patients at enrolment, namely, fentanyl (168 out of 289 patients, 58.1%), morphine sulphate (70 out of 289 patients, 24.2%), paracetamol (30 out of 289 patients, 10.4%), tramadol (65 out of 289 patients, 22.5%) and NSAIDs (76 out of 289, 26.3%). Patients could be taking more than one of these agents. The number of patients who had taken these drugs as prior medication was similar for both treatment groups across analysis sets.

Comment: The study participants represent a subset of the patient group for which approval is requested (management of moderate to severe cancer pain and severe pain that does not respond to non-opioids) as it does not include non-tumour patients. The participants have quite advanced neoplastic disease with many of them having metastatic disease (the precise number cannot be derived from the above table as patients could fit in more than one group and could not be determined from the source tables).

7.1.5.13. Results for the primary efficacy outcome

7.1.5.13.1. Primary endpoint: treatment response

The mean (± SD) baseline pain intensity (11 point NRS) prior to randomization was comparable across treatment groups and analysis sets, ranging from 1.3 ± 1.3 in the buprenorphine group of the per protocol set to 1.7 ± 1.4 in the placebo group of the full analysis set.

Table 26: PB-TTC-02 Baseline pain intensity and global evaluation

<table>
<thead>
<tr>
<th></th>
<th>Full analysis set</th>
<th>Per-protocol set</th>
<th>Modified per-protocol set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=138</td>
<td>N=118</td>
<td>N=137</td>
</tr>
<tr>
<td>Bup (n=64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pl (n=64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global evaluation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (1.1%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Excellent</td>
<td>33 (35.1%)</td>
<td>35 (37.2%)</td>
<td>26 (40.6%)</td>
</tr>
<tr>
<td>Very good</td>
<td>30 (31.9%)</td>
<td>36 (38.3%)</td>
<td>20 (31.3%)</td>
</tr>
<tr>
<td>Good</td>
<td>29 (30.9%)</td>
<td>20 (21.3%)</td>
<td>17 (26.6%)</td>
</tr>
<tr>
<td>Fair</td>
<td>1 (1.1%)</td>
<td>3 (3.2%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Baseline pain intensity</td>
<td>1.5±1.4</td>
<td>1.7±1.4</td>
<td>1.3±1.3</td>
</tr>
<tr>
<td>Baseline rescue medication</td>
<td>0.7±0.7</td>
<td>0.7±0.7</td>
<td>0.6±0.7</td>
</tr>
</tbody>
</table>

Baseline: average of 4 days before randomisation visit; Global evaluation: evaluation on Visit 2 (Day 7) of run-in period; Pl: placebo; Bup: buprenorphine patch.

Overall response rates during the double blind period were significantly higher for buprenorphine compared to placebo for the full analysis set (p = 0.0003) and the modified per protocol set (p = 0.0031).
Table 27: PB-TTC-02 Response rate. Primary efficacy endpoint

<table>
<thead>
<tr>
<th>Response by criteria</th>
<th>Full analysis set</th>
<th>Per-protocol set</th>
<th>Modified per-protocol set</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=188</td>
<td>N=118</td>
<td>N=137</td>
</tr>
<tr>
<td>Bup (n=94)</td>
<td></td>
<td>Bup (n=64)</td>
<td>Bup (n=70)</td>
</tr>
<tr>
<td></td>
<td>Pl (n=94)</td>
<td>Pl (n=54)</td>
<td>Pl (n=67)</td>
</tr>
<tr>
<td>RESP1</td>
<td>89</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>RESP2</td>
<td>87</td>
<td>64</td>
<td>65</td>
</tr>
<tr>
<td>RESP3</td>
<td>74</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td>Overall Response</td>
<td>70 (74.5%)</td>
<td>53 (82.8%)</td>
<td>54 (77.1%)</td>
</tr>
<tr>
<td>95% CI</td>
<td>65.7%-83.3%</td>
<td>73.6%-92.1%</td>
<td>67.3%-87.0%</td>
</tr>
</tbody>
</table>
| RESP1: treatment duration of at least 12 days; RESP2: mean pain intensity <5.0 during the last 6 days of treatment; RESP3: consumption of ≤2.0 tablets of rescue medication/day on average during double-blind period

The response rate was also analysed according to prior concomitant radiotherapy or chemotherapy. In the buprenorphine group, the response rate in the active treatment group was similar (74.4% for patients with prior radio/chemotherapy, 74.5% for those without prior radio/chemotherapy). However, the difference in response rates between the buprenorphine group and the placebo group was higher in patients without prior or concomitant radiotherapy or chemotherapy compared to patients with radiotherapy or chemotherapy.

7.1.5.14. Results for other efficacy outcomes

7.1.5.14.1. Open label run-in period

- Twice daily assessment of the pain intensity using 11 point NRS: The mean pain intensity at Day 1 was already lower for subsequently randomized patients (3.5 ± 2.2) than non-randomized patients (4.3 ± 2.6). By Day 14, the mean pain intensity among subsequently randomized patients had decreased by approximately 2 points (to 1.5 ± 1.5) for randomized patients compared to only 0.2 points (to 4.1 ± 2.0) for non-randomized patients.

- Incidence and time to withdrawal due to adverse events or lack of efficacy: Twenty eight patients (9.7%) withdrew during the run-in period due to lack of efficacy. Median time to withdrawal was 8 days (interquartile range; 4.5 to 13.0).

- Amount and frequency of intake of rescue medication: Mean use of rescue medication was lower in randomized patients from Day 1 (0.9) to Day 14 (0.6) compared to non-randomized patients (Day 1: 2.0; Day 14: 2.0).

Comment: The randomisation criteria at the end of the run-in phase can result in the selection of potential responders for the double blind phase and the possibility of enrichment bias.

7.1.5.14.2. Double blind period

- Twice daily assessment of the pain intensity using 11 point NRS: Differences to placebo in mean pain intensity were apparent on Day 1 on which the patch was removed before the 20:00 assessment. These differences were maintained during the course of the double blind period across all analysis sets. The mean (± SD) differences to baseline (average pain intensity during last 6 days of double blind treatment; average pain intensity during 4 days preceding randomization visit) were 0.24 ± 1.19 for buprenorphine and 1.10 ± 1.90 for placebo in the full analysis set. The 95% confidence intervals showed no overlap. Similar results were found for the other analysis sets, but with some overlap of confidence intervals.

- Incidence and time to withdrawal due to adverse events or lack of efficacy: Median and mean times to withdrawal were similar for buprenorphine and placebo in the full analysis.
set and modified per-protocol set. The PP population was not analysed because there were no withdrawals due to lack of efficacy by definition. However, only 4 patients withdrew due to lack of efficacy in the buprenorphine group compared to 14 in the placebo group of the full analysis set.

- Amount and frequency of intake of rescue medication: The difference to baseline in use of rescue medication (average rescue medication during double blind period; average rescue medication during 4 days preceding randomization visit) indicated that the intake of rescue tablets was lower in the buprenorphine group (-0.52 ± 1.28) than in the placebo group (-0.01 ± 1.78), with no overlap of the 95% confidence intervals.

The outcome for the efficacy variable Patient's global evaluation using 5 point VRS on Days 7, 16, 23 and 30 was not described.

Comment: This study demonstrates statistical efficacy in the select population of patients with severe tumour-related pain. Some caution should be taken in its interpretation due to the selection out of non-responders by the study design.

7.1.6. Study BUP4201

Study title: A double blind, double dummy, randomised, parallel group study to compare the efficacy, safety, and tolerability of buprenorphine transdermal delivery system (BTDS) applied every three days with twice a day tramadol sustained release tablets in patients with severe pain due to osteoarthritis.

7.1.6.1. Study design, objectives, locations and dates

Design: Randomised, double blind, double-dummy, parallel group, non-inferiority, multicentre study consisting of a titration period lasting one to three weeks, followed by a four week assessment period

Locations: Multicentre study carried out in the UK

Dates: 1 August 2002 to 16 June 2003

Objectives: To compare the efficacy, safety, and tolerability of buprenorphine transdermal delivery system (BTDS) applied every three days with twice a day tramadol sustained release tablets in patients with severe pain due to osteoarthritis despite previous treatment with Step II analgesic therapy (that is weak opioids or compound analgesic preparations that contain an opioid component) alone or in combination with non-steroidal anti-inflammatory drugs (NSAIDs).

7.1.6.2. Inclusion and exclusion criteria

7.1.6.2.1. Main inclusion criteria

Patients of either sex, aged = 18 years, with osteoarthritis of the spine, hip(s) and/or knee(s), which had been present for at least three months and was causing severe pain.

7.1.6.2.2. Main exclusion criteria

Patients were excluded from the study if they had received full opioid agonists, buprenorphine or tramadol in the last three months, or were on anticonvulsant therapy. They were also excluded if they had any generic exclusions to the use of opioids, or if their condition was likely to fluctuate.

7.1.6.3. Study treatments

The study had two phases with an initial titration period of 1 to 3 weeks during which the dose regimen was titrated according to three levels until acceptable pain control was achieved. If acceptable pain control could not be achieved, the patient did not continue in the study. If acceptable pain control was achieved, the patient could progress to the 4 week assessment
period. At study entry, patients were allocated to treatment with either buprenorphine patches or tramadol prolonged release tablets (at dose level 1) according to a randomisation schedule.

The study used a double dummy design so that patients received either active buprenorphine patches and placebo tramadol prolonged release tablets (appearance very similar to the active tablets), or placebo buprenorphine patches (appearance very similar to the active patches) and active tramadol prolonged release tablets. There were three dose levels of study medication (see Table 28 below) with the starting dose and titration levels for buprenorphine patches and tramadol prolonged release tablets were based on the recommendations in the product's Summary of Product Characteristics.

According to the study report, tramadol was chosen as the comparator because it is used as a WHO Step IIb analgesic and that, at the time the protocol was written, it was anticipated that buprenorphine patches would be used in place of tramadol.

Patients were advised to apply patches were applied to either the left or right hand side of the body at one of the following positions:

- The upper arm or shoulder
- The upper chest, just below the collar bone
- The upper back
- The lower side, just below the underarm area.

Table 28: BUP4201 dose levels of study medication

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Buprenorphine patches</th>
<th>Tramadol prolonged release tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Loading dose</td>
<td>Release rate</td>
</tr>
<tr>
<td>1</td>
<td>20 mg</td>
<td>35 µg/h</td>
</tr>
<tr>
<td>2</td>
<td>30 mg</td>
<td>52.5 µg/h</td>
</tr>
<tr>
<td>3</td>
<td>40 mg</td>
<td>70 µg/h</td>
</tr>
</tbody>
</table>

Patients were reviewed on a one-two weekly basis throughout the trial by the investigator. The dose levels could be adjusted by one level up to achieve better pain control or down if the patient had AEs. If the dose level was decreased during the assessment phase, the patient was withdrawn from the study. Throughout the study, patients were allowed to take paracetamol tablets as rescue medication for breakthrough pain. Patients who had been taking regular doses of NSAIDs for at least 4 weeks before entry were expected to continue these during the study. The dose and frequency had to remain the same throughout the study.

Adequacy of pain control was assessed at the investigator appointments by:

- Box Scale 11 (BS-11) pain scores
- escape medication use
- sleep disturbance due to pain
- quality of sleep
- volunteered AEs
- if the patient had had the same dose levels for six consecutive days and had taken fewer than four doses (eight tablets) of paracetamol per day for the last three full days
- if the patient wished to continue on their current dose level of medication.
7.1.6.4. **Efficacy variables and outcomes**

7.1.6.4.1. **The main efficacy variables**

7.1.6.4.1.1. BS-11 pain scores

Patients recorded their pain intensity every evening in their personal assessment book (PAB) using the BS-11 pain scale, where ‘0 = no pain’ and ‘10 = pain as bad as you can imagine’. The secondary efficacy endpoints were to be: BS-11 pain scores during the last 12 days of the assessment period in the ITT population; BS-11 pain scores at baseline and during the last six days of the titration period; change in BS-11 pain score from baseline.

7.1.6.4.1.2. Assessment of optimum pain control

At each study visit after the first week, the investigator decided whether the patient was in optimum pain control by assessing pain intensity, use of escape medication, sleep disturbance and quality of sleep, and volunteered AEs.

7.1.6.4.1.3. Escape medication use

Patients recorded in their PABs the total number of paracetamol tablets taken that day.

7.1.6.4.1.4. Sleep disturbance and quality of sleep

At each study visit, the investigator asked the patient to recall how many nights and the average number of times per night that they had been woken because of pain (that is once, twice or more than twice) during the last six nights. They also asked patients to rate the quality of their sleep over the last six nights according to a 5 point scale ranging from 1 = very poor to 5 = very good.

7.1.6.4.1.5. Acceptability of treatment

- At study entry, the investigator asked the patient: ‘How would you rate your regular painkiller at relieving your pain?’ using a 5 point scale (1 = very poor to 5 = very good)
- At completion of, or discontinuation from the study, the investigator asked the patient: ‘How would you rate the study medication at relieving your pain?’ and ‘How would you rate the study medication in relieving your pain, compared with your regular (pre-study) painkiller?’ and ‘How would you rate the study medication overall as a treatment for your osteoarthritis pain (taking into account quality of pain relief achieved and any adverse events you may have encountered)?’ using a similar 5 point scale.

7.1.6.5. **The primary efficacy outcome**

The primary objective was to confirm equivalence between the buprenorphine patch and tramadol prolonged release tablets. The measure of efficacy was the mean BS-11 pain scores recorded during the last 12 days of the assessment period in the PP population.

Analgesic equivalence between the two treatments was to be assumed if the 95% CI for the mean treatment difference fell within the range (-1.5, 1.5) boxes on the BS-11 scale. No rationale was provided for this range.

7.1.6.6. **Other measures included**

7.1.6.6.1. Safety

- AEs
- Extent of exposure. This was defined as the length of time between the first and last dose of study medication (including down titration) and was calculated for each patient.
7.1.6.6.2. Baseline characteristics

Collected at study entry and included: age, gender, weight, height, race (that is Caucasian, Black, Asian or other), disease duration, joint(s) affected, main site of pain, evidence to support diagnosis of osteoarthritis, other medical conditions, concomitant medications, vital signs.

7.1.6.7. Randomisation and blinding methods

The investigator allocated the treatment to each patient according to a randomisation list. Treatment allocation was randomised in balanced blocks and there was an equivalent allocation of patients in each treatment group.

The report states that it is possible that the blind was broken early at one site: the two patients affected (one patients who was in the tramadol group, and another who was in the buprenorphine group) were not included in the per protocol (PP) population.

7.1.6.8. Analysis populations

The intention to treat (ITT) population was to include all patients who received at least one dose of study medication and is the same as the safety population.

The per protocol (PP) population was to include all patients who had complied with the protocol and who had completed pain scores in their PAB for at least 20 days of the assessment period. Patients who met any of the following criteria were to be considered protocol violators:

- Patients who failed any of the inclusion or exclusion criteria
- Patients who did not achieve optimum pain control in the titration period, but still continued into the assessment period
- Patients who were non-compliant with use of study medication
- Patients who did not stop taking Step II analgesics at study entry.

The enrolled population (that is all patients enrolled in the study) was to be used for all listings.

7.1.6.9. Sample size

The aim was to recruit up to 300 patients to allow for a dropout rate of up to 60%. It was estimated that, with 60 completing patients per group, the study would have 90% power at the 5% significance level to confirm equivalence between buprenorphine and tramadol, assuming that the data are normally distributed with a standard deviation of 2.5.

7.1.6.10. Statistical methods

7.1.6.10.1. Primary efficacy outcome

The mean BS-11 pain scores recorded during the last 12 days of the assessment period were to be analysed for the PP population using analysis of covariance (ANCOVA) with the baseline score (that is the score recorded for pain ‘right now’ at study entry) as a covariate. Centre and treatment were also to be included as factors in the model. The estimated treatment difference and associated 95% confidence interval (CI) were to be determined. Analgesic equivalence between the two treatments was to be assumed if the 95% CI for the mean treatment difference fell within the range (-1.5, 1.5) boxes on the BS-11 scale. The rationale for the selection of this range -1.5 to 1.5) was not provided.

Other efficacy variables were analysed using Analysis of covariance (ANCOVA), 95% CIs, Wilcoxon rank sum test, Chi-square test, Mantel-Haenzel test, Hodges-Lehman method for non-parametric confidence interval (CI) determination.

7.1.6.11. Participant flow

A total of 319 patients were enrolled and 313 were randomised: 159 in the buprenorphine group and 154 in the tramadol group.
Table 29: BUP4201 Participant flow

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine patch</th>
<th>Prolonged Release Tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned</td>
<td>150</td>
<td>150</td>
</tr>
<tr>
<td>Randomised*</td>
<td>159</td>
<td>154</td>
</tr>
<tr>
<td>ITT*</td>
<td>157</td>
<td>152</td>
</tr>
<tr>
<td>Discontinued during the titration phase</td>
<td>85</td>
<td>52</td>
</tr>
<tr>
<td>Entered the assessment phase</td>
<td>72</td>
<td>102</td>
</tr>
<tr>
<td>Completed assessment period</td>
<td>47</td>
<td>87</td>
</tr>
<tr>
<td>Per Protocol group</td>
<td>41</td>
<td>78</td>
</tr>
<tr>
<td>Number withdrawn during assessment period</td>
<td>25</td>
<td>15</td>
</tr>
</tbody>
</table>

* one patient from each group was excluded from all analyses (2) as their data could not be confirmed and one patients in each group was excluded from the ITT population (2) as neither received any study drug.

Four patients were excluded from the ITT population either because their data could not be confirmed (2) or because they did not take any study drug (2).

A total of 190 patients in the ITT population were excluded from the PP population. Most of these were due to the patient not progressing into the assessment phase (85 in the buprenorphine group and 52 in the tramadol group) but 18 were excluded because they violated the protocol (nine in the buprenorphine group and nine in the tramadol group) and 26 were excluded for either violating the protocol or not completing the PAB (11 in the buprenorphine group and 15 in the tramadol group).

A total of 175 patients (57%) discontinued from the study: 110 patients (70%) in the buprenorphine group and 65 (43%) in the tramadol group. Most of the discontinuations occurred during titration period: 85 patients (77%) in the buprenorphine group and 50 (77%) in the tramadol group.

**Figure 22: Percentage of patients remaining in the study (ITT population). Study BUP4201**

![Percentage of patients remaining in the study](image-url)
The most common reason for discontinuation was AEs, with this most likely to occur early at the week 2 visit in the titration phase for both groups.

**Table 30: BUP4201 Reasons for participant withdrawal (both phases) (primary reasons for discontinuation (ITT population))**

<table>
<thead>
<tr>
<th>Reason for discontinuation</th>
<th>Buprenorphine patch (n = 110)</th>
<th>Tramadol prolonged release tablets (n = 65)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AE</td>
<td>97 (88)</td>
<td>51 (78)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>9 (8)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Protocol violation</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Resolution or remission of indication</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Consent withdrawn</td>
<td>1 (1)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Comment:** There was a high rate of discontinuations with this more marked in the buprenorphine group.

**7.1.6.12. Major protocol violations/deviations**

Protocol deviations were provided. In total, nine patients deviated from the protocol: three in the buprenorphine group and six in the tramadol group. The most common protocol deviation was failure to complete an outcome visit (three patients in the buprenorphine group and five patients in the tramadol group).

In total, 44 patients violated the protocol: 20 in the buprenorphine group and 24 in the tramadol group. The most common protocol violation was non-compliance with the study medication (13 patients in the buprenorphine group and 11 in the tramadol group).

**Comment:** This is the only information regarding protocol violations and deviations in the study report; the 'Listings' referred to were not included in the report provided in the dossier.
7.1.6.13. Baseline data

Table 31: BUP4201 Baseline characteristics (ITT population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Buprenorphine patch (n = 157)</th>
<th>Tramadol prolonged release tablets (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male (32%)</td>
<td>Female (66%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean (range) 63.4 (38 - 87)</td>
<td>Mean (range) 62.9 (27 - 89)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean (range) 81.6 (42.8 - 149.2)</td>
<td>Mean (range) 82.3 (46 - 175)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean (range) 164.6 (127 - 193)</td>
<td>Mean (range) 165.0 (142 - 190)</td>
</tr>
<tr>
<td>Race</td>
<td>Caucasian (98%)</td>
<td>Caucasian (99%)</td>
</tr>
<tr>
<td></td>
<td>Black (1%)</td>
<td>Black (0)</td>
</tr>
<tr>
<td></td>
<td>Asian (1%)</td>
<td>Asian (1)</td>
</tr>
<tr>
<td></td>
<td>Other (1%)</td>
<td>Other (1)</td>
</tr>
</tbody>
</table>

Most patients (73%) in both treatment groups had suffered with osteoarthritis pain for more than five years. The most common site of osteoarthritis and pain was the spine: 118 patients (75%) in the buprenorphine group and 119 (78%) in the tramadol group had osteoarthritis in the spine and 80 patients (51%) in the buprenorphine group and 81 patients (53%) in the tramadol group reported the spine as the main site of pain.

7.1.6.13.1. Prior pain and analgesic medications

No measure of pain prior to study entry was provided. All patients in both treatment groups were taking analgesic medication for their osteoarthritis pain before the study and most were taking an opioid: 150 patients (96%) in the buprenorphine group and 144 (95%) in the tramadol group. The most commonly used opioid analgesics were paracetamol combinations (30%) with codeine or dextropropoxyphene or dihydrocodeine. NSAID use was also common and taken by 91 patients (58%) in the buprenorphine group and 88 (58%) in the tramadol group.

7.1.6.14. Results for the primary efficacy outcome

The mean BS-11 pain scores recorded at baseline and during the last six days of the titration period and the last 12 days of the assessment period for the ITT population are shown in the table below. Pain scores decreased from baseline to the other assessment times and were stable during the last 12 days of the assessment period in both treatment groups.
Figure 23: BUP4201 Mean BS-11 pain scores (mean BS-11 pain scores at baseline and during the last 12 days of the assessment period (PP population)

![Figure 23: BUP4201 Mean BS-11 pain scores](image)

Table 32: BUP4201 Mean BS-11 pain scores (ITT population)

<table>
<thead>
<tr>
<th>BS-11 pain scores (boxes)</th>
<th>Mean (SD)</th>
<th>Buprenorphine patch (n = 157)*</th>
<th>Tramadol prolonged release tablets (n = 152)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>7.3</td>
<td>7.4</td>
<td>1.37</td>
</tr>
<tr>
<td>Titration</td>
<td>5.4</td>
<td>5.1</td>
<td>2.17</td>
</tr>
<tr>
<td>Assessment</td>
<td>4.3</td>
<td>4.3</td>
<td>2.24</td>
</tr>
</tbody>
</table>

The estimated mean (95% CI) treatment difference (buprenorphine - tramadol) for BS-11 pain scores during the last 12 days of the assessment period was 0.03 (-0.62, 0.68) boxes (ANCOVA). The 95% CI for this treatment difference was within the pre-defined limits for equivalence (-1.5, 1.5 boxes).

Figure 24: BUP4201. The test for non-inferiority

![Figure 24: BUP4201. The test for non-inferiority](image)

BUP4201 Results of the non-inferiority tests. Shown are the estimated mean difference between buprenorphine transdermal patch and tramadol prolonged release tablets of the baseline adjusted pain intensity score (0 to 10), together with the upper 95% CI.
7.1.6.15. Results for other efficacy outcomes (ITT shown)

7.1.6.15.1. Optimum pain control

Seventy five patients (48%) in the buprenorphine group and 102 (67%) in the tramadol group had reached optimum pain control by the end of the titration period. The odds ratio (95% CI) for this treatment difference was 0.44 (0.28, 0.71).

7.1.6.15.2. Responder rates

In total, 72 patients (46%) in the buprenorphine group and 101 (66%) in the tramadol group responded to treatment, that is achieved optimum pain control and entered the assessment period.

7.1.6.15.3. Response to treatment

In total, 41 out of 72 patients (57%) in the buprenorphine group and 63 out of 101 (62%) in the tramadol group showed a response to treatment, defined as a reduction of 33% or more in BS-11 pain scores during the last 12 days of the assessment period. The odds ratio (95% CI) for this treatment difference was 0.80 (0.43, 1.46).

7.1.6.15.4. Escape medication use

Escape medication use was low (averaging around 2 doses per day) in both treatment groups during the titration and assessment periods. The estimated median (95% CI) treatment difference (buprenorphine – tramadol) during the last 12 days of the assessment period was -0.42 (-1.17, 0) doses/day.

7.1.6.15.5. Sleep disturbance

Sleep was improved compared to baseline in both treatment groups.

7.1.6.15.6. Acceptability of treatment

22 patients (54%) in the buprenorphine group and 56 (72%) in the tramadol group gave the study medication an overall rating (taking quality of pain relief and AEs into account) of ‘good’ or ‘very good’. None of these treatment differences were statistically significant. Results for secondary efficacy measures for the per protocol group were similar to the ITT group.

Comment: Equivalence was shown for the two treatments, buprenorphine patch and prolonged release tramadol, with respect to BS-11 pain scores, in the treatment of pain due to osteoarthritis. This result should, however, be interpreted with caution owing to the high discontinuation rate (137 out of 313, 44%) and unequal spread of this across the two treatment groups (Buprenorphine group: 85 out of 157, 53.5% and Placebo group 52 out of 154, 33.8%).

7.1.7. Study PB-TTC-01

Study Title: Double blind, randomised, Phase IIb clinical study to compare the efficacy and safety of buprenorphine TDS 35 µg/h and tramadol SR 100 mg twice daily in patients with chronic non-tumour pain

7.1.7.1. Study design, objectives, locations and dates

7.1.7.1.1. Design

Randomised, double blind, double dummy, active controlled, two parallel groups, multicentre trial of 4 weeks duration, using fixed dosages and no run-in phase.

7.1.7.1.2. Locations

83 investigators in 14 European countries: Austria, France, Germany, Italy, Portugal, Spain, Switzerland, Belgium, Netherlands, Croatia, Slovenia, Slovak Republic, Czech Republic, Poland.
7.1.7.3. **Dates**

23 October 2002 to 15 March 2004

7.1.7.4. **Objectives**

The primary efficacy study objective was to show that transdermal buprenorphine 35 µg/h is at least as therapeutically effective as tramadol SR 100 mg twice daily (‘non inferiority trial’).

Also:

- To investigate the analgesic efficacy and safety of transdermal buprenorphine 35 µg/h (buprenorphine patch, release rate 35 µg/h) versus tramadol SR 100 mg twice daily in patients with chronic non-tumour related pain
- In an optional 6 months follow-on open phase of the study, efficacy and safety of the buprenorphine patch, with increasing doses where appropriate, was further assessed
- Pharmacogenetic evaluation with blood sampling for genotyping performed in all patients participating in the study who consented to this test. Results of this reported separately.

7.1.7.2. **Inclusion and exclusion criteria**

7.1.7.2.1. **Main inclusion criteria**

- Moderate to severe chronic pain, non-cancer origin
- Pain intensity at the time of study entry ≥ 4 based on an 11 point (0 to 10) numerical rating scale (NRS).
- Current pain treatment with weak opioids including combinations such as codeine, dihydrocodeine, dextropropoxyphene, or tildine/naloxone or pain that was insufficiently treated with non-steroidal anti-inflammatory drugs (NSAIDs), or poorly tolerated NSAID treatment

7.1.7.2.2. **Main exclusion criteria**

Any contra indication to the use of opioids, in general or buprenorphine and tramadol specifically.

7.1.7.3. **Study treatments**

Patients were randomised to either transdermal buprenorphine 35 µg/h; one patch applied every three days or to tramadol SR 100 mg taken orally as a tablet twice a day over a 4 week (28 day) period. Paracetamol, as rescue medication, was allowed (paracetamol, oral, 500 mg tablet, up to 2,000 mg per day). All additional analgesics were prohibited.

The patients were assessed by the investigator at Day 1, Day 3 (telephone), Day 7, Day 14, Day 21 and Day 28. At each review, the patient was questioned about constipation, overall functioning, global satisfaction (except visit 1), had a skin status assessment and was assessed regarding concomitant diseases and medication, compliance with diary entries and adverse events. The patient also made a self-assessment of his/her pain using the Brief Pain Inventory.

A study diary was maintained by the patient throughout his/her participation in the study. The pain intensity overnight and duration/quality of sleep was recorded in the morning. Each evening the patient assessed the pain intensity during the day and the actual pain in the evening and recorded the values in the diary. Any paracetamol taken for breakthrough pain was recorded together with the degree of resulting pain relief.

A Quality of Life questionnaire (the SF-36 health survey questionnaire) was completed at the beginning of the study (Visit 1, Day 1) and at Visit 6 (Day 28) of the blinded phase and at Visits 9 and 12 of the open phase. At the end of the double blind phase of the study and upon the final
examination at the end of the open phase of the study (or upon premature termination), the investigator made a global assessment of the treatment.

7.1.7.4. **Efficacy variables and outcomes**

The main efficacy variables were:

- Pain intensity on an 11 point numerical rating scale as recorded in the patient's diary at 08:00 h and 20:00 h every day of the study. Patients had to cross, encircle or otherwise mark the appropriate comment on the scale.
- Consumption of rescue medication: The amount of rescue medication used since the previous visit was calculated at each visit from the packages returned and entries in the patient diary.
- Number of breakthrough pain episodes: The patient recorded all episodes of breakthrough pain in the patient diary, irrespective of whether medication was taken for the pain.
- Pain intensity, interference of pain in current life, enjoyment of life and medication used for pain relief were taken from the Brief Pain Inventory that was completed by the patients at each visit.
- Quality of Life Questionnaire: Patients were questioned on their quality of life using a standard questionnaire (SF-36 Health Survey) at the first and last visit.
- Quality of sleep as recorded by the patient in the patient diary using the categories of; duration of sleep at least 6 hours uninterrupted by pain; duration of sleep 3 to 6 hours uninterrupted by pain; duration of sleep 2 to 3 hours uninterrupted by pain; duration of sleep maximum 2 hours uninterrupted by pain.
- Skin status; objective and subjective as determined by the investigator at each visit. Skin sites were examined and graded according to the presence of erythema, oedema, urticarial blistering and severity (none, mild, moderate, severe). Patients were asked about symptoms of itching, burning, paraesthesia and numbness with each recorded as present or absent.

7.1.7.5. **Primary efficacy outcome**

The primary efficacy variable was the mean actual pain intensity, as rated by the patient using a 11 point numeric rating scale (NRS), at 08:00 h and 20:00 h of each day of blinded treatment compared to the pain intensity rating at the beginning of the study. The first day of patch use were excluded from the analysis due to the latency period of the patch. Non inferiority was to be assumed if the treatment difference between the buprenorphine group and tramadol group was less than 1 unit on the 11 point scale as this was ‘the largest difference that can be judged as being clinically acceptable’. No further rationale for this choice was provided.

7.1.7.6. **Other efficacy outcomes included**

7.1.7.6.1. **Safety**

Adverse events:

- Signs and symptoms of the skin at the application site.
- Specific question on constipation.

7.1.7.6.2. **Other**

- Quality of life, (SF-36 questionnaire).
- Ability to perform routine tasks.
- Satisfaction with treatment.
7.1.7.6.3. **Pharmacogenetic evaluations**

The study included a pharmacogenetic evaluation in order to correlate the patient’s response to the study medications with their genetic disposition. Blood sampling for genotyping was performed in all patients participating in the study who consented to this test. The DNA in the blood samples was analysed for single base mismatches of different genes involved in the metabolism and/or mechanism of action of the study medication. The result of this analysis was to be reported in a separate report, this was not included in the dossier.

7.1.7.7. **Randomisation and blinding methods**

Patients were assigned to consecutive numbers starting at 0001 according to chronological entry into the study. This number assigned each patient randomly to one of the two treatment groups. The randomisation list allocated each patient number to one of the two treatment groups. The randomisation list was drawn up for numbers 1 to 1,300 and in a second step for numbers 1,301 to 2,300. The block size chosen was 4.

The study used a double dummy design so that patients received either active buprenorphine patches and placebo tramadol prolonged release tablets (appearance very similar to the active tablets), or placebo buprenorphine patches (appearance very similar to the active patches) and active tramadol prolonged release tablets.

Knowledge of the randomisation list was limited to the persons responsible for creation of the randomisation list, preparation of the random code envelopes and preparation of the investigational products until the study database was formally closed.

The random codes were dispensed in sealed envelopes to the investigators. All envelopes were returned to the sponsor at the end of the study. Two envelopes only had been opened (patient [information redacted] and patient [information redacted]). These were opened at the end of the double blind period to determine whether further treatment with buprenorphine in each patient was appropriate.

7.1.7.8. **Analysis populations**

The primary efficacy outcome analysis was performed on the per protocol population: according to the report this is the most appropriate population for a non-inferiority trial. The full analysis set (FAS) and a modified FAS, were analysed secondarily.

7.1.7.8.1. **The per protocol population**

The per protocol population was the subset of patients who were randomised and received study medication; who adhered to all protocol conditions although patients with mild (not relevant) protocol deviations were included and who completed the 28 day blinded part of the study.

7.1.7.8.2. **The FAS**

The FAS included all patients who were randomised and received study medication exposed; baseline values were carried forward in case of drop-out without efficacy assessment.

7.1.7.8.3. **The modified FAS**

The modified FAS included all patients who were randomised and received study medication and for whom there were at least pain intensity entries in the diary at Day 2 available.

7.1.7.8.4. **The safety population**

The safety population included all patients who were randomised, received study medication and had baseline measurements available, regardless of any protocol violations.

Full analysis (FA): This is the subset of patients who were randomised and received study medication.
7.1.7.9. **Sample size**

Assumptions:
- A difference of 1 unit in pain intensity difference was still clinically acceptable and where transdermal buprenorphine 35 µg/h was regarded as effective as the tramadol
- Standard deviation of 2.7 for the baseline adjusted pain intensity (based on previous studies using the 10 point NRS)
- The expected difference in means under the null hypothesis was not exactly 0 but differed by 0.1 units
- No more than 30% of randomised patients would be excluded from the per protocol set.

When the sample size in each group is 191, a two group 0.025 one sided t test would have 90% power to reject the null hypothesis that the test and standard were not equivalent (the difference in means is -1 or farther from zero in the same direction) in favour of the alternative hypothesis that the means of the two groups were equivalent. Allowing for the rate of patients who would be excluded from the PP analysis (< 30%), it was planned that 550 patients in total (275 per treatment group) were to be recruited and included into the study. The overall significance level for each of the tests would then be limited at 5%.

7.1.7.10. **Statistical methods**

7.1.7.10.1. **Missing data**

For dropouts, the last measurement prior to withdrawal was written forward for subsequent (missing) measurements (‘last observation carried forward’, LOCF) for the efficacy parameters.

For missing entries of pain intensities in the patient diary, the missing measurement was replaced with the last valid measurement. Empty data fields in the CRF were treated as missing values. Entries in the CRF outside the defined fields were ignored.

7.1.7.10.2. **Low recruiting centres**

Centres with less than four patients were pooled together into artificial centres and included in the corresponding statistical test.

7.1.7.10.3. **Primary efficacy outcome**

The baseline for the primary efficacy variable was defined as the average pain intensity during the last 24hrs as recorded at screening. The pre specified largest difference where the buprenorphine transdermal patch 35 µg/h formulation could still regarded as being as effective as the tramadol formulation, and that could be judged as being clinically acceptable, was 1 unit on an 11 point NRS. The statistical analysis was based on a two sided 95% confidence interval (CI) for the difference of baseline adjusted pain intensities between both treatment groups. In order to estimate the CI, the mean square error of an analysis of variance (ANOVA) with independent factors treatment and centre was used. If the upper bound of the confidence intervals did not include the value 1, then transdermal buprenorphine 35 µg/h could be stated as being statistically therapeutically effective as tramadol.

Also tested was whether transdermal buprenorphine 35 µg/h was statistically superior to tramadol for that parameter which showed a significant result.

7.1.7.10.4. **Secondary efficacy variables**

7.1.7.10.4.1. **Amount of Rescue Medication**

The amount of rescue medication (breakthrough medication, paracetamol) was calculated for each visit interval and compared using an ANOVA that included the factors treatment and centre.

Submission PM-2014-03891-1-1 Extract from the Clinical Evaluation Report for Transtec and three additional trade names - buprenorphine 13 December 2016
7.1.7.10.4.2. The number of breakthrough pain episodes

For the number of breakthrough pain episodes the Cochran-Mantel Haenszel Test controlled for centre was used to detect any differences between both treatment groups.

7.1.7.10.4.3. Brief pain inventory

The brief pain inventory was used to provide a number of variables including; pain intensity (sensory dimension); the arithmetic mean of the four pain scales (worst, least, average and current) pain.

Baseline adjusted values were calculated as the arithmetic difference at each visit compared to Visit 1. An ANOVA including the factors treatment and centre was used to analyse these three different baseline adjusted scales between the two treatment groups. Each visit was tested separately. In addition, a covariance analysis was done using the amount of rescue medication (as defined above) as co variable and treatment and centre as independent factors. The model included a term for centre by treatment interaction.

7.1.7.10.5. Quality of life

The SF-36 health questionnaire was analysed following the instructions as described in Ware, J.E., SF-36 Health Survey, Manual & Health Survey, 1997, The Health Institute, New England Medical Centre, Boston, Massachusetts. The SF-36 health questionnaire is a validated questionnaire that consists of 36 individual items and 8 aggregated summary scales, the Physical and Mental Health Summary Scale.

7.1.7.10.6. The duration and quality of sleep

The duration and quality of sleep was determined daily each morning in the patient diary on a four item category variable. The median outcome during each visit was calculated. The Wilcoxon two sample test was used to compare treatment groups at each visit.

7.1.7.10.7. The subjective and objective symptoms of the skin at the application site

The objective symptoms were determined at each visit on a four item category variable. The median rating during each visit was calculated. These medians were compared between treatment groups at each visit by means of the Wilcoxon two sample test. The subjective symptoms were determined at each visit on a dichotomous variable (present/absent). These frequencies were compared between treatment groups at each visit by means of the Cochran-Mantel Haenszel Test controlled for centre.

7.1.7.10.8. Other subjective ratings in the patient diary

In addition to the primary efficacy analysis, the mean actual pain intensity at baseline was compared with the mean actual pain intensity between Day 21 and Day 28. The same statistical method as for the primary efficacy analysis was used.

Graphical displays showing the course of pain (worst, average and present) between the two treatment groups during the double blind phase were prepared. Morning and evening values and averaged values between morning and evening were depicted separately.

7.1.7.11. Participant flow

560 patients were enrolled and randomised

- 372 patients completed the blinded phase
  - 148 withdrew because of adverse events (AEs)
  - 22 withdrew because of lack of efficacy.
Table 32: PB-TTC-01 Participant flow

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine patch</th>
<th>Prolonged Release Tramadol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planned</td>
<td>275</td>
<td>275</td>
</tr>
<tr>
<td>Randomised*</td>
<td>284</td>
<td>276</td>
</tr>
<tr>
<td>Completed</td>
<td>167</td>
<td>205</td>
</tr>
<tr>
<td>Number withdrawn</td>
<td>117</td>
<td>71</td>
</tr>
<tr>
<td>Reason for withdrawal (number)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event (97)</td>
<td></td>
<td>Adverse event (51)</td>
</tr>
<tr>
<td>Lack of efficacy (8)</td>
<td></td>
<td>Lack of efficacy (14)</td>
</tr>
<tr>
<td>Withdrawal of consent (12)</td>
<td></td>
<td>Withdrawal of consent (4)</td>
</tr>
<tr>
<td>Other (0)</td>
<td></td>
<td>Other (2)</td>
</tr>
<tr>
<td>Full Analysis Set (FAS)</td>
<td>284</td>
<td>276</td>
</tr>
<tr>
<td>Per Protocol group</td>
<td>110</td>
<td>138</td>
</tr>
</tbody>
</table>

There was a high withdrawal rate with 188 out of 560 (33.5%) patients who withdrew from the study early. This was unevenly spread across the two groups with 117 out of 284 (42.5%) patients in the buprenorphine patch group and 71 out of 276 (25.7%) in the tramadol group. Opioid naïve patients were over represented in the withdrawals: 78 out of 117 (66.7%) withdrawals in the buprenorphine group and 38 out of 71 (53.5%) in the tramadol group. Lack of treatment efficacy was the reason for 22 patients terminating the study early (8 out of 284 in the buprenorphine group; 14 out of 276 patients in the tramadol group).

174 out of 284 patients in the buprenorphine group and 138 out of 276 in the tramadol group were excluded from the per protocol population. The most common reasons were the use of additional analgesics and poor compliance with taking the medications.
7.1.7.12. **Major protocol violations/deviations**

Table 33: PB-TTC-01 Protocol deviations

<table>
<thead>
<tr>
<th>Main reason for protocol deviation</th>
<th>Treatment</th>
<th>Buprenorphine TDS 35µg/h n = 284</th>
<th>Tramadol SR 100mg bid n = 276</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forbidden concomitant medication</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Anti-inflammatory/anti-rheumatic products, non-steroids</td>
<td>14</td>
<td>4.9</td>
<td>22</td>
<td>8.0</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>9</td>
<td>3.2</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Analgesics</td>
<td>4</td>
<td>1.4</td>
<td>7</td>
<td>2.5</td>
</tr>
<tr>
<td>Psychoanaleptics</td>
<td>6</td>
<td>2.1</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Tramadol not stopped 14 days prior to day 1</td>
<td>2</td>
<td>0.7</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Paracetamol other than rescue medication</td>
<td>4</td>
<td>1.4</td>
<td>4</td>
<td>1.4</td>
</tr>
<tr>
<td>Topical products for joint and muscular pain</td>
<td>1</td>
<td>0.4</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lack of compliance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compliance regarding tablets not within 100% &amp;0%</td>
<td>33</td>
<td>11.6</td>
<td>23</td>
<td>8.3</td>
</tr>
<tr>
<td>Compliance regarding patches not within 100% &amp;0%</td>
<td>26</td>
<td>9.2</td>
<td>21</td>
<td>7.6</td>
</tr>
<tr>
<td>Patient diaries for blinded phase not returned</td>
<td>6</td>
<td>2.1</td>
<td>14</td>
<td>5.1</td>
</tr>
<tr>
<td>Application of 1st patch not between 08:00 and 12:00 hours</td>
<td>11</td>
<td>3.9</td>
<td>9</td>
<td>3.3</td>
</tr>
<tr>
<td>Time of application of 1st patch not known</td>
<td>4</td>
<td>1.4</td>
<td>7</td>
<td>2.5</td>
</tr>
<tr>
<td>No current pain treatment (until screening) with weak opioids or NSAIDs</td>
<td>19</td>
<td>6.7</td>
<td>13</td>
<td>4.7</td>
</tr>
<tr>
<td>Violations against inclusion/exclusion criteria which are documented in the CRF</td>
<td>1</td>
<td>0.4</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*Percentages based on number of patients in each treatment group. A patient was included only once for each protocol deviation, however a patient could have more than one relevant protocol deviation. (Data source Section 16.2.2)*

7.1.7.13. **Baseline data**

There were no marked differences in the baseline characteristics of age, height, weight and body mass index between the treatment groups. Twice as many females as males participated in the study. All of the study participants were Caucasian.

Table 34: PB-TTC-01 Baseline characteristics

<table>
<thead>
<tr>
<th>PP set</th>
<th>BUP-TDP</th>
<th>PRTram</th>
<th>FAS = Safety set</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>110</td>
<td>138</td>
<td>284</td>
</tr>
<tr>
<td>Age [years]</td>
<td>57.8 (11.5)</td>
<td>57.6 (10.8)</td>
<td>59.0 (11.8)</td>
</tr>
<tr>
<td>Male [%]</td>
<td>40.9</td>
<td>34.8</td>
<td>33.1</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>81 (16)</td>
<td>79 (15)</td>
<td>79 (15)</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>29.0 (4.7)</td>
<td>28.4 (5.0)</td>
<td>28.6 (5.2)</td>
</tr>
<tr>
<td>Cancer pain [%]</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Opioid-experienced [%]</td>
<td>44.5</td>
<td>40.6</td>
<td>32.4</td>
</tr>
<tr>
<td>Pain intensity [score 0-10]</td>
<td>6.7 (1.4)</td>
<td>7.1 (1.6)</td>
<td>7.0 (1.4)</td>
</tr>
</tbody>
</table>

The main previous medications taken by the patients were anti-inflammatory and anti-rheumatic products 21.1% of patients (n = 389), analgesics 17.3% of patients (n = 318) and agents acting on the renin-angiotensin system 5.7% of patients (n = 104).

7.1.7.13.1. **Prior pain and analgesics**

The baseline pain intensity score was 7.0 for both groups in the FAS. A total of 194 out of 560 patients (34.6%) had had previous opioid therapy with 92 out of 276 (32.4%) of the buprenorphine patch group and 102 out of 276 (37%) in the tramadol group.

**Comment:** A breakdown of the causes of pain was not provided in the report.
7.1.7.14. Results for the primary efficacy outcome

The primary efficacy variable was the mean average pain intensity during Day 2 to Day 28 of the study. There was no major difference in the baseline mean average pain in the FA data set between the two treatment groups (6.99 ± 1.44 points in buprenorphine group and 7.02 ± 1.55 points in the tramadol group). The mean pain reduction (baseline adjusted) from Day 2 to 28 was 2.00 ± 2.06 points for buprenorphine and 2.06 ± 2.03 points for tramadol on the 11 point NRS. The results for the FA dataset were similar to the results of the PP dataset that is, there was no significant difference between the two treatment groups. Statistical significant superiority of transdermal buprenorphine 35 µg/h compared to Tramadol could not be shown.

7.1.7.14.1. Non inferiority

The 95% CI for the difference of means in the PP data set (-0.4993; 0.4622) was completely within the predefined therapeutic equivalence range of –infinity; +1. Therefore, the buprenorphine patch is statistically at least as therapeutically effective as tramadol SR 100 mg bd. The results for the FA dataset for the primary efficacy variable were essentially similar to the results of the PP dataset.

Figure 25: PB-TTC-01 Results of the non-inferiority tests for the primary efficacy outcome

shown are the estimated mean difference between buprenorphine transdermal patch and tramadol prolonged release tablets of the baseline adjusted pain intensity score (0 to 10) together with the upper 95% CI.

7.1.7.15. Results for other efficacy outcomes

The study report provided results for 12 secondary efficacy outcomes for the per protocol population. Results for the full analysis set were provided for some of these outcomes.

7.1.7.15.1. Mean average pain intensity by visit (source; patient diary)

In all data sets, there was a decrease in the first week of treatment in both groups followed by a continuous slight decrease until the end of the blinded phase. The initial decrease was most marked in the PP set.
Figure 26: Mean average pain intensity (PP data set). Patient diary; mean average pain intensity by visit, baseline adjusted, blinded phase LOCF data

Similar patterns were seen for mean actual pain intensity and mean worst pain intensity for all data sets. There was some separation of the treatment groups in the FAS for these variables, with the reduction in pain intensity more marked in the buprenorphine group (p < 0.05).

Comment: The separation of the treatment groups in the FAS was less than 0.5 on the 11 point scale and may not be clinically important.

7.1.7.15.2. Use of rescue medication, the number of breakthrough pain episodes, quality of sleep, quality of life (PP set)

There was no significant difference between the treatment groups for these outcomes.

7.1.7.15.3. Mean pain score (source; brief pain inventory)

There are some differences between the two treatment groups that were statistically significant at some time points. A similar pattern was seen for the FA data set but there was no significant difference between the treatment groups.
Figure 27: PB-TTC-01 Mean pain score (PP set). Brief pain inventory; PP data set, mean pain score, blinded phase, baseline adjusted, LOCF data

Comment: This study indicates that buprenorphine patch is non-inferior to tramadol in the management of chronic non-tumour pain. However, interpretation of this outcome is difficult due to the high rate of withdrawals and over representation of these in the buprenorphine group.

7.2. Other efficacy studies

7.2.1. Open follow-up studies; PB-TTC-follow up and WIS-BUP-LTS

7.2.1.1. PB-TTC-01 follow up

7.2.1.1.1. Design

Six months follow on open phase of the study PB-TTC-01 (20 mg patch versus tramadol SR 100 mg BD).

7.2.1.1.2. Location

83 centres in Europe

7.2.1.1.3. Dates

2003 to 2004

7.2.1.1.4. Objectives

Assess efficacy and safety of the buprenorphine patch, with increasing doses where appropriate.

7.2.1.1.5. Study population

Patients with moderate to severe chronic pain of greater than 3 months duration due to non-tumour origin.

7.2.1.1.6. Study treatments

Patients were reviewed monthly by the investigator. In the blinded part of the study, patients received the lowest dose patch (20 mg/35 µg/h) only. In the open part of the study, the patch strength could be doubled (application of 2 patches). Medication for breakthrough pain during the open phase could include paracetamol, NSAIDS, or others (but not opioids).
7.2.1.1.7. Study measures
Mean actual pain intensity, as rated twice daily by the patient using a 11 point numeric rating scale (NRS), sleep quality, other pain measures.

7.2.1.1.8. Participant flow
307 out of 372 of the patients who completed the double blind phase of the study volunteered to continue in the open phase. 198 out of 307 were included in the PP population. 162 out of 307 (49.5%) did not complete the open phase: 99 (32.2%) patients terminated early due to adverse events; 20 withdrew consent due to 'personal reasons'; 19 withdrew because of lack of efficacy; 13 for other reasons and one due to protocol violations.

7.2.1.1.9. Results
The mean actual pain intensity by visit in the open phase, PP population, was 4.52 ± 2.17 at the start and gradually declined to 4.24 ± 2.19 at the end. A similar pattern was seen in the FAS: starting at 4.54 ± 2.16 and 4.26 ± 2.29 at the end. The results of the secondary variables were consistent with a persistence of effect over the 6 month period without tolerance developing (there was some dosage increase in the first month but minimal thereafter).

Comment: There was a very high dropout rate with 49.5% not completing the follow-up study. In those who did complete, there was no apparent development of tolerance during 6 months of use.

7.2.1.2. WIS-BUP-FU & WIS-BUP-LTS
WIS-BUP-FU was an interim analysis performed as part of the request for marketing authorization, covering the period from 07 September 1995 up to 17 July 1998 and is not discussed separately.

7.2.1.2.1. Design
Open, multicentre, 24 month, follow-up study of treatment with 20 mg buprenorphine patch in patients who have completed the double blind phase of Studies WIS-BUP01, WIS-BUP02 and WIS-BUP03.

7.2.1.2.2. Location
Forty three centres in Europe.

7.2.1.2.3. Dates

7.2.1.2.4. Objectives
To determine, if the efficacy and tolerability of buprenorphine transdermal therapeutic system is sustained over a longer period of time.

7.2.1.2.5. Study population
Patients with severe or very severe pain of benign or malignant origin and who had adequate pain control from patch application in WIS-BUP01, WIS-BUP02 and WIS-BUP03.

7.2.1.2.6. Study treatments
The 20 mg buprenorphine patch, worn for 72 hours, with sublingual buprenorphine tablets for breakthrough pain. A second patch could be applied (2 x 20 mg patches, 70 µg/h) if pain control was inadequate. Patients were reviewed fortnightly in the first month and then monthly by the investigator. Study duration was initially planned for 6 months but was subsequently extended to 2001.
7.2.1.2.7. Study measures

Patient's retrograde assessment of pain relief during each investigator review; number of sublingual tablets taken; tolerability of patch.

7.2.1.2.8. Participant flow

Two hundred and forty one patients were enrolled; 239 were analysed (2 patients were lost to follow-up before the first review); 134 with tumour pain and 105 with non-tumour pain. There was a rapid decline in the number remaining in the study: 55.6% at 2 months, 15.5% at one year, 7.9% at two years and 1.7% at 3 years. The most common reasons for withdrawal were adverse events (72 out of 208) and the combined measure of insufficient pain relief or physical deterioration (78 out of 208); tumour patients made up the bulk of this last group (62 out of 78).

7.2.1.2.9. Results

Of the 239, 51 patients did not conform to the study requirements: 18 patients stopped wearing the patch for some time (range 3 days to 7 months), 27 patients altered the interval between patches, and 6 did both. Of the 188 conformers, 168 patients wore one patch and 20 patients wore two. On average non-tumour patients stayed in the study for almost twice as long (6.5 months) as tumour patients (3.3 months).

One hundred and eighty five out of 239 (77.4%) of patients were able to change the patch by themselves and 38 (15.9%) with the help of another person.

Pain relief was at least satisfactory in 94.3% of non-tumour patients and 86.6% of tumour patients (90% overall). Of this 90% overall, approximately half had complete or good pain relief and half had satisfactory pain relief. Thirty seven patients completed more than 12 months in the study. They showed a constant level of efficacy without any indication of the development of tolerance.

Data for intake of sublingual tablets was incomplete but suggests that around half of the patients could manage their pain with the patch alone or with one sublingual table per day.

Comment: There was a high dropout rate with only 37 patients (15.5%) continuing for longer than one year. In these patients there was no apparent development of tolerance.

7.3. Post-marketing surveillance studies

Comment: The post-marketing studies provided in the dossier are described and discussed below. Of note is that the most recent post marketing surveillance study included in the dossier is from 2005 and that only one of the included studies uses the proposed application time of 96 hours. It is apparent from the PSURs, in the listings of ‘Newly Analysed Studies’ and ‘Published Safety Studies’, that a considerable number of more recent post-marketing studies have been performed.

Table 35: Summary of the post-marketing surveillance studies

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Study design</th>
<th>Patient group¹</th>
<th>Treatment(s)</th>
<th>Patient No</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWB Transtec 2001/1²</td>
<td>Open, uncontrolled 72 hours per patch</td>
<td>BUP patch of any marketed strength</td>
<td>13179</td>
<td>Up to 10 weeks; mean: 61 days</td>
<td></td>
</tr>
<tr>
<td>PM Transtec 2001/2 (continuation of AWB)</td>
<td>Open, uncontrolled 72 hours per</td>
<td>BUP patch of any marketed</td>
<td>2077</td>
<td>Up to 10 weeks; mean: 65 days</td>
<td></td>
</tr>
<tr>
<td>Study Identifier</td>
<td>Study design</td>
<td>Patient group¹</td>
<td>Treatment(s)</td>
<td>Patient No</td>
<td>Duration</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------</td>
<td>----------------</td>
<td>--------------------------------------------------</td>
<td>------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Transtec 2001/1)</td>
<td>patch</td>
<td></td>
<td>strength</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transtec 2003/1, 2003/2</td>
<td>Open, uncontrolled 72 hours per patch</td>
<td>Patients commencing on 30 mg or 40 mg patch</td>
<td>30 mg or 40 mg BUP patch (52.5 µg/h or 70 µg/h)</td>
<td>3644</td>
<td>10 weeks and up to 8 months mean: 22 weeks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transtec-onco 2003/0, 1</td>
<td>72 hours per patch</td>
<td>Patients with severe tumour-related pain</td>
<td>BUP patch of any marketed strength</td>
<td>412</td>
<td>Up to 8 weeks; mean 63 days</td>
</tr>
<tr>
<td>AWB Transtec Pro 2005/2 (subset analysis)</td>
<td>Open, uncontrolled 96 hours per patch</td>
<td>Patients previously treated with morphine or fentanyl</td>
<td>BUP patch of any marketed strength</td>
<td>256</td>
<td>Up to 8 weeks</td>
</tr>
<tr>
<td>GRU-BUP-2002-01</td>
<td>Open, uncontrolled 72 hours per patch</td>
<td></td>
<td>BUP patch of any marketed strength</td>
<td>1223</td>
<td>Up to 3 months; mean duration not reported</td>
</tr>
<tr>
<td>BIOC/11/03/04</td>
<td>Open, uncontrolled 72 hours per patch</td>
<td></td>
<td>BUP patch of any marketed strength</td>
<td>1648</td>
<td>Up to 9-10 weeks; mean 65 days</td>
</tr>
<tr>
<td>TTC-MATRIX-AWB-2003 ²,³</td>
<td>Open, uncontrolled 72 hours per patch</td>
<td></td>
<td>BUP patch of any marketed strength</td>
<td>10810</td>
<td>Up to 6 weeks</td>
</tr>
<tr>
<td>BUP4202</td>
<td>Open, comparator used 72 hours per patch</td>
<td></td>
<td>A: BUP-patch or B: PR tramadol Either of any marketed strength</td>
<td>A: 539</td>
<td>Up to 6 months; median: A: 77 days B: 177 days</td>
</tr>
<tr>
<td>PMS Transtec versus. Durogesic Cohort Study</td>
<td>Open, comparator used 72 hours per patch</td>
<td></td>
<td>A: BUP-patch of or B: Fentanyl patch Either of any marketed strength</td>
<td>A: 135 B: 134</td>
<td>Up to 12 months (mean duration not reported)</td>
</tr>
</tbody>
</table>

Patients with indication according to SmPC unless otherwise indicated. ¹. Prescription in accordance with the SmPC ². Include patients aged < 18 years. This is not in accordance with prescribing recommendations in the draft PI ³. Describes the use of doses < 35 µg/h; this can only be delivered by cutting the patch into smaller pieces, a process that the draft PI for Australian use advises against ⁴. This is the only efficacy study that has a patch wearing time of 96 hours.
7.3.1. AWB Transtec 2001/1

7.3.1.1. Design
Multi centre post marketing surveillance study of an analgesic treatment of moderate to severe chronic pain with buprenorphine transdermal patches with a duration of less than 10 weeks.

7.3.1.2. Location
Germany.

7.3.1.3. Dates
2001 to 2002.

7.3.1.4. Objectives
Collection of safety and efficacy data on the use of buprenorphine transdermal patches when prescribed in accordance with the Summary of Product Characteristics (SmPC).

7.3.1.5. Study population
Cancer and non-cancer patients with moderate to severe pain requiring treatment with an opioid analgesic recruited from hospitals, outpatient clinics, or general practitioners’ practices.

7.3.1.6. Study treatments
Buprenorphine transdermal patch was prescribed at the physician’s discretion according to the Transtec prescribing information.

7.3.1.7. Study measures
Efficacy: Pain relief and change in buprenorphine patch strength.
Safety: Adverse drug reactions.

7.3.1.8. Participant flow
13,179 patients were recruited. 3,327 (25%) discontinued use of the patch: 600 due to inadequate analgesia, 1,257 due to side effects, 1,339 due to hospitalisation or other.

7.3.1.9. Results
Mean age 68 ± 14 years (range 13 to 101 years). About 38% of the patients were male and 59% female (3% missing data). 3,690 (28.0%) patients had cancer pain and 9,489 (72.0%) patients had non cancer pain with the latter most commonly musculoskeletal disorders (77%) and neuropathy (23%). 66% and 72% of the cancer pain and non-cancer pain patients, respectively, had previously received opioid analgesics. Mean treatment duration was 60.8 days. Most patients (78%) received the 20 mg patch and 77% of patients did not require any increase in dose (regardless of starting dose). If a dose increase was prescribed, it most commonly occurred at the first review. Over 90% of patients changed the patch every 3 days. Immediately before starting the patch, 6% of all patients reported ‘good’ or ‘very good’ and 34% ‘satisfactory’ pain relief. 71% of all patients reported ‘good’ or ‘very good’ pain relief at the first review, 73% at the second follow-up visit and 81% at the end-of-study visit. Similar results were seen in subgroups: cancer and non-cancer patients; patients aged < 70 years and patients aged ≥ 70 years; and patients treated with opioids prior to enrolment.

The safety profile of buprenorphine transdermal patches correlated with that already known with no evidence of any previously unknown side effects.

Comment: Patients as young as 13 years were included in the study. This is not in accordance with the SmPC.
7.3.2. **PM Transtec 2001/2**

7.3.2.1. **Design**

This study was a multicentre post-marketing surveillance study of an analgesic (Transtec; transdermal buprenorphine patch, with release rates of 35 µg/h, 52.5 µg/h and 70 µg/h) in the treatment of moderate to severe non acute pain over a 10 week period.

7.3.2.2. **Location**

Germany.

7.3.2.3. **Dates**


7.3.2.4. **Objectives**

To study the efficacy and tolerability of Transtec in the treatment of moderate to severe chronic cancer and non-cancer pain.

7.3.2.5. **Study population**

Patients with moderate to severe chronic cancer and non-cancer pain enrolled by general practitioners and physicians in hospitals and out-patient pain departments.

7.3.2.6. **Study treatments**

Patients were prescribed buprenorphine patches with release rates of 35 µg/h, 52.5 µg/h or 70 µg/h according to the patients’ individual requirements. Concomitant analgesic medication was allowed.

7.3.2.7. **Study measures**

Efficacy: change in pain relief after approximately 20 days of treatment; sleep quality. Safety.

7.3.2.8. **Participant flow**

15,256 courses of therapy were recorded in 2001 and 2002.

13,179 cases were analysed and reported in 2003 (see AWB Transtec 2001/1 above). The remaining 2,077 cases were reported in PMS Transtec 2001/2 with comparison made to the ‘main group’.

7.3.2.9. **Results**

Median age 70 years (range 15 to 101); male: female ratio was 2: 3; ⅔ had non-tumour pain and ⅓ had tumour related pain; 89% had had prior analgesics; a breakdown of how many had previously been on opioids was not provided.

Seventy eight percent commenced on the 20 mg (35 µg/h) patch, 16% on the 30 mg patch and 5% on the 40 mg patch. 5.3% of patients had described pain relief ‘good’ or ‘very good’ prior to commencing buprenorphine. At the first review with 76.9% described pain relief as ‘good’ or ‘very good’ and at the end of the 8 week period, 87% of patients were describing pain relief as ‘good’ or ‘very good’.

Five hundred and nineteen out of 2,077 (25%) of the patients ceased buprenorphine patches prior to or at the final review; death was the most common reason for this (128 out of 519). 133 out of 2,077 patients had ADRs.

**Comment:** The results for the main group are presented in the report AWB Transtec 2001/1. Some of the results of both groups were compared in this study; a pooled analysis was not provided. The information above is that of the remainder group of 2,077 unless otherwise specified.
7.3.3. **AWB Transtec 2003**

Presented as study reports:
- AWB Transtec 2003/0
- AWB Transtec 2003/1
- AWB Transtec 2003/2

### 7.3.3.1. **Design**

Multi centre post marketing surveillance study of patients with moderate to severe chronic pain requiring treatment with 30 mg (52.5 µg/h) buprenorphine transdermal patches with duration of 10 weeks to 8 months.

### 7.3.3.2. **Location**

5,313 centres in Germany.

### 7.3.3.3. **Dates**

September 2001 to June 2002 (BUP patch first registered in 2001 in Germany).

### 7.3.3.4. **Objectives**

AWB Transtec 2003/1; to investigate efficacy and safety, especially of elevated doses of buprenorphine (52.5 to 140 µg/h) and to obtain knowledge with regard to switching from opioids to buprenorphine patch.

AWB Transtec 2003/2; to investigate the efficacy and tolerability of buprenorphine patches in a subpopulation of patients who had been receiving daily morphine doses of at least 120 mg before enrolment in the study.

AWB Transtec 2003/0; to investigate the AEs associated with prolonged use of buprenorphine patches.

### 7.3.3.5. **Study population**

Moderate to severe cancer pain and severe pain unresponsive to non-opioid analgesics recruited from private practices and hospital in and out patients.

### 7.3.3.6. **Study treatments**

Proposed minimum buprenorphine dose of 52.5 µg/h applied for 72 hours for 10 weeks. Patients could then continue for another 6 months.

### 7.3.3.7. **Study measures**

Efficacy: Pain relief, Sleep quality


### 7.3.3.8. **Participant flow**

3,644 patients were enrolled and included in the safety analysis. 3,340 were included in the efficacy analysis in which patients were also divided according to the WHO level analgesic taken prior to enrolment: WHO Step III group; 1,644 patients; WHO Step II group: 1,415 patients; WHO Step I group: 185 patients; Missing group: 96 patients.

### 7.3.3.9. **Results**

1,312 patients (39.3%) were male, 2,015 (60.3%) were female. Mean patient age was 68.9 years. The most common cause of pain was musculoskeletal pain (2,488 patients, 74.5%) with this due to back pain in 1,886 patients. 827 had cancer related pain. 857 patients ceased
buprenorphine during the study: 34% (292) due to death, 17.4% as analgesia was no longer required, 12% due to AEs, 12.3% due to hospitalisation and 7.8% (67) due to lack of efficacy.

49.2% of patients were taking WHO level 3 opioids prior to enrolment. 3,184 of the 3,276 patients providing details (97.2%) described ‘no response’ or only ‘weak’ or ‘satisfactory’ pain relief with the previous therapy. 87.8% of patients commenced on the 30 mg (52.5 µg/h) patch and 11.7% on the 40 mg patch. At the end of buprenorphine patch therapy, pain relief was described as ‘very good’ or ‘good’ in 2,941 (88.1%) patients.

Three hundred and eighty three patients experienced AEs.

Forty two patients had been receiving daily morphine doses of 120 to 548 mg before enrolment in the study. 73% were managed by community physicians. Mean age was 64 years; the most common cause of pain was musculoskeletal (17 out of 42); the most common reason for switching to buprenorphine patches was inadequate pain control. The median duration of treatment with the buprenorphine patch was 123 days (range 6 to 355 days). Most (29 out of 42) patients were commenced on the 30 mg (52.5 µg/h) patch; 11 out of 42 commenced on the 40 mg (70 µg/h) patch; one patient was commenced on a dose lower than 52.5 µg/h and one on a dose greater than 70 µg/h. At the end of the 8 month observation period, 35 patients were missing; 3 were using the 30 mg patch and 2 were using the 40 mg patch. Pain relief on prior therapy had been rated as ‘weak’ (17 out of 42), ‘satisfactory’ (23 out of 42), ‘good’ (2 out of 42) and none for ‘very good’. Pain relief on buprenorphine was rated ‘weak’ (1 out of 42), ‘satisfactory’ (6 out of 42), ‘good’ (13 out of 42) and ‘very good’ (19 out of 42).

Comment: Interpretation regarding efficacy is difficult given that 26% did not continue with the buprenorphine patch, with this due to death in a large number (292 out of 857). It does provide some limited information that switching from a high dose of oral morphine (> 120 mg) to a 30 mg patch rather than a 40 may be adequate. This may reflect the marked inter-individual variation in absorption from the patch.

7.3.4. AWB Transteconco2003/0, AWB Transteconco2003/1

7.3.4.1. Design

Post-marketing surveillance study of up to 8 weeks in the main part followed by a possible extension of up to three months.

7.3.4.2. Location

Germany.

7.3.4.3. Dates


7.3.4.4. Objectives

To provide data from the everyday practice on the efficacy and tolerance of the use of buprenorphine patches in patients with tumour related pain.

7.3.4.5. Study population

Patients with moderate to severe tumour related pain in whom buprenorphine was assessed as indicated were enrolled from hematologic/ oncologic medical offices and hospital out-patient departments.

7.3.4.6. Study treatments

Patients were prescribed buprenorphine patches from the following release rates of 35 µg/h, 52.5 µg/h and 70µg/h according to their individual needs. The maximum dose was to be 2 x 70 µg/h. Patches were changed 72 hourly. Concomitant analgesics were allowed.
7.3.4.7. **Study measures**

Efficacy: a number of pain measures (as assessed by the physician) and the use of rescue medication.

Safety and tolerability: AEs.

7.3.4.8. **Participant flow**

Four hundred and twelve patients were enrolled; 361 were included in the efficacy analysis, 412 were included in the safety analysis. Patients were excluded from the efficacy analysis due to medication commencement > 30 days prior to enrolment, duration of treatment < 3 days, inconsistent or essential data missing.

7.3.4.9. **Results**

Mean age 65.6 years, male: female was 1:1. The most common cancer diagnoses were breast (71 out of 361) and lung (42 out of 361) and the diagnosis of cancer had been made a median of 582 days prior to enrolment. The cancer was deemed progressive in 219 out of 361. In 169 out of 361 (46.8%), the pain was due to bony metastases. 263 out of 361 (73%) were taking opioid(s) prior to enrolment and 73% of patients were commenced on the 20 mg patch, 16% on the 30 mg patch and 6% on the 40 mg patch. At the end of the study, 32% were using the 20 mg patch, 29% the 30 mg patch, 17% the 40 mg patch and 6% were on a dose > 40 mg. A small number of patients were on a dose that was less than the 20 mg patch throughout the study.

Median duration of patch use was 63 days (range 4 to 405 days). 167 out of 361 discontinued buprenorphine during the study; in 88 patients, the reason for discontinuation was death; in 13 patients, lack of efficacy was a factor; in 6 patients, side effects were a factor.

Pain relief (on a 4 category scale from ‘poor’ to very good) was assessed as ‘good’ or ‘very good’ by 8 out of 361 patients prior to enrolment and as ‘good’ or ‘very good’ by 238 out of 361 patients at the end of the study. Other pain measures were similar in outcome.

30 out of 412 patients experienced 62 AEs.

**Comment:** A dose that is less than the 20 mg patch requires that the patch be cut into pieces.

7.3.5. **AWB Transtec Pro 2005/2**

7.3.5.1. **Design**

Sub group analysis of the post marketing surveillance study AWB Transtec Pro 2005 for up to 8 weeks.

7.3.5.2. **Location**

Germany.

7.3.5.3. **Dates**

2005.

7.3.5.4. **Objectives**

Efficacy and tolerability of the buprenorphine patch when worn for 96 hours.

7.3.5.5. **Study oopulation**

Patients from private practice, hospitals and outpatient pain departments with moderate to severe chronic pain of cancer and non-cancer origin requiring opioid therapy with either morphine or fentanyl in whom a clinical decision was made to commence buprenorphine patches.
7.3.5.6. **Study treatments**

Patients were commenced on buprenorphine patches with wearing time of 72 to 96 hrs. Recommendations for the initial dose strength were to be taken from the SmPC of the buprenorphine patch and published equipotency tables.

7.3.5.7. **Study measures**

Efficacy assessment: Pain intensity, using numeric rating scale (NRS; 11 point) with assessment before switch compared to assessment at the first review after switch to buprenorphine patch.

Safety: AEs.

7.3.5.8. **Participant flow**

3,654 patients were enrolled in the main study. 498 patients had been receiving morphine or fentanyl. 242 of these patients (49.6%) were not included in the sub-group analysis as they had been receiving other opioids in addition to morphine and fentanyl. The sub group analysed comprised 256 patients of whom 91 had been receiving morphine and 165 fentanyl.

7.3.5.9. **Results**

Male: female ratio was 1:2. Median age was 71 years (range 36 to 98). 87 out of 91 patients had a morphine dose ≤ 120 mg daily; 112 out of 165 had a fentanyl dose ≤ 50 µg/h. Forty five percent of patients were commenced on the 20 mg patch, 28% on the 30 mg patch and 18% on the 40 mg patch. Of note is that 15 patients commenced on a dose lower than the 20 mg patch and 2 commenced on 2 x 40 mg patches. In around 50%, the initial prescription was not in accordance with equipotency tables, with both lower and higher dose prescribed. The first review occurred around 20 days after commencing the patch. Eighteen patients had discontinued patch use at this time: due to AEs in 6 patients. The change in pain intensity after commencing the patch was analysed according to morphine and fentanyl, the previous dose of each and the patch dose commenced on. This resulted in very small numbers in each analysis group. Overall, 248 of 256 patients (97%) achieved pain intensity that was equal to or better than pain intensity prior to buprenorphine patch.

When switched from morphine or fentanyl to a lower than recommended dose of transdermal buprenorphine 95% of patients achieved an at least equi-analgesic effect in comparison to 96% of patients with a switch in accordance to the conversion table. When switching to a higher buprenorphine dose than recommended, all patients achieved an at least equi-analgesic effect directly after the switch. These results show that an at least equi-analgesic effect was achieved even by a lower buprenorphine patch size than stated in the conversion or equipotency tables that were used.

**Comment:** The full study AWB Transtec Pro 2005 was not included in the dossier. This study suggests that it is appropriate to commence patients who have previously received strong opioids on a lower strength patch than that indicated by equipotency tables. This would be consistent with inter-individual variability in response.

The dose < 35 µg/h is of note as it can only be delivered by cutting the 20 mg patch into smaller pieces.

7.3.6. **Gru-BUP 2002/01**

7.3.6.1. **Design**

Post authorization, prospective, uncontrolled, observational, and multicentre study over a 3 month treatment period.

7.3.6.2. **Location**

Spain.
7.3.6.3. Dates

7.3.6.4. Objectives
To evaluate the efficacy and safety of buprenorphine administered through a transdermal patch under customary usage conditions.

7.3.6.5. Study population
The subject population were hospital in and out patients with moderate to severe oncological pain and severe pain that did not respond to non-opioid analgesics and in whom a change on analgesic therapy was required.

7.3.6.6. Study treatments
Buprenorphine patch use in accordance with the SPC.

7.3.6.7. Study measures
Efficacy: degree of pain relief achieved, patterns of use in routine clinical practice, effect on the patients’ quality of life.

Safety: adverse events spontaneously reported by patients or collected by means of physician patient interviews.

7.3.6.8. Participant flow
1,223 patients were recruited, 535 did not complete the 3 month study. The main reasons for discontinuation were: adverse event (252 patients, 20.6%), loss to follow-up (111 patients, 9.1%), lack of efficacy (61 patients, 5.0%), pain improvement (41, 3.4%), and other reasons (70, 5.7%).

7.3.6.9. Results
32.34% of recruited patients were male and 67.66% female, with an average age of 64.9 ± 13 years (range 20 to 85). Pain was due to cancer in 207 patients (17.62%) and non-oncological in 968 patients (82.38%). Most patients (92.9%) were commenced on the 20 mg patch, 22.3% of patients had the dose increased during the study.

The proportion of patients who experienced good/very good pain relief increased significantly from 3.57% at baseline time to 70.55% at one month and to 85.82% after 3 months of treatment with the patch.
With regard to ease of handling, 32.1% of the patients used the patch with absolutely no problems and 63.38% considered the patch easy to use. Changing of the buprenorphine transdermal patch was done by the patient 65.4% of the time, by family members 30.2% of the time, by health care staff 3.8%.

Adverse effects were common, affecting 517 patients, and largely as expected although 1.3% developed dermatitis, an adverse effect not listed in the SmPC.

**Comment:** The report documents patients receiving \( \frac{1}{8} \) of the 20 mg patch (1 patient), \( \frac{1}{4} \) of the 20 mg patch (13 patients) and \( \frac{1}{2} \) of the 20 mg patch (44 patients). The draft PI does not describe cutting the patch into smaller pieces.

7.3.7. BIOC110304

7.3.7.1. Design

Non interventional study of buprenorphine patches in a general practice situation over 9 to 10 weeks performed in accordance with the Austrian Drugs Act.

7.3.7.2. Location

Four hundred and seven centres (GP and pain treatment outpatients departments) in Austria.

7.3.7.3. Dates

2002 to 2004

7.3.7.4. Objectives

The efficacy, safety and handling of buprenorphine patches.

7.3.7.5. Study population

Patients with tumour related pain or non-tumour pain not responding to non-opioid oral analgesics.

7.3.7.6. Study treatments

Buprenorphine 20 mg, 30 mg or 40 mg patches, each applied for 3 days and prescribed in accordance with the SOC (Austrian Codex).

7.3.7.7. Study measures

Efficacy: Evaluation of pain reduction and quality of sleep.
Safety: global tolerability and reporting of adverse events (AEs).

7.3.7.8. **Participant flow**

1,648 were enrolled: 544 had tumour related pain, 1,104 had non-tumour pain.

7.3.7.9. **Results**

Mean age was 71 years. Most (88.7%) had received at least one analgesic pre-treatment (up to 7 different medications/patient) with 50% of all patients stating that these provided poor pain reduction. After commencing buprenorphine patches, patients reported excellent (48.2%), good (34.6%) and satisfactory (6.6%) pain reduction at the end of the 9 to 10 week period. Only 1.4% of the patients experienced poor pain reduction and 0.2% no reduction at all. Most (77.2%) of all patients used 35 µg/h TTS. Three patients used doses greater than 100 µg/h (one each of 125 µg/h, 140 µg/h and 175 µg/h). Most (98%) changed the patch every 3 days. Most patients (63%) described no change in sleep quality although 21.7% reported improved sleep.

7.3.8. **TTC-MATRIX-AWB-2003**

7.3.8.1. **Design**

Non interventional study on the use of buprenorphine patches in clinical practice for the treatment of chronic cancer and non-cancer related pain over 6 weeks.

7.3.8.2. **Location**

887 centres in Belgium.

7.3.8.3. **Dates**

2002 to 2003.

7.3.8.4. **Objectives**

Collect data on the experience with transdermal buprenorphine in daily clinical practice on the treatment of chronic cancer and non-cancer related pain.

7.3.8.5. **Study population**

Patients from private clinics and hospital out-patients with chronic cancer and non-cancer related pain in whom treatment with buprenorphine patch was commenced in accordance with the normal clinical practice and in accordance with the marketing authorization.

7.3.8.6. **Study treatments**

Buprenorphine patch 20, 30 or 40 mg in accordance with SmPC.

7.3.8.7. **Study measures**

Efficacy: Pain Intensity (primary), Patient satisfaction with Pain Relief (secondary).

Safety: Patient satisfaction, adverse events (AEs).

7.3.8.8. **Participant flow**

10,810 recruited, 8,851 completed the 6 week study.

7.3.8.9. **Results**

Mean age 65.4 years (range 14 to 102 years). There were 61.4% females and 37.6% males. The majority (87.6%) of patients suffered from non-malignant pain, most commonly low back pain (40.8%) and osteoarthritis (30.5%). 84.1% started on the 20 mg patch (4.2% commenced on ½ 20 mg patch). Mean treatment duration was 44.2 days.

2,881 patients (26.7%) stopped the treatment during the study. Of these, 26.7% stopped due to AEs, 15.5% due to a combination of AEs and lack of efficacy (14.8% + 0.7%) and 2.4% solely due to lack of efficacy.
73% of patients were taking opioids prior to buprenorphine patches. 84% of patients commenced on the 20 mg patch and 46% were taking the 20 mg patch at study end. 27% of patients had a dose change during the study, most commonly to a higher dose patch and at the first review. Of note is that 459 patients were commenced on ½ 20 mg patch.

Baseline mean pain intensity was 6.6 as measured with an 11 point numeric rating scale (NRS). At Visit 2 the pain intensity had decreased to 3.7 and at Visit 3, after an average of 6 weeks follow-up the pain intensity was 2.6 (p < 0.0001).

User friendliness and patch comfort was deemed ‘satisfactory’ to ‘very satisfactory’ in 90.5% of patients after 6 weeks of follow-up.

The safety profile was in accordance with the SmPC. There was no evidence for yet unknown side effects.

**Comment:** Patients as young as 14 years were included in the study. This is not in accordance with the SmPC. A dose of ½ 20 mg patch was used. The draft PI does not describe cutting the patch into smaller pieces.

**7.3.9. BUP 4202**

**7.3.9.1. Design**

Multicentre, post-marketing, prospective, observational, cohort study in which the general practice patients would receive buprenorphine TDS or twice a day tramadol sustained release tablets.

**7.3.9.2. Location**

336 general practices in the UK.

**7.3.9.3. Dates**


**7.3.9.4. Objectives**

To compare the tolerability of the buprenorphine patches with twice a day tramadol sustained release (SR) tablets in and to determine if there are any, as yet unknown, tolerability or safety issues associated with the chronic administration of these 2 preparations.

**7.3.9.5. Study population**

Patients with moderate to severe cancer pain, and severe pain which does not respond to non-opioid analgesics who were already receiving buprenorphine patch or tramadol SR, in accordance with the SmPCs.

**7.3.9.6. Study treatments**

Patients were continued on their analgesic medicatin (buprenorphine patch of 20 mg (35 µg/h), 30 mg (52.5 µg/h), 40 mg (70 µg/h), or 2 x 40 mg (140 µg/h) or 50 mg, 75 mg, 100 mg, 150 mg, or 200 mg tramadol twice daily and followed up for 6 months.

**7.3.9.7. Study measures**

- Adverse events
- Concomitant medication use
- Medication compliance.

**7.3.9.8. Participant flow**

891 patients (593 in the buprenorphine group and 298 in the tramadol group) were recruited from 336 centres. 387 patients (43.4%) completed the study with this including fewer patients
in the buprenorphine treatment group (34.7%, compared with 60.7% of the tramadol treatment group). Adverse event was the major reason for premature discontinuation from the study: 33.2% of the patients who discontinued from the buprenorphine treatment compared to 10.4% in the tramadol treatment group.

7.3.9.9. Results

Of the 593 patients treated with buprenorphine 513 were Caucasian, 11 Black, 67 Asian and 2 other. Most patients had severe non cancer pain not responding to non-opioids (557 out of 593 and 283 out of 298). Approximately one third of patients in each treatment group had previously been prescribed buprenorphine or tramadol. The maximum dose taken by BUP patients was 105 µg/h (40 mg + 20 mg patch) in 3 patients, most patients were on 35 µg/h. Median duration of exposure to study drug was noticeably lower in the buprenorphine treatment group (77 days, compared with 177 days in the tramadol treatment group). No new or unusual safety issues relating to buprenorphine treatment were identified during the study. The adverse events reported for buprenorphine were as expected in terms of type, severity and frequency.

Comment: As with the non-inferiority studies, the buprenorphine patch seems to be less well tolerated than prolonged release tramadol. The study report refers to doses of 200 µg/h of buprenorphine; this could not be confirmed in the individual patient data.

7.3.10. PMS Transtec versus Durogesic cohort study

7.3.10.1. Design

Prospective, open, non-interventional cohort study compared two parallel treatment groups using buprenorphine or fentanyl analgesic patches.

7.3.10.2. Location

Germany.

7.3.10.3. Dates

2002 to 2003

7.3.10.4. Objectives

To determine the application properties, patient compliance, adverse events (AEs) and tolerability of the buprenorphine and fentanyl patches.

7.3.10.5. Study population

Patients with moderate to severe chronic pain (cancer and non-cancer patients) who continued their usual concomitant medication and therapy from pain centres and office based practices.

7.3.10.6. Study treatments

Three dosage strengths 35 µg/h, 52.5 µg/h and 70 µg/h of buprenorphine or four dosage strengths 25 µg/h, 50 µg/h 75 µg/h and 100 µg/h of fentanyl with the lowest possible dose for adequate pain relief to be given.

7.3.10.7. Study measures

Application properties using a questionnaire with 20 questions to be completed at each patch change.

Safety; AEs, by investigator questioning.
7.3.10.8. Participant flow

269 patients with 135 buprenorphine and 133 with fentanyl. 58 out of 269 patients had cancer related pain. 145 patients were receiving buprenorphine or fentanyl patches prior to study entry.

Seventeen (12.6%) of the buprenorphine (BUP) patients and 16 (11.9%) of the fentanyl (FEN) patients discontinued treatment with this most commonly due to inadequate analgesia (BUP patients: 7 (41.2%), FEN patients: 8 (50.0%)) or AEs/side effects (BUP patients 9 (52.9%), FEN patients: 6 (37.5%)).

Three deaths were documented in the Transtec group and two in the Durogesic group.

7.3.10.9. Results

Patch wearability:

- In 825 (88.2%) of the BUP patch changes and 741 (84.8%) of the FEN patch changes, patch handling was described as being 'without any problems' or 'easy'
- The analgesic patch required additional fixation in 65 (6.9%) of the BUP patch changes and in 198 (22.4%) of the FEN patch changes
- 557 (90.1%) of the BUP patch changes and 348 (82.1%) of the FEN patch changes reported that patch adhesion was still good after taking a shower
- 227 (86.3%) of the BUP patch changes and 157 (74.8%) of the FEN patch changes reported that patch adhesion was still good after taking a bath.

Skin sites included: the front and back and left and right of the trunk, arm and leg.

The maximum buprenorphine dose was 105 µg/h in 2 patients; the minimum dose was 17.5 µg/h (½ of a 20 mg patch) in 6 patients.

7.4. Analyses performed across trials (pooled analyses and meta-analyses)

7.4.1. Study WIS-BUP123

Study title: Analysis of the response to buprenorphine transdermal therapeutic system (TTS) measured by pain and rescue medication over three placebo controlled clinical studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03).

Comment: This is a post-hoc exploratory analysis of the placebo controlled efficacy trials WIS-BUP01, WIS-BUP02 and WIS-BUP03 prompted in part by the British MHRA (MCA) during the mutual recognition (MR) procedure performed in 2001.

7.4.1.1. Study design

A set of outcome measures were used to analyse the data pooled from the three placebo controlled trials:

1. Pain intensity and the use of rescue medication The British MHRA (MCA), during the MR procedure performed in 2001, requested that the changes in these efficacy variables be analysed parametrically and compared to placebo using ANOVA.

2. Combined response pain relief and rescue medication ('pain relief response'). Responders were defined as patients whose retrospective pain relief after the last patch application, as evaluated at Day 12 for WIS-BUP01 and Day 16 for WIS-BUP02 and WIS-BUP03, was at least satisfactory and who took in mean not more than 1 sublingual buprenorphine tablet per day, as evaluated at Days 9 to 11 for WIS-BUP01 and Day 13 to 15 for WIS-BUP02 and WIS-BUP03.
3. Combined response pain intensity and rescue-medication (‘pain intensity response’) Responders were defined as patients whose mean pain intensity during the last patch application, as evaluated at Day 12 for WIS-BUP01 and Day 16 for WIS-BUP02 and WIS-BUP03, was at most ‘mild’ and who took in mean not more than 1 sublingual buprenorphine tablet per day, as evaluated at Days 9 to 11 for WIS-BUP01 and Day 13 to 15 for WIS-BUP02 and WIS-BUP03. The mean pain intensity was calculated numerically by assigning scores to the 5 point verbal rating scale used for the assessment (1 = ‘no pain’, 2 = ‘mild pain’, 3 = ‘moderate pain’, 4 = ‘severe pain’, 5 = ‘very severe pain’; data from diaries) and equated to a mean pain intensity ≤ 2.0 for responders.

The combined measures for response rates were developed post-hoc as slightly different definitions had been used in the three trials. The underlying measurements of pain relief, pain intensity, and consumption of rescue medication were recorded for all studies with the same methodology.

7.4.1.2. Analysis population

Patients with chronic tumour related and non-tumour related pain who were included in the original placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 were included in this post-hoc analysis. Patients who discontinued the study prematurely because of AEs or unsatisfactory pain relief were considered as non-responders. For all other cases of premature termination the assessment used in the analysis of the original study was used as well. Patients from the randomised withdrawal, placebo controlled study, PB-TTC-02), were not included due to the different study design.

7.4.1.3. Study summaries

Table 36: WIS-BUP123 Summary of the individual trials. Key features of conventional placebo controlled studies

<table>
<thead>
<tr>
<th>Study period</th>
<th>WIS BUP-01</th>
<th>WIS BUP-02</th>
<th>WIS BUP-03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Randomised, double-blind, placebo controlled</td>
<td>Randomised, double-blind, placebo controlled</td>
</tr>
<tr>
<td>Groups</td>
<td>Placebo, BUP-TDP 35</td>
<td>Placebo, BUP-TDP 35</td>
<td>Placebo, BUP-TDP 35</td>
</tr>
<tr>
<td></td>
<td>BUP-TDP 52.5</td>
<td>BUP-TDP 52.5</td>
<td>BUP-TDP 70</td>
</tr>
<tr>
<td>Patients randomised</td>
<td>151</td>
<td>157</td>
<td>137</td>
</tr>
<tr>
<td>Run-in period</td>
<td>5 days, open, SL BUP</td>
<td>no run-in</td>
<td>6 days, open, SL BUP</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td>6 days (2 patches)</td>
<td>15 days (5 patches)</td>
<td>9 days (3 patches)</td>
</tr>
<tr>
<td>Centres</td>
<td>18</td>
<td>16</td>
<td>17</td>
</tr>
</tbody>
</table>

7.4.1.4. Statistical methods

Evaluations were performed for the data of the single studies WIS-BUP01, WIS-BUP02 and WIS-BUP03, and for the pooled data of the studies WIS-BUP01/02 as well as WIS-BUP01/02/03. The analysis was performed by individual dose groups (placebo, TTS 50, TTS 75, TTS 100) as well as for all active treatments combined (verum).

The response rates were analysed by absolute and relative frequencies (over all centres) including 95% CI, and by relative frequencies including 95% CI for the difference to placebo (over all centres). Exploratory tests were performed using the Cochran-Mantel-Haenszel test adjusted for stratum ‘study’ at the level α = 0.05. The hypothesis of no interaction between study and treatment was explored with the Breslow-Day test at the level of α = 0.05.
7.4.1.5. Results

7.4.1.5.1. Analysis of the main efficacy variables of pain intensity and the use of rescue medication

This analysis indicated some significant differences between the active treatments and placebo treatment in the changes in pain intensity since baseline for the Studies WIS-BUP01 and WIS-BUP03. Differences in spared consumption of rescue medication were also shown for each group comparison to placebo for Study WIS-BUP02, Study WIS-BUP03, but only for the overall comparison in Study WIS-BUP01.

Table 37: WIS-BUP123 Pain intensity and rescue medication

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Pain intensity [cm]</th>
<th>Rescue medication [mg]</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIS-BUP01</td>
<td>BUP-TDP 35</td>
<td>0.4429 (0.1553, 0.7304)*</td>
<td>0.118 (-0.046, 0.284)</td>
</tr>
<tr>
<td></td>
<td>BUP-TDP 52.5</td>
<td>0.4741 (0.1973, 0.7509)*</td>
<td>0.127 (-0.034, 0.288)</td>
</tr>
<tr>
<td></td>
<td>BUP-TDP 70</td>
<td>0.4103 (0.1285, 0.6921)*</td>
<td>0.158 (-0.005, 0.321)</td>
</tr>
<tr>
<td></td>
<td>combined</td>
<td>0.4433 (0.2199, 0.6666)*</td>
<td>0.135 (0.005, 0.285)*</td>
</tr>
<tr>
<td>WIS-BUP02</td>
<td>BUP-TDP 35</td>
<td>0.2065 (-0.3321, 0.7452)*</td>
<td>0.300 (0.100, 0.500)*</td>
</tr>
<tr>
<td></td>
<td>BUP-TDP 52.5</td>
<td>0.2112 (-0.3308, 0.7553)*</td>
<td>0.328 (0.127, 0.529)*</td>
</tr>
<tr>
<td></td>
<td>BUP-TDP 70</td>
<td>0.3326 (-0.2169, 0.8820)</td>
<td>0.327 (0.120, 0.534)*</td>
</tr>
<tr>
<td></td>
<td>combined</td>
<td>0.2483 (-0.1806, 0.6771)</td>
<td>0.318 (0.156, 0.480)*</td>
</tr>
<tr>
<td>WIS-BUP03</td>
<td>BUP-TDP 35</td>
<td>0.3009 (0.0776, 0.5242)*</td>
<td>0.168 (0.103, 0.233)*</td>
</tr>
</tbody>
</table>

Comment: The UK MHRA (MCA) registered the product in the UK in 2002

7.4.1.5.2. Combined response pain relief and rescue-medication (‘pain relief response’)

This showed a trend towards the buprenorphine patch compared to placebo but this reached significance for only some groups.

Figure 29: WIS-BUP123 Combined response of pain relief and rescue medication (‘verum’ = pooled group for all three patch strengths from the three trials)

Horizontal bars represent 95% confidence intervals calculated according to Fleiss.
7.4.1.5.3. Combined response pain intensity and rescue-medication ('pain intensity response')

For the 'pain intensity response', the differences to placebo were less pronounced than for the 'pain relief response' above. The study summary felt that this analysis provided further evidence for a dose dependent effect, in particular the combined analysis of WIS-BUP01/02 and WISBUP01/02/03.

**Figure 30: WIS-BUP123 Combined response of pain intensity and rescue medication. Difference versus placebo and confidence interval**

Horizontal bars represent 95% confidence intervals calculated according to Fleiss.

**Comment:** The results for these two response rate measures suggest some difference between the patches and placebo, and that this may be dose dependent, but are not conclusive (confidence interval includes zero for almost all groups). The study summary provided in the dossier argues that the failure of the combined response rates analysis to show efficacy was due to the individual components of the response rate being inter dependent (pain intensity could be reduced by an increase in rescue medication and pain relief increased by more rescue medication).

7.5. Evaluator's conclusions on clinical efficacy

This section presents the evaluator's conclusions on clinical efficacy for the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.

The sponsor seeks to establish efficacy through the presentation of:

- 6 efficacy studies with
  - 3 pivotal placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) in patients with tumour or non-tumour related pain
  - 1 placebo controlled withdrawal Study (PB-TTC-02) in patients with tumour related pain
7.5.1. Efficacy and the pivotal studies: WIS-BUP01, WIS-BUP02, WIS-BUP03 and WIS-BUP123

The dossier presented 3 ‘pivotal’ randomised, double blind placebo controlled efficacy studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03. The three studies were all performed in Europe between 1995 and 1998. No more recent placebo controlled studies on the whole target population were included in the dossier. The three studies shared similar efficacy measures but each had a different design.

Table 38: Summary of the ‘pivotal’ efficacy trials

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Type of trial</th>
<th>Patient group</th>
<th>Treatments</th>
<th>Patient No</th>
<th>Duration</th>
</tr>
</thead>
</table>
| WIS-BUP01        | Placebo-controlled, double blind, parallel group trial; 5 day open run-in phase (BUP SL); 6 day (2 patches) double blind; 72 hours per patch | Chronic tumour and non-tumour pain. | A: placebo  
B: 20 mg patch  
C: 30 mg patch  
D: 40 mg patch  
All groups: rescue medication BUP SL | A: 37  
B: 35  
C: 41  
D: 38  
Total: 151 | 11 days |
| WIS-BUP02        | Placebo-controlled, double blind, parallel group trial; no run-in, 15 days (5 patches); 72 hours per patch | Chronic tumour and non-tumour pain. | A: placebo  
B: 20 mg patch  
C: 30 mg patch  
D: 40 mg patch  
All groups: rescue medication BUP SL | A: 38  
B: 41  
C: 41  
D: 37  
Total: 157 | 15 days |
| WIS-BUP03        | Placebo-controlled, double blind, parallel group trial; 6 day open run-in (BUP SL); 9 day (3 patches) double blind; 72 hours per patch | Chronic tumour and non-tumour pain. | A: placebo  
B: 20 mg patch  
All groups: rescue medication BUP SL | A: 90  
B: 47  
Total: 137 | 15 days |

From review of the studies, they all had appropriate randomisation, blinding and statistical analyses. Inclusion criteria were consistent with the proposed indication and exclusion criteria were consistent with the contra indications to the use of buprenorphine listed in the draft PI. All study participants were accounted for and there were no breaches in protocol that would invalidate the results.

All three studies used a primary efficacy outcome of response rate with responders defined by the combination of the patient’s retrospective perception of pain relief as being ‘at least satisfactory’ on a four point scale and the use of rescue medication being less than a pre-specified level (‘not more than 1 additional SL buprenorphine tablet per day’ in WIS-BUP01 and WIS-BUP02 and ‘at least 40% fewer buprenorphine sublingual tablets than in the run-in phase’
in WIS-BUP03). Secondary efficacy measures included retrospective pain relief, pain intensity, sleep duration, and the use of rescue medication.

There are a number of issues in the study design, and factors that limit generalisability, including:

- **Sample size calculations:** These were based on unexplained assumptions regarding response rates for both the active and the placebo groups. The estimated response rate in the active group that was used in the calculations was 40% (WIS-BUP02 and WIS-BUP03) and 55% (WIS-BUP01) for the 20 mg patch strength. Higher response rates were assumed for the other patch strengths. The estimated placebo response rate used was 15% (WIS-BUP02 and WIS-BUP03) and 20% (WIS-BUP01). There was no explanation provided for the estimates of the active group and placebo response rates, nor is it clear why they should differ between the studies. In each study, the decision was also made after the sample size calculations to analyse the groups according to tumour or non-tumour sources of pain. The final analysis was stratified by patch strength and source of pain, resulting in small patient numbers in some groups.

- **Enrichment:** Both WIS-BUP01 and WIS-BUP03 used a study design in which only those patients who had at least satisfactory pain relief on a regimen of sublingual buprenorphine tablets were able to be enrolled in the double blind assessment phase. This could potentially select out those patients who were likely to be responders for inclusion in the double blind phase.

- **Participant number:** The sample size calculations resulted in treatment groups that were around 40 patients in WIS-BUP01 and WIS-BUP02, although slightly larger in WIS-BUP03. Response to therapies in chronic pain is recognised as being highly variable and it can be expected that only a minority of patients with chronic pain are likely to benefit from a specific therapy. Consequently, larger trials may be needed to demonstrate a treatment effect.40

- **Use of sublingual buprenorphine as rescue medication in all groups:** this potentially enabled patients in the placebo group to self-titrinate until pain reached an acceptable level that is the ‘placebo’ effect may have been more of a sublingual buprenorphine effect and may have contributed to the high response rates seen in the placebo groups. The pharmacokinetic arm of Study WIS-BUP02 found that plasma buprenorphine levels (although highly variable) were not dissimilar in the placebo group compared to those achieved in the active patch groups.

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Figure 31: WIS-BUP02PK: Plasma buprenorphine levels for patients taking none or one additional buprenorphine tablet prior to patch placement and then at removal of each of the 5 patches

- End point: The level of pain relief chosen in the response rate definition in the three studies was ‘at least satisfactory’ on a four point scale (unsatisfactory, satisfactory, good and complete). This is a relatively crude measure of pain relief and has largely been replaced by scales that allow finer discrimination with a greater number of points, for example the Box Scale 11, an 11 point scale used in PB-TTC-02. It could also be argued that, from a patient’s perspective, the aim of pain relief that is ‘at least good’ would be more desirable. The use of retrospective assessment of pain relief may also introduce inaccuracy as it is dependent on the patient’s memory of sensation.

- Prior pain and analgesics: no measure of pain intensity prior to study entry was provided. The majority of patients had been receiving opioids in each study.

- Duration: the studies were of relatively short duration (15 days or less). Medications for chronic pain can be assumed to have use that extends over months and years. Longer clinical trials are, therefore, essential to exclude a transient effect and to investigate such issues as tachyphylaxis, tolerance, dependence and safety. It is recommended that trials investigating therapies for chronic pain have duration of at least 12 weeks.41

- Ethnicity: all participants were Caucasian (except for one or two of African descent). Opioids are generally accepted as being ethnically sensitive, with genetic polymorphisms resulting in different responses in different ethnic populations. Although over 90% of the Australian population has Caucasian ancestry there are other ethnic groups represented, including Aboriginal and Torres Strait Islanders (2.5%), Chinese (4%) and Indian (2%).42

- Age: only adults were included, although the elderly were not excluded.

- Special populations: patients with any major organ disease were excluded from the studies. Concomitant disease was, however, common.

41 CPMP/EWP/252/03Guideline on clinical medicinal products intended for the treatment of neuropathic pain.
• Use of opioids: the majority of study participants had previously used opioids, for both tumour related and non-tumour related pain. The use of opioids for non-tumour pain such as osteoarthritis would be unusual in Australia.

Table 39: Results for the primary outcome measure (response rate)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Response Rate (%)</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>WIS-BUP01</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>31.4</td>
<td>16.9 – 49.3</td>
</tr>
<tr>
<td>20 mg patch</td>
<td>34.3</td>
<td>19.1 – 52.2</td>
</tr>
<tr>
<td>30 mg patch</td>
<td>36.6</td>
<td>22.1 – 53.1</td>
</tr>
<tr>
<td>40 mg patch</td>
<td>50.0</td>
<td>33.4 – 66.6</td>
</tr>
<tr>
<td><strong>WIS-BUP02</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>placebo</td>
<td>16.2</td>
<td>6.2 – 32.0</td>
</tr>
<tr>
<td>20 mg patch</td>
<td>36.6</td>
<td>21.2 – 53.1</td>
</tr>
<tr>
<td>30 mg patch</td>
<td>47.5</td>
<td>31.5 – 63.9</td>
</tr>
<tr>
<td>40 mg patch</td>
<td>33.3</td>
<td>18.6 – 51.0</td>
</tr>
<tr>
<td><strong>WIS-BUP03</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>46.7</td>
<td>31.7 – 62.1</td>
</tr>
<tr>
<td>30 mg patch</td>
<td>57.5</td>
<td>46.4 – 68.0</td>
</tr>
</tbody>
</table>

As shown by the response rates (and 95% CI) above, none of the three 'pivotal' randomised double blind placebo controlled studies (WIS-BUP01, WIS-BUP02, WIS-BUP03) were able to show that the patch was significantly better than placebo for the primary efficacy outcome measure of response rate. Secondary efficacy measures in these three studies (including retrospective pain relief, pain intensity and sleep duration) were, in general, suggestive of efficacy with the buprenorphine patch group showing some improvements over placebo, although there were inconsistencies across patch strengths.

Given that sublingual buprenorphine tablets were used for breakthrough pain, the placebo group may have had a higher response rate due to high consumption of these tablets. WIS-BUP01 and WIS-BUP03 included run-in phases during which sublingual buprenorphine was used to control pain. Comparing the baseline of rescue medication consumption during run-in to consumption during the randomised phase of WIS-BUP01, all groups had a similar average daily consumption of sublingual buprenorphine during the run-in phase (0.9 to 1.0 mg) and all groups had a lower consumption during the double blind phase (placebo group: reduced by 0.5 mg, all active patch groups: reduced by 0.6 mg). In WIS-BUP03, comparing the average daily doses of sublingual buprenorphine in the steady state phase to the run-in phase, there was a reduction of 0.6 mg (from 1.1 mg to 0.5 mg) in the buprenorphine patch group and a reduction of 0.4 mg, (from 0.9 mg to 0.5 mg) in the placebo group (p = 0.0288). The reduction in consumption of sublingual buprenorphine seen in the placebo groups in both studies suggests
that the placebo response in these two studies was not simply due to use of more sublingual buprenorphine. However, in BUP 02, patients in the placebo group were found to take, on average, 2 more 0.2 mg sublingual buprenorphine tablets per day: average daily dose of 0.7 mg compared to 0.3 mg for all active patch strengths.

There was no consistent dose response for the three patch strengths that were assessed in WIS-BUP01 and WIS-BUP02. For the secondary outcome measures in WIS-BUP01, the 40 mg patch performed better than the 20 mg patch, but the 30 mg patch was not better than the 20 mg patch. In WIS-BUP02, the performance of the 40 mg patch in the secondary outcome measures was worse than both the 20 mg patch and the 30 mg patch.

In most of the analyses there was no consistent difference between the non-tumour and tumour related pain, although interpretation is difficult given that the number of patients in the non-tumour groups was as low as seven.

7.5.2. WIS-BUP123

This post-hoc pooled analysis combined the data of the three pivotal studies. It used efficacy endpoints that were common to the three studies, although some manipulation was needed to enable roughly similar time-points to be used. Analysis was of each patch strength separately, and of the combined patch strengths. Outcome measures used were pain intensity and the use of rescue medications, analysed separately, and two combined outcome measures (pain intensity + the use of rescue medication and pain relief + the use of rescue medication).

The separate analyses of pain intensity and use of rescue medication was prompted by the UK MHRA during the mutual recognition process in 2001 and showed improvement in the active groups over placebo, although this was not consistent across the three studies or the three patch strengths:

- Pain intensity
  - in WIS-BUP01, pain intensity was significantly less than placebo for all patch strengths and for the combined patch strengths
  - in WIS-BUP02, pain intensity was not significantly less than placebo for any patch strength or the combined group
  - in WIS-BUP03, pain intensity was significantly less than placebo in the 20 mg patch group.

- Use of rescue medication
  - in WIS-BUP01, the use of rescue medication was only less than placebo for the combined patch strengths and not for the patch strengths individually
  - in WIS-BUP02, the use of rescue medication was less than placebo for all patch strengths
  - in WIS-BUP03, the use of rescue medication was less in the 20 mg patch group than placebo.

The combined outcome measures failed to show consistent improvement over placebo. Of note are the very wide confidence intervals in the results of these analyses.

7.5.3. Efficacy and the supportive Studies: PB-TTC-01 and PB-TTC-02, BUP4201

Supportive studies provided included the placebo controlled withdrawal Study, PB-TTC 02, and two non-inferiority studies that used prolonged release tramadol as comparator, PB-TTC-01 and BUP4201. These studies were performed in the early 2000’s and used a patch application time of 72 hours. The design details for these studies are provided in the table below. Review of the study reports shows these studies to be well designed and well run.
These studies were performed on subgroups of the target population. The placebo controlled withdrawal Study PB-TTC-02, was performed on patients with severe chronic tumour related pain. The non-inferiority Studies PB-TTC-01 and BUP4201, were performed in patients with non-tumour pain: PB-TTC-01 included patients with various types of chronic non-tumour pain and BUP4201 included patients with chronic pain due to osteoarthritis.

The choice of tramadol as the comparator is problematic. The dossier positions transdermal buprenorphine as suitable for patients transitioning from WHO level 2 analgesics to WHO level 3 analgesics (strong opioids). Tramadol has a mixed analgesic action with part of this due to agonist effects at the mu-opioid receptor. It is generally regarded as a weak opioid that fits into WHO level 2. The use of tramadol as the active comparator in these non-inferiority studies is not consistent with the presentation of transdermal buprenorphine as a WHO level 3 analgesics.

Table 40: Supportive efficacy studies

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Type of trial</th>
<th>Patient group</th>
<th>Treatments</th>
<th>Patient No</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB-TTC-02</td>
<td>Placebo-controlled, double blind parallel group withdrawal study; 15 day open label run-in, 15 day (5 patches) double blind; 72 hours per patch</td>
<td>Chronic tumour pain</td>
<td>A: placebo B: 40 mg patch All groups: rescue medication BUP SL</td>
<td>A: 88 B: 88 Total: 176</td>
<td>15 day run-in then 15 day double blind</td>
</tr>
<tr>
<td>BUP4201</td>
<td>Active-controlled (Tramadol SR), double dummy, double blind, non-inferiority trial; titration period up to 3 weeks; assessment period of 4 weeks; 72 hours per patch</td>
<td>Chronic pain due to osteoarthritis</td>
<td>A: patch of any marketed strength B: Tramadol PR 150 or 200 mg bd.</td>
<td>A: 159 B: 154 Total: 313</td>
<td>31 to 59 days</td>
</tr>
<tr>
<td>PB-TTC-01</td>
<td>Active-controlled (Tramadol SR), double dummy, double blind, non-inferiority study; no run-in; 72 hours per patch</td>
<td>Chronic non-tumour pain</td>
<td>A: 20 mg patch B: Tramadol PR 100 mg BD All groups: rescue medication paracetamol</td>
<td>A: 284 B: 276 Total: 560</td>
<td>28 days</td>
</tr>
</tbody>
</table>

7.5.4. PB-TTC-02

PB-TTC-02 used a withdrawal design and recruited patients with severe tumour related pain who had previously received opioids at an equi-analgesic dose range equivalent to 90 to 150 mg morphine orally per day (the study report and protocol did not indicate how the morphine equivalences were determined). Patients were stabilised on 40 mg (70 µg/h) buprenorphine patches over a 1 to 3 week period, with sublingual buprenorphine tablets as required for breakthrough pain. If adequate pain control on the buprenorphine patch was achieved, patients were then randomised to continue on an active patch or a placebo patch. All patients continued to use sublingual buprenorphine tablets for breakthrough pain during the double blind withdrawal phase.

The primary efficacy measure was the proportion of responders, where a responder was defined by a combination of three efficacy variables:

1. completion of at least 12 days of the double blind period
2. pain intensity less than 5 on an 11 point scale (scale from 0 to 10, where '0' was No Pain and '10 was Pain as bad as you can imagine')

3. use of rescue medication of less than 2 tablets on average per day.

Of the 289 patients enrolled in the initial titration phase, 189 were randomised into the withdrawal phase, with the efficacy analysis including only those patients in the randomised withdrawal phase. Of the 100 patients who were not randomised, 28 withdrew due to lack of efficacy and 50 did not meet the criteria for adequate pain control using the patch in the titration phase, suggesting that likely non-responders to buprenorphine had been selected out prior to the withdrawal phase. Supportive of this is the analysis of pain intensity during the titration phase for the two groups (those that met the criteria for randomisation and those that did not meet the criteria). This showed that the mean pain intensity had decreased by approximately 2 points in the group that was subsequently randomised compared to virtually no change for the non-randomised patients.

The active and placebo groups were evenly matched on baseline characteristics, including the number with advanced malignancies (as shown by the presence of metastases). The overall mean (± SD) baseline pain intensity (11 point NRS) at the end of the titration phase was comparable across treatment groups and analysis sets: 1.3 ± 1.3 in the buprenorphine group and 1.6 ± 1.4 in the placebo group for the per protocol set; 1.5 ± 1.4 in the buprenorphine group and 1.7 ± 1.4 in the placebo group of the full analysis set. Overall response rates (using the three part responder definition described above) showed that buprenorphine performed significantly better than placebo for the full analysis set of 188 patients: buprenorphine response rate 74.5% (95% CI 65.7 to 83.3%) compared to placebo response rate 50.0% (95% CI 39.9 to 60.1%). Similar results were obtained for the PP set and modified PP set.

The secondary efficacy measure of twice daily assessment of the pain intensity showed that the differences to baseline were 0.24 ± 1.19 (95% CI -0.01 to 0.49) for buprenorphine and 1.10 ± 1.90 (95% CI 0.66 to 1.54) for placebo in the full analysis set. Similar results were found for the other analysis sets, but with some overlap of confidence intervals. The difference to baseline in use of rescue medication (average rescue medication during double blind period – average rescue medication during 4 days preceding randomization visit) indicated that the intake of rescue tablets was lower in the buprenorphine group (-0.52 ± 1.28) than in the placebo group (-0.01 ± 1.78), with no overlap of the 95% confidence. The mean amount of rescue medication used on Day 1 was similar for both groups (buprenorphine: 1.0 ± 1.3 tablets; placebo: 1.1 ± 1.4 tablets). By Day 14, mean use of rescue medication was lower in the buprenorphine group (0.8 ± 1.1 tablet compared 1.2 ± 1.2 tablets). Median and mean times to withdrawal were similar for buprenorphine and placebo in the full analysis set and modified per protocol set. Of the patients withdrawing due to lack of efficacy, there were 4 in the buprenorphine group compared to 14 in the placebo group of the full analysis set.

The results of Study PB-TTC-02 demonstrate efficacy of the 40 mg buprenorphine patch in a very select group of patients that is those patients with severe cancer related pain previously requiring high doses of strong opioids and who had achieved adequate pain control using a 40 mg buprenorphine patch. Of note is that one third of patients who entered to study (100 out of 289) were unable to meet the criteria for continuing in the double blind withdrawal phase, and that the most common reasons for this were lack of efficacy and inadequate pain control (78 out of 100).

7.5.5. **BUP4201**

The non-inferiority Study BUP4201 was performed in patients with chronic pain due to osteoarthritis of the spine, knees or hips and used a double dummy design with two phases, each of up to 4 weeks in duration. At study enrolment, patients were randomised to either buprenorphine patch with 72 hour application time or prolonged release tramadol twice daily and entered a titration phase of up to four weeks during which the analgesic medications were
titrated as required (to maximum dose of 40 mg patch or 200 mg prolonged release tramadol). Patients who had a stable analgesic dose, acceptable pain control, and no significant adverse effects, continued into the 4 week assessment phase. Paracetamol was used for breakthrough pain in all patients. Long-term (> 4 weeks) NSAIDs could be continued at the same dose as prior to study entry.

A total of 319 patients were enrolled and 313 were randomised: 159 in the buprenorphine group and 154 in the tramadol group. A total of 175 patients (57%) discontinued from the study: 110 patients (70%) in the buprenorphine group and 65 (43%) in the tramadol group. Most of the discontinuations occurred during titration period and the most common reason was AEs. Of the discontinuations, 9 out of 110 of the buprenorphine group and 11 out of 65 of the tramadol group withdrew due to lack of efficacy.

The primary efficacy endpoint was the mean Box Scale 11 (BS-11) pain scores recorded during the last 12 days of the assessment period. Equivalence between buprenorphine patch and prolonged release tramadol was to be assumed if the 95% CI for the mean treatment difference (buprenorphine - tramadol) for the primary efficacy endpoint fell within the range (-1.5, 1.5) boxes on the BS-11 scale. The rationale for the selection of this range (-1.5 to 1.5) was not provided and may be clinically excessive. The Study PB-TTC-01 used the range of 1.0 box on an 11 point scale to demonstrate non inferiority.

Baseline mean BS-11 pain scores (SD) were 7.3 ± 1.26 for the buprenorphine group and 7.3 ± 1.37 for the tramadol group and consistent with poor pain control prior to study entry. The mean scores during the assessment period were 4.3 ± 2.16 for the buprenorphine group and 4.3 ± 2.24 for the tramadol group. The test for non-inferiority, using the mean BS-11 pain scores recorded during the last 12 days of the assessment period compared to the mean baseline scores, showed that the buprenorphine patch was statistically non-inferior to prolonged release tramadol for both the ITT and PP populations. This result must, however, be interpreted with caution given the high withdrawal rate, with this disproportionately affecting the buprenorphine group.

7.5.6. PB-TTC-01

The other non-inferiority Study PB-TTC-01, compared the 20 mg buprenorphine (35 µg/h) patch (applied every three days) to prolonged release tramadol 100 mg orally BD over a 4 week period. Patients were included in the study if they had chronic non-tumour pain that was inadequately controlled by treatment with weak opioids or non-steroidal anti-inflammatory drugs (NSAIDs), or poorly tolerated NSAID treatment. Patients were randomised to either 20 mg buprenorphine patch applied every three days or to tramadol SR 100 mg taken orally as a tablet twice a day over a 4 week (28 day) period. Paracetamol (up to 2,000 mg per day) was used for breakthrough pain. No other analgesics were allowed.

The primary efficacy variable was the mean actual pain intensity, as rated by the patient using an 11 point numeric rating scale (NRS), twice daily during blinded treatment compared to the pain intensity rating at the beginning of the study. Non-inferiority was to be assumed if the treatment difference between the buprenorphine group and tramadol group was less than 1 unit on the 11 point scale as this was 'the largest difference that can be judged as being clinically acceptable'. No further rationale for this choice was provided.

Of the 560 patients who were enrolled and randomised, 372 patients completed the study, with the buprenorphine patch patients disproportionately represented amongst the discontinuations. Of the patients randomised to the buprenorphine patch, 117 out of 284 (42.5%) withdrew, 97 out of 117 due to AEs and 8 out of 117 due to lack of efficacy. Of the 275 patients randomised to tramadol, 71 out of 275 (25.7%) withdrew with 51 out of 71 due to AEs and 14 out of 71 due to lack of efficacy.

There was no major difference in the baseline mean average pain on the 11 point NRS in the FA data set between the two treatment groups (6.99 ± 1.44 points in buprenorphine group and
7.02 ± 1.55 points in the tramadol group). The mean pain reduction from Day 2 to 28 was 2.00 ± 2.06 points for buprenorphine and 2.06 ± 2.03 points for tramadol.

The 95% CI for the difference of means in the PP data set and the FAS was within the predefined therapeutic equivalence range. Therefore, the buprenorphine patch was statistically non inferior to prolonged release tramadol. Statistical significant superiority of the 20 mg buprenorphine patch compared to tramadol could not be shown.

7.5.7. Other studies

7.5.7.1. Open follow-up studies

Two open follow-up studies were provided

7.5.7.1.1. PB-TTC-follow up

PB-TTC-follow up included patients from PB-TTC-01 for up to 6 months. Patients were treated with buprenorphine patches titrated to effect

- 307 patients entered the follow-up phase
- 145 completed the 6 months (49.5% withdrawal rate)
- 61% of withdrawals were due to AEs, 12% due to lack of efficacy
- After some titration in the first month, the patch dose strength remained unchanged for most patients for the rest of the study
- Analysis of the mean actual pain intensity, as rated twice daily by the patient using the 11 point NRS showed that there was a small decline in pain intensity of around 0.3 across the six months in both the ITT and PP populations. This change is too small to be clinically relevant but does suggest that any analgesic effect of the buprenorphine patch is sustained for up to six months.

7.5.7.1.2. WIS-BUP-LTS

WIS-BUP-LTS included patients from WIS-BUP01, WIS-BUP02 and WIS-BUP03. It was initially planned for 6 months but ended up continuing for up to 5 years in a small number of patients. Patients were treated with buprenorphine patches titrated to effect.

- 241 patients were enrolled but this number rapidly declined: 134 remained at 2 months, 37 at one year and 4 at 3 years. Mean duration of non-tumour patients was 6.5 months and tumour patients, 3.3 months
- Efficacy was determined by the patient’s retrograde assessment of pain relief on a 4 point VRS at the regular investigator appointments. 188 patients conformed to patch wearing requirements and were analysed: 42.7% had complete and good pain relief and 47.3% satisfactory pain relief
- The 37 patients who completed 12 months showed a constant level of efficacy without any indication of the development of tolerance.

Both follow-up studies had a rapid drop off in participants. However, those patients who remained in each study for 6 or 12 months appeared to experience reasonably constant analgesia without development of tolerance.

7.5.7.2. Post-marketing studies

Nine post-marketing surveillance studies were provided, with study duration of 6 to 8 weeks in general, although some continued for up to 12 months. Two studies provided a comparator: prolonged release tramadol in the six month Study BUP4202 and fentanyl patch in the 12 month Study PMS Transtec versus Durogesic cohort study. In one Study, AWB Transtec Pro 2005/2, the buprenorphine patch was worn for 96 hours. In all of the studies, patients who were to be
commenced on buprenorphine patches for the management of moderate to severe tumour or non-tumour pain were recruited from general practice clinics, specialty clinics, and hospital outpatients. Prescription and dosing were to be in accordance with the SPC. Large numbers (in the 1,000’s) were recruited to most of these studies. Discontinuation rates ranged from 18 to 46%.

These studies made varying assessments of efficacy.

- In AWB Transtec 2001/1, 13,179 patients were recruited and 25% discontinued. Immediately before starting the patch, 6% of all patients reported ‘good’ or ‘very good’ pain relief using a four point VRS. This increased to 71% of all patients at the first review after commencing the patch, with this persisting to the final study visit. The analysis of a further 2,077 patients from this study was reported in PM Transtec 2001/2; the efficacy result was similar to the main group.

- In AWB Transtec 2003, 3,644 patients were recruited and 23.5% discontinued during the 10 week study. The efficacy analysis of 3,340 patients found that pain relief, using a four point VRS, was ‘very good’ or ‘good’ in 2,941 (88.1%) patients at the end of the study.

- In AWB Transteconco2003, 412 patients with cancer related pain were enrolled. The efficacy analysis of 361 of these patients found that pain relief on a 4 point VRS was assessed as ‘good’ or ‘very good’ by 8 out of 361 patients prior to enrolment with this increasing to 238 out of 361 patients at the end of the 8 week study.

- In Study AWB Transtec Pro 2005/2, a subset of 256 patients who had previously been taking morphine or fentanyl was analysed. Using an 11 point scale for pain intensity and evaluation after 20 days of buprenorphine patch wearing, it was found that 248 of 256 patients (97%) achieved pain intensity that was equal to or better than pain intensity prior to buprenorphine patch.

- In Gru-BUP 2002/01, 1,223 patients were recruited and 535 (44%) did not complete the 3 month study. The proportion of patients who experienced good to very good pain relief increased significantly from 3.57% at baseline to 70.55% at one month and to 85.82% after 3 months of treatment with the patch.

- The Study TTC-MATRIX-AWB-2003 recruited 10,810 patients of whom 2,881 (26.7%) discontinued buprenorphine patches during the 6 week study. Baseline mean pain intensity, as measured with an 11 point Numeric Rating Scale (NRS), was 6.6. At Visit 2 this had decreased to 3.7 and at Visit 3, after an average of 6 weeks follow-up the pain intensity was 2.6 (p < 0.0001).

- The Study BIOC 110304, enrolled 1,648 patients and 82.8% of patients reported excellent or good pain reduction at the end of the 9 to 10 week period.

### 7.5.7.3. Dose dependent response

WIS-BUP01 and WIS-BUP02 compared the three patch strengths. Inconsistent results were found across the two studies such that dose dependent responses cannot be established. For example, all patch strengths in WIS-BUP01 had a reduction of 0.6 mg in the amount of sublingual buprenorphine in the randomised phase compared to the run-in phase; plotting of the mean pain intensity scores across 15 days in WIS-BUP02 showed no clear separation in the scores of the doses at all of the time points; however, the overall proportion of patients in WIS-BUP02 with ‘no’ or ‘mild’ pain increased in a dose dependent fashion: placebo patch: 40.3%; 20 mg patch: 47.3%; 30 mg patch: 58.7% and 40 mg patch: 62.2%.

### 7.5.7.4. Proposed maximum dose

The draft PI proposes a maximum dose of two 40 mg patches worn simultaneously. This dose was not tested in any of the efficacy studies and its use was only rarely described in the post-
marketing surveillance studies (134 patients of 33673 patients). There is insufficient evidence to support the proposed maximum dose and there would appear to be little clinical need for it.

7.5.7.5. Special populations

Children, pregnant or lactating women and patients with severe hepatic impairment were excluded from the efficacy studies. Patients with renal impairment and other major organ disease were excluded from most of the clinical efficacy studies. The draft PI advises against use in these groups, except for patients with renal impairment.

7.5.7.6. Opioid naïve

The efficacy studies predominately enrolled patients who had previously taken opioids. The most common reason for patient withdrawals in most of these studies was AEs typical to opioids. Analysis in some studies, such as PB-TTC-01, showed that withdrawal due to AEs was more common in opioid naïve patients. It was not uncommon for the post-marketing surveillance studies to describe the use of doses smaller than the 20 mg patch (545 of 33,673 patients), with these delivered by cutting the patch into smaller pieces, despite advice in the SmPC that this should not be done. These two factors would seem to indicate that this formulation of buprenorphine patch may be 'too strong' for opioid naïve patients. In support of this, the Therapeutic Guidelines: Analgesic recommend a buprenorphine patch starting dose of 5 µg/h; this dose can be delivered using one of the lower strength patches available in the 7 day Norspan version.

7.5.8. Summary

The dossier does not provide sufficient evidence to convincingly establish efficacy of the buprenorphine patch in the management of moderate to severe chronic pain. The pivotal studies did not establish superiority over placebo for the pre-specified primary efficacy outcome measures. The wide confidence intervals seen in the results for the primary outcome variable for the three studies, and the pooled analysis, suggest that they were underpowered to show a response. The studies did show some efficacy for the secondary measures, but this was not consistent across the patch strengths. The guideline that was developed by the European Medicines Agency, and adopted by the TGA in 2005, expresses the opinion that: 'In pivotal clinical trials where pre-defined primary variable analysis has failed to demonstrate efficacy, favourable results on secondary variables will not be enough to grant a marketing authorisation'. This guideline was adopted some 8 years after these studies were performed but it is appropriate that the studies be judged according to current regulatory standards.

The supportive studies were suggestive of efficacy but only in select groups and the results must be interpreted with caution. In the placebo controlled withdrawal study, the highest strength patch did appear to be superior to placebo in patients with severe cancer related pain but the study design was such that there is the strong possibility of enrichment bias with non-responders not entering the withdrawal phase. The two active controlled studies suggest that the buprenorphine patch was non inferior to the WHO Level II opioid, tramadol, but interpretation of both of these studies is difficult due to high withdrawal rates with the buprenorphine group disproportionately affected. The patients receiving buprenorphine had a much higher incidence of AES resulting in early discontinuation compared to the patients receiving prolonged release tramadol. This suggests that the buprenorphine patch may be non-inferior in efficacy to a Level 2 analgesic but is considerably worse with regard to tolerability.

The post hoc pooled analysis of the three conventional placebo controlled studies showed efficacy using the separate analyses of pain intensity and use of rescue medication but not for these two measures combined. There were also inconsistencies across patch strengths. The open studies were also limited by high withdrawal rates but suggest that, in those patients who found the buprenorphine patch efficacious, this effect could continue for some months without development of tolerance.
Of note is that the dossier submitted for the related product Norspan also had difficulties in establishing efficacy in its initial evaluation. In this case, review of the dossier through the appeal process, led to two of the pivotal studies being categorised as ‘failed’ rather than ‘negative’ and considerable weight was placed on supportive studies to establish efficacy.3

7.5.9. Conclusion
The buprenorphine patch may be efficacious but this has not been satisfactorily established by the dossier for the proposed indication.

8. Clinical safety
Comment: Safety was inadequately discussed in the clinical overview and summary of clinical safety. The clinical overview is dated 2014 but does not appear to have been substantially updated; the most recent reference cited is from 2005. The summary of clinical safety is dated 2005 and has not been updated; the most recent PSUR referred to was from 2005. The dossier relies on the reputation of buprenorphine as being safe by other routes of administration for many of the aspects of clinical safety but does not provide a review and summary of the relevant literature in the clinical overview to support this.

The risk management plan (RMP) is dated 2014 and includes significant cardiovascular risks that are not referred to in the clinical overview and the summary of clinical safety. It refers to articles more recent than 2005 that address hepatotoxicity, cardiovascular effects, immune system effects, exposure during pregnancy, skin hypersensitivity reactions, use in elderly and young, use in paediatric patients, use in patients with liver impairment, abuse and dependence potential, potential for medication errors, off-label use (depression and restless legs syndrome), use in post-operative pain, and reversal of respiratory depression by naloxone that are not discussed in the clinical overview. These recent references were not provided in the dossier. The RMP also refers to [information redacted] sponsored studies that are not discussed elsewhere.

The information below was extracted independently from the dossier using available materials unless otherwise specified.

8.1. Studies providing evaluable safety data
The following studies provided evaluable safety data:

Efficacy studies:
- Placebo controlled, WIS-BUP01, WIS-BUP02 and WIS-BUP03
- Placebo controlled withdrawal PB-TTC-02
- Non inferiority studies PB-TTC-01 and BUP4201.

Follow-up studies:
- WIS-BUP-LTS (Follow-up study for WIS-BUP01, WIS-BUP02 and WIS-BUP03)
- PB-TTC-01 Follow-Up (Follow-up study for PB-TTC-01)

Note: The descriptions of the follow-up studies are included immediately following the relevant controlled studies in the sections below. Each follow-up study used the same methods for collecting and categorising AEs as the parent study.
• Ten non interventional post-marketing surveillance studies (from the years 2000 to 2005). Two of these studies had comparator arms (tramadol, fentanyl patch).
Periodic Safety Update Reports (PSURs) covering the years 2000 to 2013 were also provided.

8.1.1. Placebo controlled efficacy studies

8.1.1.1. WIS-BUP01, WIS-BUP02 and WIS-BUP03 (duration 14 to 15 days)
The three placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 all collected the following safety data:
• General adverse events (AEs): assessed by self-reporting by the patient in the patient’s diary that was kept throughout the study and through a general question by the investigator to the patient at the regular appointments ‘On the previous days of treatment has anything special struck you?’ The investigator was to document the nature and intensity of the adverse events, time of onset, duration, its relation to the study medication and the feasible countermeasures in the case report form (CRF)
• Skin status: assessed by the investigator at each patch change and categorised as presence of swelling, erythema, pruritus, signs of infection, other (all as yes/no items). Skin abnormalities were also differentiated by at patch or not. Relevant skin reactions were recorded as adverse events and were documented in the CRF with nature, intensity and relation to the study medication as were skin reactions reported by the patient
• Laboratory tests not done
• Vital signs (WIS-BUP02 only) including heart rate, blood pressure and respiratory rate.

Breakthrough pain was managed with sublingual buprenorphine throughout the studies in all treatment groups. Both WIS-BUP01 and WIS-BUP03 had a run-in phase during which patients were managed with regular and as needed sublingual buprenorphine tablets. Patients who did not progress to the double blind phase, and so were not exposed to buprenorphine patches, were included in the safety population but analysed separately.

8.1.1.2. PB-TTC-02 (duration 30 days)
Safety data collected was:
• Adverse events; adverse events were monitored continuously, or asked about at each visit. The occurrence of all adverse events was documented in the case report form
• Vital signs; pulse rate, supine blood pressure, respiratory rate were taken at enrolment, regular intervals during the study, at the final examination and at the follow-up visit
• Physical examination; performed at enrolment and at the final examination.

PB-TTC-02 was a withdrawal study, with all patients in the run-in phase managed with buprenorphine patches. Patients from the run-in phase who did not progress to the double blind phase were included in the safety population. No data were available for 3 patients (2 in the run-in period and 1 in the placebo group of the double blind period).

8.1.2. Active controlled efficacy studies
Both studies used prolonged release tramadol as the comparator.

8.1.2.1. BUP4201 (Duration up to 49 days)
Safety data collected was:
• General AEs; at each visit after study entry, the investigator checked for any new symptoms and any deterioration in existing conditions as possible AEs. The investigator recorded any volunteered AEs in the patient’s CRF with a description of the AE(s) including intensity (that
is mild, moderate or severe), action taken and assigned causality (that is not related, improbable, possible, probable or definite)

- Extent of exposure; this was defined as the length of time between the first and last dose of study medication (including down titration) and was calculated for each patient.

**8.1.2.2. PB-TTC-01 (Duration 28 days)**

Safety data collected at the monthly investigator appointments were:

- General AEs. Definition and categories of AEs are provided in the study report but no description as to how they should be elicited
- Constipation through specific questioning by the investigator
- Skin site assessment by the investigator for erythema, oedema, urticarial, blistering. The patient was questioned about any itching, burning, paraesthesia and numbness at current or previous patch sites. Abnormalities were recorded in the CRF.

**8.1.3. Open follow-up studies**

**8.1.3.1. WIS-BUP-LTS (duration up to 5 years, small numbers only after 6 months)**

Safety data were collected at regular investigator appointments as for WIS-BUP01, WIS-BUP02 and WIS-BUP03:

- General adverse events (AEs): as volunteered by the patients and through a general question by the investigator to the patient at the regular appointments 'On the previous days of treatment has anything special struck you?' Any AEs and their description were documented in the CRF
- Skin status: assessed by the investigator at each patch change and categorised as presence of swelling, erythema, pruritus, signs of infection, other (all as yes/no items). Skin abnormalities were also differentiated by at patch or not. Relevant skin reactions were recorded as adverse events and were documented in the CRF with nature, intensity and relation to the study medication as were skin reactions reported by the patient.

**8.1.3.2. PB-TTC-O1 follow up (duration up to 6 months)**

Safety data were collected at the monthly investigator appointments as for PB-TTC-01:

- General AEs. Definition and categories of AEs are provided in the study report but no description as to how they should be elicited
- Constipation through specific questioning by the investigator and recorded in the CRF
- Skin site assessment by the investigator for; erythema, oedema, urticarial, blistering. The patient was questioned about any itching, burning, paraesthesia and numbness at current or previous patch sites. Abnormalities were recorded in the CRF.

**8.1.4. Post-marketing surveillance studies**

**Comment:** All of the post marketing studies that were provided in the dossier are described and discussed below. Not all of the provided post marketing studies were discussed in the clinical overview or summary of clinical safety. The letter of application states: ‘the following 4 post-marketing studies are not referred to in the clinical overview as they do not describe the efficacy and safety of the product and are included for historical reference only: WIS-BUP-FU, AWB Transtec 2003/3, AWB Transtec ONCO 2003/2 and AWB Transtec Pro 2005/2’. These studies are included below given that useful safety data may be obtained, if only from reports of deaths and SAEs and given that only AWB Transtec Pro 2005/2 includes the proposed 96 hour application time.
Of note is that the most recent post marketing surveillance study included in the dossier is from 2005, and the most recent one discussed in the clinical overview and summary of clinical safety is from 2003. It is apparent from the PSURs, under the listings of ‘newly analysed studies’ and ‘published safety studies’, that a considerable number of more recent post-marketing studies have been performed (up to 9 since 2007). These may have provided further insights into the safety of the product, particularly with regards to some sub-groups and 96 hour application time, but were not included in the clinical dossier and, therefore, were not evaluable.

Table 41: Post-marketing surveillance studies

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Duration</th>
<th>Safety Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWB Transtec 2001/1</td>
<td>Up to 10 weeks</td>
<td>ADRs</td>
</tr>
<tr>
<td>PM Transtec 2001/2</td>
<td>Up to 10 weeks</td>
<td>ADRs</td>
</tr>
<tr>
<td>AWB Transtec 2003/2</td>
<td>10 weeks, 6 months</td>
<td>AEs, ADRs</td>
</tr>
<tr>
<td>AWB Transteconco2003/01</td>
<td>Up to 8 weeks</td>
<td>ADRs</td>
</tr>
<tr>
<td>GRU-BUP-2002-01</td>
<td>12 weeks</td>
<td>AEs</td>
</tr>
<tr>
<td>BIROC/11/03/04</td>
<td>10 weeks</td>
<td>AEs, Global evaluation of tolerability</td>
</tr>
<tr>
<td>TTC-MATRIX-AWB-2003</td>
<td>6 weeks</td>
<td>AEs, Patient satisfaction</td>
</tr>
<tr>
<td>AWB Transtec Pro 2005/2</td>
<td>Up to 8 weeks</td>
<td>ADRs</td>
</tr>
<tr>
<td>(subset analysis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP4202</td>
<td>Up to six months</td>
<td>AEs</td>
</tr>
<tr>
<td>PMS Transtec versus Durogesic</td>
<td>Up to 12 months</td>
<td>AEs</td>
</tr>
<tr>
<td>Cohort Study</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

8.2. Pivotal studies that assessed safety as a primary outcome

Not applicable.

8.2.1.1. Other studies evaluable for safety only

Not applicable.

8.2.1.2. Clinical pharmacokinetic studies

Study HP5303/01, HP5303/02 and HP5303/04 were performed in healthy volunteers who received buprenorphine patches for 3 to 9 days. The three studies collected the same safety data in the same ways: AEs, physical examination, ECG, laboratory variables (haematology, biochemistry), skin reactions and vital signs.

8.3. Patient exposure

The details of patient exposure as described in the available studies are provided in the tables below. In the open studies, the dose was titrated to the patient’s needs: an individual patient may have the dose increased and/or decreased during the study. Dose changes could be accomplished by using a different strength patch and/or using a combination of patches.
**Table 42. Exposure to buprenorphine patch in the clinical efficacy studies**

1 sublingual buprenorphine used as rescue medication for all treatment groups in the placebo controlled studies; dummy patch used for all placebo groups. 2 all patients were exposed to buprenorphine patch during the run-in phase. 3 one patient from each group was excluded from all analyses (2) as their data could not be confirmed and one patients in each group was excluded from the safety population (2) as neither received any study drug. 4 2 patients were lost to follow-up before the first review 5 dummy patch worn by control group.

**Table 43: Exposure to Buprenorphine patch in the post-marketing surveillance studies**

<table>
<thead>
<tr>
<th>Study type/ Study identification/type Indication</th>
<th>Controlled studies</th>
<th>Comparator studies</th>
<th>Buprenorphine Patch (any strength)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Marketing Surveillance Studies1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No comparator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transtec 2001/1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PM Transtec 2001/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transtec 2003/2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transteconco 2003/01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GRU-BUP-2002-01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIOC/11/03/04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTC-MATRIX-AWB-2003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWB Transtec Pro 2005/2 (subset analysis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUP4202</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS Transtec versus Durogesic Cohort Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub Total</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Dose titrated to clinical effect
Table 44: Exposure to buprenorphine patch in the pharmacokinetic studies

<table>
<thead>
<tr>
<th>Study type/Indication</th>
<th>Total Buprenorphine Patch (any strength)</th>
<th>Buprenorphine Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td>Clinical Pharmacokinetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HP5303/01 (crossover)</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>HP5303/02</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>HP5303/04</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>68</td>
</tr>
</tbody>
</table>

Table 45: Total exposure to buprenorphine patch all studies

<table>
<thead>
<tr>
<th>Study type</th>
<th>Total Buprenorphine Patch (any strength)</th>
<th>Buprenorphine Patch</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 mg</td>
</tr>
<tr>
<td>Clinical Efficacy (pain)</td>
<td></td>
<td>452</td>
</tr>
<tr>
<td>Clinical Pharmacokinetic</td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-Marketing Surveillance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>526</td>
</tr>
</tbody>
</table>

Special populations (children, pregnant or breast feeding women, major hepatic or renal impairment) were not included in the clinical trial development program for the buprenorphine patch. Patients with respiratory disease or convulsive disorders were also excluded. Elderly patients were included.

8.3.1. Exposure duration and exposure to the proposed maximum dose (2 x 40 mg patches)

The controlled clinical studies all had a relatively short duration given that long-term therapy with the buprenorphine patch may be required in the management of chronic pain, particularly of non-cancer origin. In the follow-up study, WIS-BUP-LTS, 18 patients participated for up to 2 years and 6 patients were observed for up to 5 years. The longest period of observation in the post-marketing surveillance studies was up to 12 months.

No patients in the clinical trial program were exposed to the proposed maximum dose of 2 x 40 mg patches (140 µg/h). The post marketing surveillance studies describe the use of multiple
patches in some patients. The exact number who used 2 x 40 mg patches (dose 140 µg/h) was unable to be determined as dose description in the studies was provided as a dose range only (> 70 µg/h and ≤ 140 µg/h). The number of patients receiving a dose within this range was 131/33,673 (0.4%) and only 2 patients received this dose for longer than 6 months. In addition, two patients were described as receiving a dose of 175 µg/h and one was described as receiving a dose of 200 µg/h for one month. A larger number of patients (545) were reported to have used a dose smaller than the proposed minimum of 20 mg (35 µg/h); this can only be delivered by cutting the 20 mg patch into smaller pieces.

The Table 46 describes exposure to the buprenorphine patch by the target population. The clinical pharmacology studies are not included; exposure in these studies was of 109 healthy subjects for 9 to 15 days with none of them receiving the proposed maximum dose.

**Table 46. Exposure to buprenorphine patch in clinical studies according to dose and duration**

<table>
<thead>
<tr>
<th>Study type/ Indication ; Pain</th>
<th>Proposed dose range</th>
<th>Proposed maximum dose (available only as the dose range 71 to 140 µg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 3 m</td>
<td>≥ 3 m</td>
</tr>
<tr>
<td>Placebo-controlled</td>
<td>612</td>
<td>0</td>
</tr>
<tr>
<td>Active-controlled</td>
<td>441</td>
<td>0</td>
</tr>
<tr>
<td>Open follow up studies</td>
<td>443</td>
<td>240</td>
</tr>
<tr>
<td>Post-marketing surveillance studies1</td>
<td>33,538</td>
<td>1,531</td>
</tr>
<tr>
<td>TOTAL</td>
<td>35,034</td>
<td>1,771</td>
</tr>
</tbody>
</table>

1 Includes 2 patients receiving 175 µg/h and one who received a dose of 200 µg/h for one month.

**Comment:** The Risk Management Plan (RMP) states that 48 patients have been exposed to a 17.5 µg/h patch during the clinical development programme (no such study was included in the submission) and that 52 patients have been exposed for more than one year in the trial programme to 2014 (this does not match the number above taken from other documents). This would suggest that some of the information in the RMP is based on trials that have not been included in the submission.

**8.4. Adverse events**

**8.4.1. All adverse events (irrespective of relationship to study treatment)**

**8.4.1.1. Adverse events: placebo controlled efficacy studies (and open follow-up phases)**

Interpretation of AEs in the placebo controlled studies is made difficult by the use of sublingual buprenorphine tablets for breakthrough pain in all phases of the studies and in all treatment groups. Analysis of the plasma buprenorphine levels in a small number of patients in the pharmacokinetic arm of WIS-BUP02 showed that plasma buprenorphine levels in the placebo group were not dissimilar to those achieved in the active patch groups.
8.4.1.1.1. **WIS-BUP01, WIS-BUP02 and WIS-BUP03 adverse events**

AEs from the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 are presented pooled as the studies used the same means to collect AEs, the same coding dictionary was used and the studies were conducted for similar periods of time (9 to 15 days). Sublingual buprenorphine was used in all three studies as rescue medication for all treatment groups: placebo patients had exposure to buprenorphine, although not in the transdermal formulation. Dummy patches were worn by the placebo group so that all groups were exposed to the matrix and adhesive. AEs were common in all groups as shown in Table 47 below.

Table 47: Most frequent AEs in WIS-BUP01, WIS-BUP02 and WIS-BUP03

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=122)</th>
<th>BUP-TDP 35 (n=166)</th>
<th>BUP-TDP 52.5 (n=82)</th>
<th>BUP-TDP 70 (n=75)</th>
<th>Any BUP-TDP (n=323)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>46</td>
<td>37.7</td>
<td>63</td>
<td>38.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Central nervous syst.</td>
<td>28</td>
<td>23.0</td>
<td>38</td>
<td>22.9</td>
<td>34.1</td>
</tr>
<tr>
<td>- Nausea</td>
<td>13</td>
<td>10.7</td>
<td>16.3</td>
<td>15.8</td>
<td>16.3</td>
</tr>
<tr>
<td>- Dizziness</td>
<td>6</td>
<td>4.9</td>
<td>10</td>
<td>6.0</td>
<td>4.9</td>
</tr>
<tr>
<td>- Tiredness</td>
<td>3</td>
<td>2.5</td>
<td>5</td>
<td>3.0</td>
<td>7.2</td>
</tr>
<tr>
<td>- Headache</td>
<td>1</td>
<td>0.8</td>
<td>1</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>- Gastrointestinal tract</td>
<td>15</td>
<td>12.3</td>
<td>15</td>
<td>9.0</td>
<td>16.9</td>
</tr>
<tr>
<td>- Constipation</td>
<td>5</td>
<td>4.1</td>
<td>9</td>
<td>5.4</td>
<td>4.1</td>
</tr>
<tr>
<td>- Body as a whole</td>
<td>10</td>
<td>8.2</td>
<td>12</td>
<td>7.2</td>
<td>14.6</td>
</tr>
<tr>
<td>- Diaphoresis</td>
<td>3</td>
<td>2.5</td>
<td>5</td>
<td>3.0</td>
<td>6.7</td>
</tr>
<tr>
<td>- Oedema legs</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.6</td>
<td>2.4</td>
</tr>
<tr>
<td>- Pruritus</td>
<td>4</td>
<td>3.3</td>
<td>4</td>
<td>2.4</td>
<td>2</td>
</tr>
<tr>
<td>- Urinary tract</td>
<td>5</td>
<td>4.1</td>
<td>8</td>
<td>4.8</td>
<td>1.2</td>
</tr>
<tr>
<td>- Respiratory tract</td>
<td>3</td>
<td>2.5</td>
<td>2</td>
<td>1.2</td>
<td>3.7</td>
</tr>
<tr>
<td>- Dyspnoea</td>
<td>3</td>
<td>2.5</td>
<td>1</td>
<td>0.6</td>
<td>3.7</td>
</tr>
</tbody>
</table>

*All AEs that occurred in at least 5 patients in the pooled buprenorphine transdermal patch group.*

Occurrence and type of AEs in the placebo group is not dissimilar to the treatment groups, although the frequency is less for some AEs. Note that as all patients were exposed to buprenorphine as sublingual tablet ± patch, an estimate of ADRs due to exposure to the buprenorphine patch cannot be readily determined.

In WIS-BUP01, 2 patches were worn sequentially, in WIS-BUP03, 3 patches were worn and in WIS-BUP02, 5 patches were worn sequentially. Comparison between studies shows a higher incidence of opioid type reactions, in particular nausea, in WIS-BUP02 compared to WIS-BUP01 and WIS-BUP03 (30.3% compared to 7% and 11% respectively). The incidence of nausea in the placebo group of WIS-BUP02 was 28.9%; this may reflect the high consumption of SL buprenorphine as rescue medication in the placebo group of this study.

8.4.1.1.2. **WIS-BUP01, WIS-BUP02 and WIS-BUP03 application site reactions**

Overall, skin reactions at the application site were observed in approximately 30% of patients, with local erythema and pruritus most commonly reported. The symptoms were mild to moderate and usually lasted less than 24 hours. Similar patch site reactions were seen in the placebo group; this group also wore a matrix patch that did not contain the active compound. The incidence for some reactions was greater in the buprenorphine patch group for example pruritus and erythema in WIS-BUP03 was seen in 28.9% of buprenorphine patch patients and 23.4% of the placebo group, erythema in WIS-BUP02 occurred at the patch site for around 30%
of the buprenorphine group and 18% of the placebo group. There was no evidence of any severe skin damage caused by the patch in any of these studies.

8.4.1.2. **WIS-BUP-LTS**

This was the follow up study for the placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03. Follow-up was initially planned for 10 weeks but, through a succession of extensions, some patients continued in the study for over 5 years. Collection of and definition of AEs (at patch site or not) was the same as in the placebo controlled studies. Adverse events, irrespective of their relationship to the study medication and location, occurred in 67.8% of all patients. Of these AEs, most 113 (47.4%) were not at the patch site, 23 (9.6%) at the patch site, 26 (10.9%) at both and the remainder reported no AE (32.2%).

**Table 48: WIS-BUP-LTS most common AEs (not at patch site)**

<table>
<thead>
<tr>
<th>WIS-BUP-LTS</th>
<th>buprenorphine patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>MedDRA SOC*</td>
<td>No</td>
</tr>
<tr>
<td>Total Number of enrolled patients</td>
<td>239  100</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>30  12.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15  6.3</td>
</tr>
<tr>
<td>Constipation</td>
<td>9  3.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7  2.9</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>16  6.7</td>
</tr>
<tr>
<td>Headache</td>
<td>6  2.5</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>6  2.5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11  4.6</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>9  3.8</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td>5  2.1</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>15  6.3</td>
</tr>
</tbody>
</table>

* terms used in study report approximated to MedDRA terms ** All terms with at least 5 occurrences.
The most frequently observed skin reactions at patch site were erythema (12.6%), pruritus (10.5%) and exanthema (8.8%). In three patients localised swelling occurred (1.3%) and in another three patients, local allergic reactions (1.3%) occurred. Other symptoms, such as skin discoloration (one tumour and one non-tumour patient), skin inflammation (one non-tumour patient), and infection (one non-tumour patient), burning skin (one non-tumour patient) and skin atrophy (one non-tumour patient) were reported only in isolated cases. A total of 49 out of 239 patients experienced local reactions; 23 of these patients terminated the long-term study as their skin reactions were described as deteriorating following multiple patch application over a period of 25 to 1,114 days.

8.4.1.3. \textit{PB-TTC 02}

In the run-in phase of this withdrawal study, all patients were treated with buprenorphine patches (40 mg patch strength). Sublingual buprenorphine tablets were used for breakthrough pain during both phases and in all treatment groups. AEs were common in the run-in phase with 139 of 289 patients (48.1%) experiencing a total of 292 adverse events (AEs). The most frequent AEs were consistent with known side effects of opioids and included nausea (12.5%), vomiting (9.3%), constipation (8.7%) and dizziness (4.8%). Of the 289 patients in the run-in phase, 189 continued in the double blind withdrawal phase. Of the 100 who did not continue, 21 withdrew due to AEs, 8 due to death, 36 due to inadequate pain control and the rest for other reasons. During the double blind phase, 29 of 94 patients (30.9%) on buprenorphine and 24 of 95 patients (25.3%) on placebo experienced adverse events.
Table 49: Study PB-TTC-02 most frequent AEs (BUP TDP 70 = 40 mg patch, 70 µg/h)

<table>
<thead>
<tr>
<th>MedDRA SOC / PT</th>
<th>Run-in (%)</th>
<th>Double-blind (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>289 (100)</td>
<td>95 (100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>34 (12.5)</td>
<td>7 (7.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (9.3)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Constipation</td>
<td>25 (8.7)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>6 (2.1)</td>
<td>0</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>2 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (0.7)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>31 (10.7)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8 (2.9)</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>29 (10.0)</td>
<td>6 (6.3)</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>9 (3.1)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7 (2.4)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>6 (2.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4 (1.4)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>14 (4.8)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>16 (5.5)</td>
<td>4 (4.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (1.7)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Confusional state</td>
<td>4 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>3 (1.0)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>8 (2.8)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>3 (1.0)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Reproductive system and breast disorders</td>
<td>0</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Female genital-digestive tract fistula</td>
<td>0</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and unspecified</td>
<td>14 (4.8)</td>
<td>2 (2.1)</td>
</tr>
<tr>
<td>Metastasis to bone</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>8 (2.8)</td>
<td>3 (3.2)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>8 (2.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>8 (2.8)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>6 (2.1)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (1.0)</td>
<td>0</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>5 (1.7)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>5 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>4 (1.4)</td>
<td>0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td>5 (1.7)</td>
<td>1 (1.1)</td>
</tr>
</tbody>
</table>

The frequency of gastrointestinal AEs was reduced in the double blind phase for both the placebo and the buprenorphine group; this may indicate some adjustment to the use of opioids or the use of anti-emetics and laxatives. There were small differences only between the treatment groups in the double blind phase. There was no evidence for an effect of the buprenorphine patch on vital signs. Haematology and clinical laboratory data were not collected.

8.4.2. Adverse events: active controlled studies (and open follow-up phase)

8.4.2.1. PB-TTC-01 together with open follow up study

This study compared the use of buprenorphine patch and prolonged release tramadol in the management of chronic non-cancer pain with an initial blinded phase followed by an open
phase. As the blinded phase had a double dummy design, all patients were exposed to a matrix bearing patch (no active component in tramadol group). All patients in the open phase were treated with the buprenorphine patch; 171 of 307 patients had not been exposed to it in the blinded phase.

Altogether 1,906 adverse drug reactions were experienced by 456 patients (81% of all patients) during the blinded phase. 236 patients in the buprenorphine 20 mg (35 µg/h) patch group had 1,034 adverse drug reactions (total number of adverse events = 1,105) and 220 patients in the tramadol group had 872 adverse drug reactions (total number of adverse events = 936).

During the open phase of the study, when patients could chose to continue with, or commence on, the buprenorphine patch, 1,265 adverse events were experienced by 82.0% of patients (n = 251). Most of the adverse events in both phases were reported as being either mild or moderate (Blinded phase - buprenorphine group: 87.1%; tramadol group: 93.2%. Open phase; buprenorphine group: 88.9%). The AEs are shown in the table below.

**Table 50: PB-TTC-01 AEs; blinded and follow-up phases**

<table>
<thead>
<tr>
<th>PB-TTC-01</th>
<th>BUP patch</th>
<th>Tramadol SR</th>
<th>BUP patch, open phase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>%</td>
<td>No</td>
<td>%</td>
</tr>
<tr>
<td>MedDRA SOC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Number of coded symptoms (PT)</td>
<td>1,064</td>
<td>893</td>
<td>1,098</td>
<td>3,055</td>
</tr>
<tr>
<td>Total Number of enrolled patients</td>
<td>284</td>
<td>100</td>
<td>276</td>
<td>100</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>132</td>
<td>46.5</td>
<td>74</td>
<td>26.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>96</td>
<td>33.8</td>
<td>44</td>
<td>15.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>87</td>
<td>30.6</td>
<td>81</td>
<td>29.3</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>11</td>
<td>3.9</td>
<td>8</td>
<td>2.9</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>1</td>
<td>0.4</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2</td>
<td>0.7</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorder</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>9</td>
<td>3.2</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>56</td>
<td>19.7</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>Somnolence</td>
<td>32</td>
<td>11.3</td>
<td>21</td>
<td>7.6</td>
</tr>
</tbody>
</table>
The most common AEs were in keeping with those expected from the side effects of opioids; nausea and vomiting, dizziness and constipation. Nausea and vomiting was more common in patients using the buprenorphine patch compared to the tramadol group (80.3% compared to 42.7% respectively).

Reactions at the application site were common (up to 30%) in both the active patch and the placebo patch (worn by the tramadol group). The abnormal sensations of itching and burning at

<table>
<thead>
<tr>
<th>PB-TTC-01</th>
<th>BUP patch</th>
<th>Tramadol SR</th>
<th>BUP patch, open phase</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>20</td>
<td>7</td>
<td>16</td>
<td>5.8</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td>6</td>
<td>2.1</td>
<td>5</td>
<td>1.8</td>
</tr>
<tr>
<td>Sedation</td>
<td>12</td>
<td>4.2</td>
<td>6</td>
<td>2.2</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>7</td>
<td>2.5</td>
<td>1</td>
<td>0.4</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site erythema</td>
<td>65</td>
<td>22.9</td>
<td>85</td>
<td>30.8</td>
</tr>
<tr>
<td>Application site pruritus</td>
<td>86</td>
<td>30.3</td>
<td>104</td>
<td>37.7</td>
</tr>
<tr>
<td>Application site urticaria</td>
<td>32</td>
<td>11.3</td>
<td>38</td>
<td>13.8</td>
</tr>
<tr>
<td>Application site vesicles</td>
<td>16</td>
<td>5.6</td>
<td>20</td>
<td>7.2</td>
</tr>
<tr>
<td>Application site anaesthesia/paraesthesia</td>
<td>13</td>
<td>4.6</td>
<td>12</td>
<td>4.4</td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>2</td>
<td>0.7</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>6</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disorder/insomnia</td>
<td>11</td>
<td>3.9</td>
<td>8</td>
<td>2.9</td>
</tr>
<tr>
<td>Anxiety</td>
<td>4</td>
<td>1.4</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised pruritus</td>
<td>2</td>
<td>0.7</td>
<td>6</td>
<td>2.2</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>14</td>
<td>4.9</td>
<td>18</td>
<td>6.5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia, decreased appetite</td>
<td>15</td>
<td>5.3</td>
<td>5</td>
<td>1.8</td>
</tr>
</tbody>
</table>

* All terms with > 10 coded symptoms (PT)
the skin site persisted throughout the follow-up phase, although paraesthesia and numbness declined with time.

**Table 51: PB-TTC 01 Uncontrolled phase; application site reactions**

<table>
<thead>
<tr>
<th></th>
<th>Month 2</th>
<th></th>
<th>Month 3</th>
<th></th>
<th>Month 4</th>
<th></th>
<th>Month 5</th>
<th></th>
<th>Month 6</th>
<th></th>
<th>Month 7</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
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<td>%</td>
<td>n</td>
<td>%</td>
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<td>%</td>
</tr>
<tr>
<td>Itching</td>
<td>20</td>
<td>12.0</td>
<td>19</td>
<td>13.9</td>
<td>26</td>
<td>21.1</td>
<td>24</td>
<td>21.4</td>
<td>25</td>
<td>23.8</td>
<td>31</td>
<td>20.5</td>
</tr>
<tr>
<td>Burning</td>
<td>4</td>
<td>2.4</td>
<td>5</td>
<td>3.6</td>
<td>7</td>
<td>5.7</td>
<td>6</td>
<td>5.4</td>
<td>10</td>
<td>9.5</td>
<td>12</td>
<td>7.9</td>
</tr>
<tr>
<td>Paraesthesia</td>
<td>3</td>
<td>1.8</td>
<td>1</td>
<td>0.7</td>
<td>1</td>
<td>0.8</td>
<td>1</td>
<td>0.9</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Numbness</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
<td>0.0</td>
<td>1</td>
<td>0.8</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>0.0</td>
<td>-</td>
<td>0.0</td>
</tr>
</tbody>
</table>

**8.4.2.2. ** **BUP4201**

During this study, in which buprenorphine patches or prolonged release tramadol were used to manage severe pain due to osteoarthritis, 149 patients (95%) in the buprenorphine transdermal patch group and 134 (88%) in the tramadol prolonged release group reported AEs. The most common AEs (those reported by ≥ 10% of patients in either treatment group) are shown in the table below.

**Table 52: BUP4201 Most common treatment emergent AEs (safety population)**

<table>
<thead>
<tr>
<th>AE</th>
<th>Number (%) of patients</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buprenorphine patch</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>(n = 157)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Tramadol prolonged</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>release tablets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 152)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Digestive</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>83 (53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>59 (38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>37 (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>52 (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>24 (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Body as a whole</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>27 (17)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>24 (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Skin and appendages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash at patch site</td>
<td>14 (9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus at patch site</td>
<td>13 (8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>25 (16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Chi-square test

Significantly more patients in the buprenorphine group reported nausea, vomiting, dizziness and asthenia. There were no statistically significant treatment differences in the numbers of patients reporting any of the other common treatment emergent AEs.

**8.4.3. ** **Adverse events: clinical pharmacology studies**

The incidences of AEs were higher in the clinical pharmacology studies, HP5303/01, HP5303/02 and HP5303/04, than in the conventional placebo controlled studies. It should be noted that most patients in the latter were opioid experienced, whereas the healthy subjects in the clinical pharmacology studies, were not.
Table 53: Clinical pharmacokinetic studies; most common AEs

<table>
<thead>
<tr>
<th>MedDRA SOC</th>
<th>HP5303 /01</th>
<th>HP5303 /02</th>
<th>HP5303 /04</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of enrolled patients</td>
<td>49</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Total Number of Symptoms</td>
<td>126</td>
<td>380</td>
<td>60</td>
</tr>
<tr>
<td>No %</td>
<td>No %</td>
<td>No %</td>
<td>No %</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>19.8</td>
<td>40</td>
</tr>
<tr>
<td>Vomiting</td>
<td>26</td>
<td>20.6</td>
<td>40</td>
</tr>
<tr>
<td>Constipation</td>
<td>39</td>
<td>10.3</td>
<td>7</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>7</td>
<td>5.6</td>
<td>6</td>
</tr>
<tr>
<td>Hiccup</td>
<td>16</td>
<td>4.2</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td></td>
<td>17</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Headache</td>
<td>23</td>
<td>18.3</td>
<td>34</td>
</tr>
<tr>
<td>Disturbance in attention</td>
<td></td>
<td></td>
<td>11</td>
</tr>
<tr>
<td>Muscle fasciculation</td>
<td></td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>18</td>
<td>14.3</td>
<td>34</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised pruritus</td>
<td>14</td>
<td>11.1</td>
<td>46</td>
</tr>
<tr>
<td>Hot flushes</td>
<td></td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5</td>
<td>4.0</td>
<td>10</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia, decreased appetite</td>
<td></td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retention</td>
<td>8</td>
<td>6.3</td>
<td></td>
</tr>
</tbody>
</table>
Terms used in study reports changed to equivalent MedDRA terms to facilitate comparison. Symptom occurrence > 5.

The late onset opioid type symptoms itching, constipation, and micturition disorder occurred more often in the multiple administration study HP5303/02 than in single dose study HP5303/01. Two further symptoms were recorded with a relatively high incidence in study HP5303/02: hiccup and muscle fasciculation. The incidences of these AEs were higher than those reported in the clinical studies. All of these AEs were interpreted as opioid type effects.

8.5. Adverse events: post-marketing surveillance studies

These studies mainly reported ADRs. Results are provided in the section below.

8.5.1. Treatment related adverse events (adverse drug reactions)

8.5.1.1. ADRs: placebo controlled studies

8.5.1.1.1. WIS-BUP01, WIS-BUP02 and WIS-BUP03

The type and number of AEs that were attributable to the buprenorphine patch could not be readily extracted from the study reports. The information was contained in multiple tables with a variety of breakdowns (tumour and non-tumour patients; run-in phase and double blind phase; patch strength; at patch site and not at patch site) spread over 100 pages or more in each study report. No summary tables were provided in the study reports or the summary of clinical safety. Review of the summary table of AEs that was provided (included above) shows that the most common AEs were consistent with mu-opioid receptor side effects.

8.5.1.1.2. WIS-BUP-LTS

Adverse events related to the study medication were mainly in the central nervous system category and reported in 16.3% of all patients. The most frequent symptoms in this group were nausea (9.2%), dizziness (4.6%) and tiredness (2.9%). Other symptoms, such as headache, loss of appetite, taste and smelling alteration, sleepiness, and visual disturbance only occurred in isolated cases. Gastrointestinal AEs assessed as related to the buprenorphine patch occurred in 8.4% with vomiting (4.2%) and constipation (3.8%) the most common of these. Amongst skin disorders related to the study medication but not at the patch site (4.6%), erythema (2.1%), pruritus (1.7%), and exanthema (1.3%) were most frequently reported. Diaphoresis was reported in 3.8% of the patients.

Patch site reactions were common. All of them except for one episode of erythema were attributed to the medication.

Table 54: WIS-BUP-LTS patch site ADRs

<table>
<thead>
<tr>
<th></th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Erythema</td>
<td>7</td>
<td>2.9</td>
<td>12</td>
<td>5.0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>2.1</td>
<td>10</td>
<td>4.2</td>
</tr>
<tr>
<td>Exanthema</td>
<td>7</td>
<td>2.9</td>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>Swelling non-inflammatory</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0.8</td>
</tr>
<tr>
<td>Skin discoloration</td>
<td>1</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin infection</td>
<td>1</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>1</td>
<td>0.4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin atrophy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Skin inflammation NOS</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Burning skin</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0.4</td>
</tr>
</tbody>
</table>

*All percentage related to all safety evaluable = 238 patients*
8.5.1.1.3. **PB-TTC-02**

In this withdrawal study, all patients were exposed to the buprenorphine patch during the run-in phase. During this phase, 139 out of 289 patients (48.1%) experienced a total of 292 adverse events. During the double blind withdrawal phase, 29 out of 94 patients (30.9%) on buprenorphine experienced 57 ADRs and 24 out of 95 patients (25.3%) on placebo experienced 45 ADRs. During the run-in period, 43.2% of AEs were assessed as having a possible/probable/definite relationship to the buprenorphine patch. During the double blind period, 35.1% in the buprenorphine group and 33.3% in the placebo group were classified as possibly/probably/definitely drug related. ADRs were not otherwise described. Review of the summary table of AEs included above shows that the most common AEs (nausea, vomiting, constipation, dizziness and fatigue) were consistent with mu-opioid receptor side effects and that the frequency was greater in the patch group compared to the placebo group in the blinded phase.

8.5.1.2. **ADRs: active controlled studies**

8.5.1.2.1. **BUP4201**

ADRs were reported by 134 (85%) patients in the buprenorphine group, and 123 (81%) in the tramadol group during the study (see Table 55). The most commonly affected body system was the digestive system: 106 (68%) patients in the buprenorphine group and 87 (57%) in the tramadol group had ADRs affecting this body system. In both treatment groups, the severity of the most common ADRs was mild or moderate in 70% or more of cases.

Table 55: BUP4201. Incidence of most frequent* possible ADRs**

<table>
<thead>
<tr>
<th></th>
<th>Buprenorphine patch (n = 157)</th>
<th>Tramadol prolonged release tablets (n = 152)</th>
<th>P value***</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Nausea</td>
<td>74</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>53</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>36</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>49</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>24</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>23</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Rash at application site</td>
<td>13</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Pruritus at application site</td>
<td>13</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Sweating</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
</tbody>
</table>

* Preferred terms reported by ≥ 10% of patients in one group. ** AEs considered as at least possibly related by the investigator(s). *** Chi-squared test.

8.5.1.2.2. **PB-TTC-01**

The controlled phase of this study had a double dummy design so that all patients were exposed to a matrix bearing patch (no active component in tramadol group). All patients in the open phase were treated with the buprenorphine patch; 171 of 307 patients had not been exposed to it in the blinded phase. The most common AEs were in keeping with those expected from the side effects of opioids; nausea and vomiting, dizziness, and constipation.

Nausea and/or vomiting were more common in patients using the buprenorphine patch compared to the tramadol group (51.8% compared to 30.8% respectively). The rate was also high in patients newly exposed to buprenorphine patches in the follow-up phase. A sub group analysis of the occurrence of nausea and vomiting in opioid naïve patients compared to those patients previously receiving opioids was performed. This found that nausea and/or vomiting was more common in opioid naïve patients exposed to buprenorphine than opioid naïve patients exposed to tramadol (62% compared to 32%).
Constipation is also a recognised adverse drug reaction of opioids and was experienced by 168 patients during the blinded phase (30.6% of patients using transdermal buprenorphine and by 29.3% of patients taking tramadol).

Application site reactions were experienced by 43.8% of all patients (n = 245) in the blinded phase: 39.1% (n = 111 patients) buprenorphine patch group; 48.6% (n = 134 patients) tramadol group, that is, wearing the placebo patch. Given that local adverse drug reactions were reported with similar frequency for both the active and placebo patch, it is likely that the physical occlusion and/or excipients in the patch itself and not the active ingredient were the reason for the application site reactions.

Table 56: PB-TTC-01: Most common ADRs

<table>
<thead>
<tr>
<th>High level term</th>
<th>Treatment</th>
<th>Total</th>
<th>Open</th>
<th>Treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>blinded</td>
<td></td>
<td>open</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of subjects enrolled</td>
<td>284</td>
<td>100</td>
<td>276</td>
<td>100</td>
<td>560</td>
</tr>
<tr>
<td>Application and instillation site reactions</td>
<td>111</td>
<td>39.1</td>
<td>134</td>
<td>48.6</td>
<td>245</td>
</tr>
<tr>
<td>Nausea and vomiting symptoms</td>
<td>147</td>
<td>51.8</td>
<td>86</td>
<td>30.8</td>
<td>232</td>
</tr>
<tr>
<td>Gastrointestinal atomic and hypomotility disorders</td>
<td>87</td>
<td>30.6</td>
<td>81</td>
<td>29.3</td>
<td>168</td>
</tr>
<tr>
<td>Neurological signs and symptoms NEC</td>
<td>56</td>
<td>19.7</td>
<td>36</td>
<td>13.0</td>
<td>92</td>
</tr>
<tr>
<td>Disturbances in consciousness NEC</td>
<td>43</td>
<td>15.1</td>
<td>27</td>
<td>9.8</td>
<td>70</td>
</tr>
<tr>
<td>Headaches NEC</td>
<td>20</td>
<td>7.0</td>
<td>16</td>
<td>6.8</td>
<td>36</td>
</tr>
<tr>
<td>Apocrine and exocrine gland disorders</td>
<td>14</td>
<td>4.9</td>
<td>18</td>
<td>6.5</td>
<td>32</td>
</tr>
<tr>
<td>Asthenic conditions</td>
<td>19</td>
<td>6.7</td>
<td>11</td>
<td>4.0</td>
<td>30</td>
</tr>
<tr>
<td>Appetite disorders</td>
<td>15</td>
<td>5.3</td>
<td>1</td>
<td>1.8</td>
<td>20</td>
</tr>
</tbody>
</table>

Adverse drug reactions: MedRA coding by high level group term and patient safety data set. A patient was only included one in each high level term. Percentages are based on total number of patients enrolled in each treatment group, respectively in open phase. Adverse drug reaction: event rated as least as possible related to study drug.

8.5.1.3. ADRs: Post-marketing surveillance studies

The post-marketing studies mainly reported ADRs in the safety assessment.

Table 57: Summary of post-marketing surveillance studies: AEs and ADRs

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Duration</th>
<th>Total Patient Number</th>
<th>Number of AEs (%)</th>
<th>Number of ADRs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWB Transtec 2001/1</td>
<td>Up to 10 weeks</td>
<td>13,179</td>
<td>2873 (21.8)</td>
<td>1330 (10.1)</td>
</tr>
<tr>
<td>PM Transtec 2001/2</td>
<td>Up to 10 weeks</td>
<td>2,077</td>
<td>NA</td>
<td>234 (11.3)</td>
</tr>
<tr>
<td>Study Identifier</td>
<td>Duration</td>
<td>Total Patient Number</td>
<td>Number of AEs (%)</td>
<td>Number of ADRs (%)</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>---------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>AWB Transtec 2003/1</td>
<td>10 weeks, 6 months</td>
<td>3,644</td>
<td>666 (18)</td>
<td>584 (16)</td>
</tr>
<tr>
<td>AWB Transteconco2003/01</td>
<td>Up to 8 weeks</td>
<td>412</td>
<td></td>
<td>62 (15)</td>
</tr>
<tr>
<td>GRU-BUP-2002-01</td>
<td>12 weeks</td>
<td>1,223</td>
<td>914 (74)</td>
<td>633 (51.8)</td>
</tr>
<tr>
<td>BIOC/11/03/04</td>
<td>10 weeks</td>
<td>1,648</td>
<td>262 (16)</td>
<td>117 (7)</td>
</tr>
<tr>
<td>TTC-MATRIX-AWB-2003</td>
<td>6 weeks</td>
<td>10,810</td>
<td>6828 (63)</td>
<td>2694 (25)</td>
</tr>
<tr>
<td>AWB Transtec Pro 2005/2 (subset analysis)</td>
<td>Up to 8 weeks</td>
<td>256</td>
<td>NA</td>
<td>9</td>
</tr>
<tr>
<td>BUP4202 (Comparator Prolonged release tramadol)</td>
<td>Up to six months</td>
<td>See below</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMS Transtec versus Durogesic Cohort Study (Comparator; fentanyl patch)</td>
<td>Up to 12 months</td>
<td>See below</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADRs were reported using WHO-ART classification or MedDRA classification. Given the overlapping terminology for the ADRs seen, the terms have been changed to the equivalent MedDRA terms to facilitate comparison. The reported data for comparable studies are provided in the table below, where available.
Table 58: Post-marketing studies: ADRs

<table>
<thead>
<tr>
<th>Condition</th>
<th>AWB Transtec 2001/1</th>
<th>PM Transtec 2001/2</th>
<th>AWB Transtec 2003/1</th>
<th>AWB Transtec Pro 2003/0</th>
<th>GRU-BUP-2002/01</th>
<th>BIOC-12/03/40</th>
<th>TLC/WRIL-AWB-2003</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Number of Patients</td>
<td>13179</td>
<td>2077</td>
<td>3644</td>
<td>412</td>
<td>1223</td>
<td>1648</td>
<td>10810</td>
</tr>
<tr>
<td>MedDRA SOC/WHO-ART</td>
<td>NO %</td>
<td>NO %</td>
<td>NO %</td>
<td>NO %</td>
<td>NO %</td>
<td>NO %</td>
<td>NO %</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>512</td>
<td>3.9</td>
<td>53</td>
<td>2.5</td>
<td>84</td>
<td>2.3</td>
<td>9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>210</td>
<td>1.6</td>
<td>29</td>
<td>1.4</td>
<td>53</td>
<td>1.4</td>
<td>5</td>
</tr>
<tr>
<td>Constipation</td>
<td>128</td>
<td>1</td>
<td>13</td>
<td>0.6</td>
<td>61</td>
<td>1.7</td>
<td>5</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>252</td>
<td>1.9</td>
<td>33</td>
<td>1.6</td>
<td>25</td>
<td>0.7</td>
<td>3</td>
</tr>
<tr>
<td>Somnolence</td>
<td>50</td>
<td>0.4</td>
<td>18</td>
<td>0.8</td>
<td>3</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>34</td>
<td>0.3</td>
<td>18</td>
<td>0.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vertigo</td>
<td>8</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oedema peripheral</td>
<td>30</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>82</td>
<td>0.6</td>
<td>9</td>
<td>0.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalised pruritus</td>
<td>88</td>
<td>0.7</td>
<td>11</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>59</td>
<td>0.4</td>
<td>5</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermatitis (total)</td>
<td>5</td>
<td>0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enzymes (total)</td>
<td>2</td>
<td>0.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site reaction</td>
<td>NA</td>
<td>NA</td>
<td>199</td>
<td>5.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micturition disorder</td>
<td>19</td>
<td>0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADRs described if occurrence</td>
<td>&gt;0.2%</td>
<td>&gt;=5</td>
<td>&gt;5</td>
<td>&gt;=3</td>
<td>&gt;10</td>
<td>&gt;=5</td>
<td>NA</td>
</tr>
</tbody>
</table>

Those studies not included in the table are described below:

- **AWB Transtec 2001/1**: According to the clinical overview there were 13 reports of respiratory depression documented, although only one was regarded as related to treatment with the buprenorphine patch. This data was not apparent in the study report so the accuracy of the attribution could not be assessed.

- **AWB Transtec Pro 2005/2** (subset analysis): data regarding AEs was not provided in this subset analysis. There were 9 out of 256 patients in whom ADRs were reported: nausea/vomiting: 5; application site reaction: 2; generalised rash/pruritus: 1, ‘inner restlessness’: 1.

- **BUP4202** used the comparator of prolonged release tramadol in a study that continued for up to 12 months. All AEs in both the buprenorphine and tramadol groups were recorded. All AEs were categorised as ‘related’ or not; how this was determined was not described in the study report.
Table 59: BUP4202 most frequent AEs* and ADRs

<table>
<thead>
<tr>
<th>System Organ Class / Preferred term</th>
<th>BUP-TDP (N = 593)</th>
<th>Tramadol (N = 298)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>any related</td>
<td>any related</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>99 (16.7%)</td>
<td>18 (6.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>56 (9.4%)</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>42 (7.1%)</td>
<td>10 (3.4%)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Application site reaction</td>
<td>14 (2.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Ill-defined disorders NOS</td>
<td>12 (2.0%)</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower respiratory tract infection NOS</td>
<td>23 (3.9%)</td>
<td>12 (4.0%)</td>
</tr>
<tr>
<td>Urinary tract infection NOS</td>
<td>13 (2.2%)</td>
<td>9 (3.0%)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>4 (0.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>47 (7.9%)</td>
<td>15 (5.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>21 (3.5%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>15 (2.5%)</td>
<td>6 (2.0%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>17 (2.9%)</td>
<td>4 (1.3%)</td>
</tr>
<tr>
<td>Sweating increased</td>
<td>12 (2.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Incidence in ≥ 2% in either group. Note that the report did not specify the rule for considering a case as ‘related’.

Of note is the much higher occurrence of the opioid type side effects of nausea, vomiting, constipation, headache, dizziness and hyperhidrosis in the buprenorphine patch group compared to the tramadol group.

- PMS Transtec versus Durogesic Cohort Study used the comparator of fentanyl patch. Data regarding AEs was only collected for patients treated with buprenorphine patches. A total of 40 adverse events (AEs) were reported in 25 (18.5%) of the 135 patients treated with buprenorphine patch. These included; nausea: 8; vomiting: 2; pruritus: 6; dizziness: 5; tiredness: 3 and erythema: 3. Most of the AEs (92.5%) were consistent with the side effects described in the Summary of Product Characteristics (SmPC).

8.5.2. Deaths and other serious adverse events

Comment: All narratives of deaths and SAEs that occurred in the controlled studies were reviewed. Those narratives that were provided in English in the post-marketing studies were also reviewed. The conclusions of the investigators in classing the events as related to, or not related to, the study drug were agreed with.

8.5.2.1. Deaths and SAEs: placebo controlled studies

8.5.2.1.1. WIS-BUP01, WIS-BUP02 and WIS-BUP03

Eighteen patients experienced treatment emergent SAEs in the three placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03.

Table 60: WIS-BUP01, WIS-BUP02 and WIS-BUP03. Numbers of deaths and SAEs

<table>
<thead>
<tr>
<th>Study Identifier</th>
<th>Number of Deaths</th>
<th>Number of SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIS-BUP01</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>WIS-BUP02</td>
<td>5</td>
<td>6</td>
</tr>
</tbody>
</table>
1 patient died during the run-in phase before exposure to the patch. 3 SAEs occurred in patients during the run-in phase before exposure to the patch.

Details regarding the deaths and SAEs that occurred during exposure to the patch are provided in the table below (episodes occurring in the run-in phase of WIS-BUP01 and WIS-BUP03 are not included as there was no exposure to the patch). Of these events, only the occurrence of severe somnolence in patient [information redacted] from study WIS-BUP02 and the adverse events experienced by patient [information redacted] from study WIS-BUP03 were considered to be possibly attributable to the buprenorphine patch and are known adverse reactions of opioids. All other cases were assessed as being related to the underlying disease.

Table 61: WIS-BUP01, WIS-BUP02 and WIS-BUP03. Details of deaths and SAEs
8.5.2.1.2. **WIS-BUP-LTS**

In total 37 patients died during \( n = 32 \) or a short time after completion \( n = 5 \) of the long-term study. None of the deaths was assessed as being related to the study medication. Serious adverse events (including death) were reported for 40 patients. Severe constipation that occurred in two patients (after one months and six months treatment respectively) was classed as at least possibly related to buprenorphine transdermal patch.

8.5.2.1.3. **PB-TTC-02**

Eleven patients died during the study, 8 during the run-in period and 3 during the double blind period (2 in the placebo group and 1 in the buprenorphine group). Cause of death was attributed solely to disease progression in 6 patients, and to disease progression and other factors not related to the study drug in a further 3 patients. Unrelated coma and hepatic coma were reported as the causes of death in 2 patients. A further five patients died during follow-up of serious adverse events. Four of these deaths were due to disease progression, or serious adverse events probably related to disease progression. The remaining patient died of subclavian catheter thrombosis, not classified as causally related to the study drug.

A total of 44 serious adverse events (SAEs, including AEs with fatal outcome) were reported in 22 patients, mostly related to underlying disease. Thirty of these occurred during the run-in period and 14 during the double blind period. In one patient in the active treatment group, nausea and vomiting were considered probably related to the study drug.

8.5.2.2. **Deaths and SAEs: active controlled studies**

8.5.2.2.1. **BUP4201**

No patients died during the study. Five patients reported non-fatal serious AEs (four patients in the buprenorphine group and one in the tramadol group). In one patient (shown as "[information redacted] in the table below) in the buprenorphine group, the serious AE was definitely related to treatment. This patient suffered severe nausea, dizziness and vomiting. They recovered after stopping treatment and were discontinued from the study.

**Table 62: BUP4201 SAEs reported during the study**

<table>
<thead>
<tr>
<th>Patient number</th>
<th>SAE</th>
<th>Relationship to treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine patch:</td>
<td>Hospitalisation (hernia)</td>
<td>Not related</td>
</tr>
<tr>
<td></td>
<td>Hospitalisation (pain) Choleithiasis</td>
<td>Improbable</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>Definite</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>Definite</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>Definite</td>
</tr>
<tr>
<td></td>
<td>Bone neoplasm</td>
<td>Not related</td>
</tr>
<tr>
<td></td>
<td>Pain</td>
<td>Not related</td>
</tr>
<tr>
<td></td>
<td>Neuralgia</td>
<td>Not related</td>
</tr>
</tbody>
</table>

| Tramadol prolonged release tablets: | Hospitalisation (abscess) | Not related |

8.5.2.2.2. **PB-TTC-01 (blinded and open phases)**

No deaths were reported during the study.
A total of 22 patients experienced 42 serious adverse events (SAEs) during both phases of the study. The majority of SAE reports were assessed as unlikely or not related to the study medication by the investigator and/or the sponsor. For 4 of the patients, the SAE(s) was reported by the investigator as being certain, likely, possibly or probably related to the study medication:

- One patient was hospitalised for a complex illness, including Mallory-Weiss syndrome. The Mallory-Weiss syndrome was attributed to bouts of vomiting that the investigator regarded as related to buprenorphine

- One patient was hospitalised with a confusional episode and respiratory insufficiency. The investigator considered these to be possibly and probably (respectively) related to buprenorphine patch

- One patient developed nausea, vomiting, and numbness of the legs that was categorised as serious and certainly related to buprenorphine by the investigator

- One patient developed nausea and vomiting that was categorised as serious and certainly related to buprenorphine by the investigator.

8.5.2.3. Deaths and SAEs: clinical pharmacology studies

No deaths or SAEs occurred in the pharmacokinetic studies HP5303/01, HP5303/02 and HP5303/04.

8.5.2.4. Deaths and SAEs: post marketing surveillance studies

These were variously reported in the post marketing surveillance studies. Data is provided as available from the study reports and summary of clinical safety. It was not always clear if the number of SAEs provided included deaths.

- AWB Transtec 2001/1: 1,640 SAEs in 1,267 patients, including 883 deaths, were reported. Of the SAEs, 97 events in 43 patients were regarded as ADRs (including vomiting in 18, nausea in 10 and dizziness in 7). None of the deaths was regarded as related to buprenorphine patch

- PM Transtec 2001/2: Occurrence of SAEs was not described in the study report

- AWB Transtec 2003/1: 15 SAEs occurred in 9 patients. These were listed using WHO-ART terms and no determination provided as to whether they were related to the study drug. The categories of the reactions described were all consistent with AEs due to buprenorphine, except for one case of pneumonia, but no individual case descriptions were provided

- AWB Transteconco2003/0: 16 SAEs occurred in 7 patients. None were regarded as related to the study drug

- GRU-BUP-2002-01: SAEs were reported as occurring in 73 patients, of whom 57 died. None of the deaths, but 2 non-fatal SAEs were considered as at least possibly attributable to the buprenorphine patch

- BIOC11/03/04: 9 SAES were reported with 4 considered related to buprenorphine patch; 111 deaths with none considered related to buprenorphine patch (descriptions of deaths provided in German only)

- TTC-MATRIX-AWB-2003: 235 SAEs were reported, including 196 deaths. None of the deaths was considered to be related to buprenorphine patch. 15 of the SAEs were considered to be related to buprenorphine patches: most of these were consistent with the reported side effects of the buprenorphine patch (as listed in the SPC)
• AWB Transtec Pro 2005/2 (subset analysis): data regarding SAEs was not provided in this subset analysis

• BUP4202: SAEs were reported for both the buprenorphine and tramadol groups. In total, 54 patients had serious adverse events, and there were 30 deaths. There was a higher incidence of deaths in the buprenorphine treatment group (4.4%) than in the tramadol treatment group (1.3%). None of the deaths was considered related to study drug; common causes included carcinoma, cardiac or pulmonary disorders. The incidence of serious adverse events other than death during the study was comparable between treatment groups (3.7% and 3.0% for buprenorphine and tramadol treatment groups, respectively). Three of the serious adverse events were considered to be probably or definitely related to study drug and were reported for 2 patients, both in the buprenorphine treatment group (severe application site reaction, and severe dehydration and moderate somnolence).

• PMS Transtec versus Durogesic Cohort Study (Comparator; fentanyl patch): Serious AEs were reported only for the buprenorphine group. SAEs were reported in 3 patients, each with a fatal outcome: one case was metastasising bronchial cancer, another cancer and a third patient who died in a multi-morbid condition. None of the SAEs were considered to be related to buprenorphine patch.

8.6. Discontinuation due to adverse events

8.6.1. Discontinuation due to AEs: placebo controlled studies

8.6.1.1. WIS-BUP01

Seven patients discontinued the trial due to adverse event(s). Two had a fatal outcome (see above) and two more experienced serious AEs (see above). The remaining three patients discontinued due to severe pruritus (2 patients after buprenorphine patch 52.5 µg/h) and severe nausea with vomiting (1 patient after buprenorphine patch 70 µg/h).

8.6.1.2. WIS BUP02

Study treatment was discontinued for a total of 23 patients, in 17 patients due to adverse events, in 6 patients due to withdrawal of consent. The AEs leading to discontinuation were death (5 patients, see above), serious adverse events (two patients, see above) and non-serious adverse events (10 patients). In the 6 patients, who withdrew their consent, adverse events could not be excluded as the real reason (moderate or severe nausea, severe dizziness, severe tiredness and severe skin reaction).

8.6.1.3. WIS BUP03

Study treatment was discontinued in 5 patients due to adverse events. Two of these events were serious: one patient in the active treatment group was discontinued prematurely due to hospital admission for restlessness, pruritus, dizziness, cramps in the extremities, disturbed concentration and thinking; one patient in the placebo group was lost to follow-up after a suicide attempt.

8.6.1.4. WIS BUP-LTS

Treatment with the buprenorphine patch was discontinued in 42 patients due to AEs. In 23 patients, discontinuation was due to worsening skin reactions following multiple patch application over a period of 25 to 1,114 days.

8.6.1.5. PB-TTC-02

During both study periods, a total of 28 patients withdrew due to adverse events, including fatal adverse events, (21 during the run-in period and 7 during the double blind period (6 in the placebo group, 1 in the active treatment group)). The most common events leading to
withdrawal were vomiting (reported in 6 patients), dizziness (reported in 6 patients) and nausea (reported in 5 patients). No patients withdrew because of skin reactions.

8.6.2. Discontinuation due to AEs: active controlled studies

8.6.2.1. BUP4201

A total of 175 patients discontinued from the study: 110 patients (70%) in the buprenorphine group and 65 (43%) in the tramadol group. For those patients who discontinued, the most common reason for discontinuation was AEs: 97 patients (88%) in the buprenorphine group and 51 (78%) in the tramadol group discontinued for this reason. Table 58 below shows the most common AEs leading to discontinuation (that is those reported by at least 10% of patients in either treatment group). These AEs were all known side effects of opioid analgesics. Of those patients who discontinued because of AEs, most did so in the first two weeks; 52 (54%) in the buprenorphine group and 25 (49%) in the tramadol group.

Table 63: BUP4201 Most common AEs leading to discontinuation

<table>
<thead>
<tr>
<th>AE</th>
<th>Buprenorphine patch (n = 97)*</th>
<th>Tramadol prolonged release tablets (n = 51)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>56 (58)</td>
<td>20 (39)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>49 (41)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>33 (34)</td>
<td>10 (20)</td>
</tr>
</tbody>
</table>

*Numbers of patients who discontinued from the study because of AEs

8.6.2.2. PB-TTC-01

Of the patients who terminated the study early (n = 188), 148 patients withdrew due to adverse events. In the buprenorphine group 34.2% of all withdrawals (n = 97 patients) were due to adverse events. In the tramadol SR 100 mg bid group, 18.5% (n = 51) of withdrawals were due to adverse events.

Of the 372 patients completing the controlled part of this study, 307 patients proceeded into the open uncontrolled phase and 155 completed it. A total of 152 discontinued this uncontrolled part prematurely; 99 (32.2%) due to adverse events and 19 (6.2%) because of lack of efficacy. Discontinuation rates were highest during the first two months of this uncontrolled study part. During the first month of this part of the study the discontinuation rate was higher in the group treated with tramadol in the double blind part who were newly exposed to the buprenorphine patch.

8.6.3. Discontinuation due to AEs: clinical pharmacology studies

• HP5303/01: One subject withdrew for personal reasons and was replaced

• HP5303/02: Seven subjects discontinued the study prematurely, 6 of these due to multiple AEs and one due to personal reasons unrelated to study treatment. Most common AEs in these 6 subjects were nausea, vomiting, dizziness, and miscellaneous other CNS symptoms. These subjects were withdrawn between 3 to 6 days on treatment, 4 were withdrawn from the highest dose (40 mg buprenorphine patch)

• HP5303/04: Two subjects withdrew for personal reasons.

8.6.4. Discontinuation due to AEs: post-marketing surveillance studies

Data regarding discontinuations was inconsistently provided in the post-marketing surveillance studies. In general, discontinuations occurred most commonly early in the course of the study.
Of note in study BUP4202, in which buprenorphine patch and tramadol were compared, the proportion of patients who had an adverse event that led to discontinuation from the study was 3 times higher in the buprenorphine treatment group than in the tramadol treatment group (37.9% compared with 13.1%).

8.7. Laboratory tests

Comment: From the summary of clinical safety: ‘Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine’. The clinical overview provided support for this statement by referring to a general review of buprenorphine from 2002 (sponsored by [information redacted]), an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine. Of note is that the review article does not specifically address the use of buprenorphine in special populations, any possible effects on organ function or laboratory parameters or possible effects of long-term administration. Also of note is that The RMP refers to more recent articles that address hepatotoxicity, cardiovascular effects, immune system effects, exposure during pregnancy, skin hypersensitivity reactions, use in elderly and young, use in paediatric patients, use in patients with liver impairment, abuse and dependence potential, potential for medication errors, off-label use (depression and restless legs syndrome), use in post-operative pain, and reversal of respiratory depression by naloxone. These are not discussed in the clinical overview or summary of clinical safety.

If reliance is to be placed on buprenorphine administered by other routes for aspects of the safety evaluation, a current review of the existing literature should be provided.

In general, the clinical efficacy studies performed laboratory testing, vital signs and ECG at study entry for baseline comparison of the treatment groups. These were not repeated subsequently.

8.7.1. Liver function

8.7.1.1. Pivotal studies

Not recorded. The clinical efficacy studies WIS-BUP01, WIS-BUP03, PB-TTC-02 did not specifically exclude patients with severe hepatic impairment but serial liver function tests or other assessments of liver function were not performed. Nor was the effect of impaired liver function on plasma buprenorphine levels investigated.

8.7.1.2. Other studies

Serial LFTs were recorded in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant abnormalities were reported apart from elevation in the level of alanine transaminase (ALT) in a few patients. These elevations were considered minor and the effect of buprenorphine patches on liver function was not further investigated.

8.7.2. Kidney function

8.7.2.1. Pivotal studies

Not recorded. The clinical efficacy studies WIS-BUP01, WIS-BUP03, PB-TTC-01 and PB-TTC-02 did not specifically exclude patients with severe renal impairment but serial measures of renal function were not performed. Nor was the effect of impaired renal function on plasma buprenorphine levels investigated.
8.7.2.2. Other studies

Serial laboratory tests of renal function were recorded in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant changes were reported.

8.7.3. Other clinical chemistry

8.7.3.1. Pivotal studies

Not recorded.

8.7.3.2. Other studies

Serial biochemistry testing were recorded in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant changes were reported.

8.7.4. Haematology

8.7.4.1. Pivotal studies

No serial testing performed.

8.7.4.2. Other studies

Serial haematology tests were performed in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant changes were reported.

8.7.5. Plasma buprenorphine levels

8.7.5.1. Pivotal studies

Not performed, except for WIS-BUP02PK. The results in this study were extremely limited due to the number of missing or mislabelled specimens.

8.7.5.2. Other studies

Serial plasma buprenorphine levels were performed in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). These showed considerable inter-patients variation. This was not further investigated in the clinical study programme, except for WIS-BUP02PK (see above comment).

8.7.6. Electrocardiograph

8.7.6.1. Pivotal studies

Serial ECGs were not performed in the clinical efficacy studies.

8.7.6.2. Other studies

Serial ECGs were recorded in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant abnormalities were reported.

8.7.7. Vital signs

8.7.7.1. Controlled efficacy studies

In general, the clinical efficacy studies recorded vital signs only at study entry to enable baseline comparison of treatment groups.

In study PB-TTC-01 body temperature, pulse rate and blood pressure were measured at screening and at the Day 1 and Day 28 visits during the blinded phase and at the Month 7 visit in the open phase. The values were unremarkable and there was no evidence that transdermal buprenorphine or tramadol influenced body temperature, pulse rate or blood pressure. Hypertension was reported as an adverse drug reaction in one patient in the buprenorphine patch group during the blinded phase and in one patient in the open phase. Hypotension was reported as an adverse drug reaction by one patient in the buprenorphine patch group.
8.7.7.2. Other studies

Serial vital signs were recorded in the clinical pharmacokinetic studies (109 healthy volunteers with study duration up to 15 days). No clinically relevant abnormalities were recorded apart from transient changes in blood pressure in a few patients.

8.7.8. Skin site absorption

8.7.8.1. Pivotal studies

Four application sites were described as being used in these studies (right and left infra-clavicular, right and left suprascapular). Comparative absorption from these sites was not tested. Factors that could affect absorption and adherence (activity, body heat, locally applied heat) were not tested.

8.7.8.2. Other studies

Four application sites were described as being used in most of the clinical efficacy studies (right and left infra-clavicular, right and left suprascapular). Comparative absorption from these sites was not tested. Factors that could affect absorption and adherence (activity, body heat, locally applied heat) were not tested. The pharmacokinetic study HP5303/02 inadvertently found increased absorption with re-use of a skin site at 3 days. This was not further investigated.

8.7.9. Respiratory function

8.7.9.1. Pivotal studies

Not recorded. All studies excluded patients with impaired respiratory function.

8.7.9.2. Other studies

Not recorded. All studies excluded patients with impaired respiratory function.

8.8. Post-marketing experience

Data from the post-marketing surveillance studies provided in the dossier are described above.

8.8.1. Periodic safety update reports

According to the RMP, the total cumulative post authorisation patient exposure to buprenorphine TDS is 505.6 million Patient Treatment Days (PTD) calculated according to Intercontinental Marketing Services (IMS) since IBD (23 June 2000).

Table 64: Post-marketing exposure 23 June 2000 to 30 July 2014 in patient treatment days (PTD) as calculated by the intercontinental marketing services (IMS)

<table>
<thead>
<tr>
<th>Region</th>
<th>35μg/h</th>
<th>52.5μg/h</th>
<th>70μg/h</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>282889361</td>
<td>122922775</td>
<td>85908149</td>
<td>491.720.285</td>
</tr>
<tr>
<td>Latin America</td>
<td>11.664.392</td>
<td>2244.736</td>
<td>85908149</td>
<td>13.909.128</td>
</tr>
<tr>
<td>Overall</td>
<td>294.553.753</td>
<td>125.167.511</td>
<td>85908149</td>
<td>505.629.413</td>
</tr>
</tbody>
</table>

Periodic safety update reports (PSURs) covering the years 2000 to 2013 (17 reports with 2 to 11 volumes per year) were provided. Only the PSURs from 2000 to 2005 were discussed in the Summary of Clinical Safety and clinical overview. A bridging summary for the years 2000 to 2005 was also provided.
Table 65: Periodic Safety Update Reports (PSURs) for buprenorphine transdermal patch

<table>
<thead>
<tr>
<th>Document Number</th>
<th>Reporting Period</th>
<th>Number of AEs Reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSUR1</td>
<td>23 Jun 2002 to 23 Jan 2002</td>
<td>241</td>
</tr>
<tr>
<td>PSUR2</td>
<td>24 Jan 2002 to 23 Jun 2002</td>
<td>224</td>
</tr>
<tr>
<td>PSUR3</td>
<td>24 Jun 2003 to 23 Jan 2003</td>
<td>494</td>
</tr>
<tr>
<td>PSUR4</td>
<td>24 Jan 2003 to 23 Jul 2003</td>
<td>742</td>
</tr>
<tr>
<td>PSUR5</td>
<td>24 Jul 2003 to 23 Jan 2004</td>
<td>609</td>
</tr>
<tr>
<td>PSUR6</td>
<td>24 Jan 2004 to 23 Jul 2004</td>
<td>746</td>
</tr>
<tr>
<td>PSUR7</td>
<td>24 Jul 2004 to 23 Jan 2005</td>
<td>379</td>
</tr>
<tr>
<td>PSUR8</td>
<td>24 Jan 2005 to 23 Jul 2005</td>
<td>654</td>
</tr>
<tr>
<td>PSUR9</td>
<td>24 Jul 2005 to 23 Jan 2006</td>
<td>537</td>
</tr>
<tr>
<td>PSUR10</td>
<td>24 Jan 2006 to 13 Dec 2006, 2 volumes</td>
<td>990</td>
</tr>
<tr>
<td>PSUR11</td>
<td>14 Dec 2006 to 30 Jul 2007, 11 volumes</td>
<td>476</td>
</tr>
<tr>
<td>PSUR12</td>
<td>31 Jul 2007 to 30 Jul 2008</td>
<td>958</td>
</tr>
<tr>
<td>PSUR13</td>
<td>31 Jul 2008 to 30 Jul 2009</td>
<td>1019</td>
</tr>
<tr>
<td>PSUR14</td>
<td>31 Jul 2009 to 30 Jul 2010</td>
<td>968</td>
</tr>
<tr>
<td>PSUR15</td>
<td>31 Jul 2010 to 30 Jul 2011</td>
<td>863</td>
</tr>
<tr>
<td>PSUR16</td>
<td>31 Jul 2011 to 30 Jul 2012</td>
<td>778</td>
</tr>
<tr>
<td>PSUR17</td>
<td>31 Jul 2012 to 30 Jul 2013</td>
<td>1080</td>
</tr>
</tbody>
</table>

Comment: The appendix attached to the PSURs from 2003 onwards became increasingly lengthy, containing:
- cumulative tabulations of listed and unlisted reactions to buprenorphine
- updated version of the SPC
- post-marketing surveillance study reports
- newly published articles regarding buprenorphine or transdermal preparations of other drugs
- scientific evaluations performed by [information redacted] regarding specific aspects of the buprenorphine patch.

The contents of the appendix could not always be readily determined as the PSUR table of contents commonly did not include the contents of the appendix. When the TOC did include the contents of the appendix, there were often no links or page numbers provided so that access to the appendix contents required scrolling through the whole document (up to 3,000 pages) to locate the item of interest.

The most commonly reported symptoms in the PSURs were consistent with those seen in the clinical studies: localised application site reactions, nausea, vomiting, pruritus and constipation. Rates of occurrence of side effects described in the SPC were adjusted as more information became available. The most recent company core data sheet (in PSUR17) provides the frequencies shown in Table 66 below.

Table 66: Frequency of undesirable effects (company core data sheet 2013)

<table>
<thead>
<tr>
<th>Undesirable Effect</th>
<th>Estimated Frequency</th>
<th>Definitions of terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>Very common</td>
<td>Very common (≥ 1/10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>Common</td>
<td>Common (≥ 1/100, &lt; 1/10)</td>
</tr>
<tr>
<td>Pruritus, erythema</td>
<td>Very common</td>
<td>Uncommon (≥ 1/1,000, &lt; 1/100)</td>
</tr>
</tbody>
</table>
### Undesirable Effect

<table>
<thead>
<tr>
<th>Undesirable Effect</th>
<th>Estimated Frequency</th>
<th>Definitions of terms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Common</td>
<td>Rare (≥ 1/10,000, &lt; 1/1,000)</td>
</tr>
<tr>
<td>Dizziness, Headache</td>
<td>Common</td>
<td>Very rare (≤ 1/10,000)</td>
</tr>
<tr>
<td>Fatigue, tiredness</td>
<td>Common</td>
<td></td>
</tr>
<tr>
<td>Confusion, agitation</td>
<td>Uncommon</td>
<td></td>
</tr>
<tr>
<td>Administration site reactions</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

These are consistent with the findings of the clinical studies except for administration site reactions. These occurred in up to 30% of patients in the studies. Site reactions that were thought to be allergic were, however, rare.

Additional side effects were added to the company core data sheet and SPC as these were revealed and substantiated through the post marketing reporting of adverse event:

- The potential for hypotension occurring early in treatment and confusion was added in 2002
- Restlessness, anxiety, nightmares and decreased erection was added to ‘undesirable effects’ in 2003
- Urticaria was added to ‘undesirable effects, skin’ in 2006.

Case reports of serious adverse events that are probably related or definitely related to buprenorphine are listed below and referred to in the following sections of the safety evaluation.

#### 8.8.1.1. Drug interactions

- Co-administration with other sedating agents:
  - resulting in excessive sedation with 12 reports requiring hospitalisation
  - resulting in acute confusional state with 2 reports requiring hospitalisation
  - One report of unconsciousness and respiratory failure followed by death in a 66 year old who was commenced on ½ 20 mg buprenorphine patch whilst also on clonazepam, amitriptyline and baclofen. Symptoms initially improved with naloxone but subsequent deterioration and death due to hypoxic encephalopathy and multiple organ failure
  - One report of respiratory arrest in male patient in hospital who was being treated with 2 x 40 mg patch and who received parenteral fentanyl and morphine peri-operatively.
- Co-administration with agents that alter metabolism (CYP 3A4 inhibitors and inducers)
  - Reduced efficacy during co-administration with carbamazepine
  - Increased buprenorphine side effects when co-administered with the CYP 3A4 inhibitor fluoxetine and requiring hospitalisation
  - Drug interaction between prednisolone, buprenorphine and phenprocoumon resulting in severe nausea, vomiting and weight loss.

#### 8.8.1.2. Overdose

- At excessive dose:

[Table continued...]

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Submission PM-2014-03891-1-1 Extract from the Clinical Evaluation Report for Transtec and three additional trade names - buprenorphine 13 December 2016
– One patient applied 5 patches simultaneously for back pain resulting in nausea and vomiting requiring hospitalisation
– One patient applied 4 patches simultaneously due to misunderstanding of instructions in CMI causing dizziness, nausea and vomiting requiring hospitalisation
– In one case, excessive somnolence, nausea and vomiting requiring hospitalisation occurred after a 71 year old patient mistakenly applying 4 x 30 mg patches at once. Symptoms rapidly improved after administration of 0.8 mg naloxone. Repeated doses of naloxone were required over the next 10 hours
– One case of hypoventilation, drowsiness and vomiting requiring hospitalisation in a patient who applied 2 x 20 mg patches ( instructed to commence on one patch)
– Patient presenting to hospital with confusional state found to have 5 patches applied to back. Treated with naloxone and improved but subsequently died from unrelated cardiac failure.

• Due to increased absorption:
– Patch applied to painful area and TENS then also applied resulting in symptoms (not described) requiring hospitalisation
– One case of reduced conscious state and respiratory depression requiring hospitalisation and intensive care in a five year old after his mother accidentally applied family member’s buprenorphine patch to a foot cut instead of a Band-Aid
– One case of hypotension, nausea and dizziness requiring hospitalisation after a patient inadvertently applied a buprenorphine patch to a recent burn
– Vertigo and drowsiness requiring hospitalisation in a male patient after working outside in intensive sunshine while wearing 20 mg patch.

• At therapeutic dose:
– 88 year old patient developed respiratory depression and hypoventilation requiring hospitalisation following an increase in buprenorphine dose from 20 mg patch to 30 mg patch
– Four reports of severe nausea and vomiting requiring hospitalisation; 55 year old 18 hrs after application of first buprenorphine patch (¼ of a 20 mg patch); 81 year old after increase in buprenorphine dose from ¼ of 20 mg patch to ½ patch; elderly male after increase from 30 mg to 40 mg patch; one patient after increase in dose from 20 mg to 30 mg
– Acute agitation culminating in suicide attempt in 82 year old after increase from 20 mg to 30 mg patch
– Confusional state in 78 year old requiring hospitalisation 7 days after commencing 20 mg buprenorphine patch
– 81 year old with ‘bronchopneumopathy’ developed respiratory failure requiring hospitalisation and treatment with CPAP 5 days after commencing 30 mg buprenorphine patch.

• At therapeutic dose and requiring treatment with naloxone:
– One case of respiratory depression 4 to 6 hrs after application of 20 mg patch, requiring hospitalisation. Resolved after administration of 2 ampoules of naloxone
– One case of ‘intoxication’ in an 85 year old after application of the second (sequential) 20 mg patch requiring hospitalisation and treatment with naloxone
– 47 year old developed respiratory failure and stupor requiring hospitalisation during treatment with buprenorphine patch. Symptoms resolved with administration of 0.2 mg naloxone

– 77 year old patient developed increasing somnolence that worsened following hospitalisation (patch continued) and required treatment with naloxone

– Unresponsiveness in a hospitalised patient after an increase in dose from 10 µg/h to 35 µg/h (20 mg) patch. Responded to a total of 2.5 mg naloxone.

• Drug abuse:
  – Several accounts of patients with known drug dependence who had been found dead from presumed overdose. Noted to have measurable levels of buprenorphine (and other drugs) on routine toxicology. Route of administration of buprenorphine not known
  – Three reports of patch misuse, two with extraction of active drug from the matrix (dissolved in alcohol or acetone) and one in which the patch was chewed.

• Drug dependence:
  – Four patients unable to cease patch wearing, despite resolution of pain, due to withdrawal symptoms.

• Liver failure:
  – Two reports of ‘liver failure’ with elevated LFTs that resolved with cessation of buprenorphine in 2012. No further detail
  – Three reports of hepatic abnormalities (‘drug induced acute cholestatic hepatitis’, ‘fulminant hepatitis’, ‘cholestasis’) that resolved after multiple medications (including buprenorphine patch) were ceased
  – One report of abnormal LFTs 6 months after commencing buprenorphine patches that resolved with discontinuation of the patch.

• Skin reactions:
  – 2 localised weeping reactions attributed to allergic reaction to the patch
  – One case of anaphylactic shock with possible relation to buprenorphine patch.

• Use in children:
  – Adverse events were reported in children ranging from 21 months old to 17 years (28 reports).

• Accounts of use in late pregnancy:
  – 4 reports of neonatal opiate withdrawal where the mother was treated with transdermal buprenorphine in late pregnancy.

• Cardiac events:
  – Paroxysmal tachycardia requiring hospitalisation reported in an 88 year old male in 2013
  – Palpitations together with sweating and nausea requiring hospitalisation in a 74 year old male reported in 2012
  – Sudden unexpected death in an 82 year old in 2010. Note that a dose of ¼ of the 20 mg patch was prescribed
  – Syncopal episode in 67 year old requiring hospitalisation reported in 2009; no organic cause found
– Syncopal episodes following episodes of vomiting reported in 3 patients in 2008 to 2009
– Bradycardia and reduced consciousness in 63 year old reported in 2008
– Syncopal episodes in an elderly female reported in 2009.

8.9. Safety issues with the potential for major regulatory impact

8.9.1. Overdose

No specific actions were taken in the trials to investigate the potential for overdose adverse events were the only safety monitoring conducted during the trials. No adverse events due to overdose were reported in the clinical studies. The clinical overview regards unintended overdose to be unlikely with a ‘rate controlled delivery system’ and does not discuss this risk further. The only information regarding unintended overdose is that found in the PSURs with the reports described above. These reports describe symptoms of overdose requiring hospitalisation that occurred at doses less than the proposed range, at therapeutic doses, and with an increase in dose. This unpredictable behaviour is consistent with the considerable inter patient variability in absorption, and subsequent plasma levels, observed in the clinical pharmacokinetic studies. There were other case reports in which overdose occurred due to excessive application of the patches (too many) or to increased absorption (applied to cut or burn, TENs application, physical exertion in hot weather). Symptoms of overdose included drowsiness, stupor, respiratory depression, confusion and severe nausea and vomiting. Several patients were treated with naloxone. Effective doses of naloxone were reported as being 0.2 to 2.5 mg.

8.9.2. Drug abuse and dependency

No specific actions were taken in the trials to investigate the potential for abuse or drug dependency and no adverse events related to these were reported in the clinical studies. Reports of drug abuse involving buprenorphine were not infrequent in the PSURs. The most common scenario was that a measurable level of buprenorphine, together with other drugs, was found on routine toxicological testing in a person who had been found dead from presumed overdose. The source and route of buprenorphine ingestion was not known. Instances of extraction of buprenorphine from the patch with subsequent ingestion were less commonly reported. The clinical overview argues that drug abuse is unlikely given the difficulty in extraction of buprenorphine from the patch.

Buprenorphine is also described in the dossier as having a low dependence potential. There were no reports of withdrawal symptoms occurring following cessation of buprenorphine in the clinical studies but these were of short duration and follow-up of the patients after study end was not described. A small number of case reports included in the PSURs describe patients developing withdrawal symptoms on trying to cease buprenorphine after long-term use.

8.9.3. Respiratory depression

Respiratory depression is a concern with any opioid. The dossier presents the argument that buprenorphine is safer than other opioids due to the postulated ‘ceiling effect’ on respiration, based on a study that found no difference in the respiratory depressant effect of 2 doses of parenteral buprenorphine (0.2 mg and 0.4 mg) in 10 healthy males. The clinical pharmacokinetic studies performed serial measurements of respiratory rates during patch application and found no convincing reduction in respiratory rate in healthy volunteers. There were no AEs relating to respiratory depression reported in the clinical efficacy studies, but patients with pre-existing respiratory disease were, in general, excluded from these studies.

In the PSURs, there were several reports of respiratory failure occurring at therapeutic doses of buprenorphine or with inadvertent overdoses or in combination with other sedating agents. There was one case report of a respiratory arrest in a patient who received parenteral opioids
whilst wearing a buprenorphine patch and one report of death from hypoxic brain injury and multiple organ failure following respiratory failure due to the co-administration of buprenorphine with other potentially sedating agents.

8.9.4. Liver toxicity

There were no instances of 'Hy's Law cases' reported in the clinical studies or in the PSURs. There were several reports of 'hepatic failure' as shown by elevated liver enzymes that subsequently resolved after ceasing buprenorphine patches described in the PSURs. Insufficient clinical detail was provided for these to be evaluated. Of note is that elevation in the level of alanine transaminase (ALT) was reported in a few patients in the pharmacokinetic studies in a few patients (as described above). The effect of buprenorphine patches on liver function has not been further investigated according to the materials available in the dossier.

Comment: According to the Risk Management Plan briefly refers to this by: ‘even in patients with elevated risk studies did not show evidence for buprenorphine induced liver toxicity (Vergara- Rodriguez et al. 2011\textsuperscript{43}, Saxon, 2013\textsuperscript{44})’. This research is not elsewhere described in the dossier and the articles referred to were not included in the dossier. From their titles, both studies refer to the use of buprenorphine in the management of opioid dependency. It is concerning that the effects of the buprenorphine patch (both active substance and excipients) on liver function has not been adequately described within the clinical overview.

8.9.5. Haematological toxicity

There were no cases of agranulocytosis, aplastic anaemia or severe thrombocytopenia attributable to buprenorphine reported in the clinical studies, post marketing surveillance studies or PSURs.

8.9.6. Serious skin reactions

Local skin reactions such as erythema, oedema and itching, at the site of the patch were common. Generalised mild skin reactions including pruritus and erythema were reported as SAEs in most of the clinical studies. More severe localised skin reactions, including vesiculation and desquamation, were reported infrequently, including in the PSURs. None of these reactions were labelled as erythema multiforme, Stevens Johnson syndrome or toxic epidermal necrolysis.

Comment: The Risk Management Plan comments that ‘Long term occlusion of the skin increases the risk for skin sensitisation and development of an allergic skin reaction.’ This risk is not further discussed nor is it discussed in the clinical overview or the summary of clinical safety.

8.9.7. Cardiovascular safety

Two serious potential risks associated with buprenorphine patches have been identified.

8.9.7.1. Risk of polymorphic ventricular tachycardia (also known as Torsades de Pointes, (TdP))

Pre-clinical data show that buprenorphine inhibits the Human Ether-a-Go-Go-Related Gene (HERG) channel in in vitro models, although at concentrations said to be at least 200 fold higher than therapeutic plasma concentrations achieved in humans. This raises the concern that myocardial repolarisation may be prolonged in vivo with the risk of causing polymorphic ventricular tachycardia (also known as Torsades de Pointes, (TdP)). TdP is of serious concern as


it can present as sudden death. QT prolongation is commonly used as a surrogate marker for the risk of TdP.

A sponsor for the 7 day buprenorphine patch performed a ‘thorough QT study’, BUP1011, in the course of the development of this product in the USA. The study report was finalised in 2004; a copy of this is located in the appendix of PSUR10. This study is not referred to in the clinical overview nor is the study available in the body of the dossier. It is referred to in the Risk Management Plan. BUP1011 evaluated the effect of the buprenorphine transdermal patch on QT interval at a dose of 10 mg and 40 mg. The patches used in this study are 5 mg, 10 mg, 20 mg strength and worn for 3 or 4 days. The lower patch strengths are available in the 7 day patches (tradename Norspan in Australia) and are identical to the patches in this submission, apart from a lower range of doses. The application time used in the study was the same as that proposed for the buprenorphine patches in the submission. A description of this study is provided in the appendix to this evaluation. Moxifloxacin was used as an active control in the study as it is recognised to cause QT prolongation and has been associated with episodes of TdP in patients with other risk factors.

The results of this study were that:

- single moxifloxacin doses of 400 mg (Days 6 and 13) produced the expected prolongation in time averaged and time matched placebo corrected change from baseline QTci, which establishes assay sensitivity for this study
- the dose of BTDS 10 mg has no effect on QTci
- the dose of 2 x BTDS 20 mg (40 mg) prolongs QTci to an extent comparable to 400 mg of moxifloxacin.

To provide clinical perspective of this, the EMA document ‘Points to Consider: The Assessment Of The Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products’ indicates that QTc interval values (msec) after Bazett’s correction (QTcb):

- Are considered to be prolonged if > 450 msec in males and > 470 msec in females
- Individual changes between 30 to 60 msec are more likely to represent a drug effect and raise concern about the potential risk of inducing arrhythmias including TdP.
- Individual changes greater than 60 msec raise clear concerns about the potential risk of inducing arrhythmias including TdP.

A prolongation of QTc > 500 msec during therapy is usually regarded as a threshold of particular concern.

Although QT prolongation was found in Study BUP1011, these levels on average were not exceeded in the patients in the study. An additional analysis of outliers was performed and found that only one patient, who was in the moxifloxacin group, had an increase in QTcb > 60msec. A number of patients in all groups (placebo, moxifloxacin and BTDS) had changes of 30 to 60 msec but these results were considered comparable across the groups.

The findings of this study remain of considerable concern given that the proposed dose range for buprenorphine patches is up to 140 mg (3.5 times the dose tested in study BUP1011). Common co-existing conditions known to increase the QT interval (such as hypokalaemia, hypomagnesaemia, heart failure, myocardial hypertrophy) and medications (such as macrolide antibiotics, anti-retroviral agents, antihistamine drugs) may also potentiate the risk of TdP. A number of drugs worldwide have been withdrawn from marketing in some, or all, countries because of drug induced TdP, including astemizole, cisapride, and terfenadine. Drug induced TdP is extremely rare (< 1 case per 10,000 or 100,000 exposures) and the total number of attributable cases of torsades with each of these drugs is said to be no more than a few dozen
out of millions or tens of millions of patients exposed. Such a rare side effect is unlikely to be detected in a pre-marketing programme of several thousand subjects and will continue to be difficult to detect even after marketing when the rate of exposure is greatly increased. Given that the likely presentation is sudden death, the possibility of recognising a signal in a population with a high expected mortality (such as patients treated with buprenorphine for cancer related pain) is problematic.

The International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use ICH Harmonised Tripartite Guideline: The Clinical Evaluation Of Qt/Qtc Interval Prolongation And Proarrhythmic Potential For Nonantiarrhythmic Drugs E14 from 2005 states:

*The Torsade de pointes is very infrequently captured in clinical databases, even those for drugs known to have significant proarrhythmic effects. Given this, the failure to observe an episode of TdP in a drug application database is not considered sufficient grounds for dismissing the possible arrhythmogenic risks of a drug when these are suspected on the basis of ECG and other clinical data.*

This guideline recommends that monitoring should include the events of Torsade de Pointes; sudden death; ventricular tachycardia; ventricular fibrillation and flutter; syncope and seizures as, although some of these adverse events are less specific for an effect on cardiac repolarization, they may be more commonly captured and an imbalance in their frequency between study groups can signal a potential proarrhythmic effect of the investigational agents.

The risk of Torsades de Pointes is not discussed in the clinical overview. It is briefly addressed, and dismissed, in the Risk Management Plan (RMP). With regard to the results of study BUP1011, and using information largely taken from [information redacted]'s scientific evaluation performed in 2006 (see below), the RMP concluded that: *Several limitations around study design and data recording, which possibly confounded the results were identified during an independent re-assessment of the electrocardiographic data* and that *Aside from the trends of mean QTcI values, no QTcI outlier was identified which could be considered a concern with regard to pro-arrhythmic potential*. The RMP offered further support for the cardiovascular safety of buprenorphine in that:

- there is no report of TdP in association with buprenorphine in the company’s database
- there is one health care professional confirmed case of TdP in the WHO Vigibase (Q2, 2014) but in this buprenorphine was reported as suspected drug together with methadone and that the latter has a well-established association with TdP
- there are three case reports in the literature on successfully using buprenorphine therapy after methadone induced TdP in opioid addicted patients.


- With regard to the in vitro reports of inhibition of the HERG potassium channel, this evaluation argues that concentrations that are approximately 4000-fold higher than therapeutic free maximal plasma concentrations achieved in humans would be required to inhibit the HERG potassium channel, providing a more than adequate safety margin for in vivo use.
- With regard to the study BP1011, it noted that there was considerable inter and intra patient variability in QT intervals, that there was no statistical difference in the number of subjects with mean QT increase of 30 to 60 msec between groups and that no individual had

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an absolute QT prolongation of > 500 msec or increase from baseline > 60 msec. Other criticisms of both study design and conduct were provided.

• With regard to post marketing experience:
  – a search of the literature was conducted. This revealed one case report of a patient who had recurrent episodes of TdP on high dose methadone and who was changed to buprenorphine with resolution of QT prolongation and no further episodes of TdP
  – a search of the WHO Vigibase for the narrow terms of 'Torsades de Pointes' and 'QT prolonged' as well as the less specific terms of 'Cardiac Arrest', 'Cardio Respiratory Arrest', 'Fibrillation Cardiac', 'Fibrillation Ventricular', 'Sudden Death', 'Syncope', 'Tachycardia Ventricular', 'Unconsciousness', 'Ventricular Fibrillation paroxysmal'. This search was up to the third quarter of 2005. It showed no reports of TdP or QT prolongation in association with buprenorphine (all routes of administration). There were 36 reports of cardiac arrest, 8 reports of sudden death, 82 of syncope and 3 of ventricular tachycardia. The PPR (proportional reporting rate for the combination of a particular drug and particular ADR) showed a signal of disproportionate reporting for sudden death. This signal was assessed as weak and likely to be a false positive given the small number of cases
  – A search of the [information redacted] corporate drug safety database on Transtec was conducted for case reports up to 23 January 2006 using the terms 'Electrocardiogram QT corrected interval prolonged', 'Electrocardiogram QT prolonged', 'Electrocardiogram QT interval abnormal', 'Torsade de pointes', 'Sudden death' and 'Sudden cardiac death'. No case report for these terms was found.

An independent expert was engaged to review the potential for transdermal buprenorphine to cause TdP. His conclusion was that ‘any proarrhythmic torsadogenic toxicity of Buprenorphine is very unlikely’.

The overall conclusion of the evaluation was that ‘there appears to be no signal that buprenorphine may have a pro-arrhythmic effect in the range of exposure achieved with transdermal systems or even higher doses.’

The product information for the 7 day patch (Butrans in the USA, Norspan in Australia) carries this warning:

‘QTc Prolongation

• A positive controlled study of the effects of Butrans on the QTc interval in healthy subjects demonstrated no clinically meaningful effect at a Butrans dose of 10 µg/hour; however, a Butrans dose of 40 µg/hour (given as two Butrans 20 µg/hour Transdermal Systems) was observed to prolong the QTc interval

• Consider these observations in clinical decisions when prescribing Butrans to patients with hypokalemia or clinically unstable cardiac disease, including: unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, or active myocardial ischemia. Avoid the use of Butrans in patients with a history of Long QT Syndrome or an immediate family member with this condition, or those taking Class IA antiarrhythmic medications (for example, quinidine, procainamide, disopyramide) or Class III antiarrhythmic medications (for example, sotalol, amiodarone, dofetilide).’

Of note is that the most recent PSURs, from 2008 to 2013, include 6 case reports consistent with the ICH recommendations regarding search terms (one each of paroxysmal tachycardia, palpitations, sudden death and 3 episodes of syncope).

**Comment:** It is unacceptable that the study BUP1011 was not submitted in the dossier proper, that an updated evaluation of this risk has not been provided and that this risk is not addressed in the clinical overview. The risk is briefly mentioned, and dismissed,
in the Risk Management Plan. It is concerning that important documents are only provided within the appendices of the PSURs.

8.9.8. Risk of coronary vasospasm

This risk is described in the Risk Management Plan. It is not discussed in the clinical overview or the summary of clinical safety.

According to the RMP, two well documented individual case safety reports were received during post marketing surveillance that were suggestive of vasospastic angina induced by buprenorphine. Both cases were reported as serious, requiring hospitalisation, and both recovered. No further information could be located regarding this risk in the dossier.

8.9.9. Unwanted immunological events

A number of skin reactions, described as localised weeping rashes, that were included in AEs in the clinical studies and case reports in the PSURs were considered to be hypersensitivity reactions due to the patch. There was also one case report of anaphylaxis assessed as being possibly related to the patch included in PSURs.

No other immunological actions of buprenorphine were described although the dossier suggests that buprenorphine does not have the immune suppressant actions attributed to some other opioids.

8.10. Other safety issues

8.11. Safety in special populations

Safety in special populations was not specifically addressed in the clinical study programme. Children (< 18 years), pregnant or breastfeeding women and patients with severe liver impairment were excluded from the clinical studies. Patients with renal failure were excluded from most, but not all, of the clinical studies. No separate analysis of any patients with renal failure who were included was provided. Case reports in the PSURs show that transdermal buprenorphine has been used in all of these groups.

8.11.1. Use in children

The summary of clinical safety advises that buprenorphine transdermal patch was not studied in patients under 18 years of age and is not recommended for this age group.

8.11.2. Use in pregnancy and lactation

Studies into the use of buprenorphine transdermal patch in pregnant women have not been conducted. The SPC of the buprenorphine transdermal patch refers to studies in animals which have shown reproductive toxicity. There is little data available from which to estimate the potential risk for humans. Sublingual buprenorphine is used in the management of opioid dependence. Infants born to mothers in such programmes were reported to not show teratogenic effects. High doses of buprenorphine administered to women towards the end of pregnancy were reported as able to induce respiratory depression in the neonate, even after a short period of administration. Long-term administration of buprenorphine during the last three months of pregnancy may cause a withdrawal syndrome in the neonate. This may occur with transdermal buprenorphine, as is shown in some of the case reports in the PSURs.

Buprenorphine is excreted in human milk. In rats, buprenorphine is reported to inhibit lactation. The summary of clinical safety recommends that buprenorphine transdermal patch should not be used during lactation.
8.11.3. Use in the elderly

The use of transdermal buprenorphine was not specifically addressed in the clinical study programme, although elderly patients were not excluded and the mean age of patients in the trials was around 50 to 65 years. No separate analyses of elderly patients who were included was provided in the clinical overview. The summary of clinical safety states that:

- no relevant age dependent differences in buprenorphine’s absorption, distribution, metabolism, or elimination were observed upon intravenous or sublingual administration of buprenorphine
- subgroup analyses of the post marketing surveillance study AWB Transtec 2001/1 did not show any differences in safety (or efficacy) of the buprenorphine transdermal patch in patients younger or older than 70 years.

8.11.4. Use in hepatic impairment

The summary of clinical safety states that as de-alkylation of buprenorphine to norbuprenorphine is catalysed by CYP3A4, and this enzyme is reduced in severe chronic liver diseases, buprenorphine should administered with caution in such patients. Evidence of the safety of administration ‘with caution’ is not provided.

8.11.5. Use in renal impairment

The summary of clinical safety states that as renal clearance of buprenorphine is not altered in patients with renal impairment its use is possible in such patients. Evidence in support of this is discussed in the pharmacokinetic section of this evaluation.

8.12. Safety related to drug-drug interactions and other interactions

There are two main groups of drug-drug interactions described as potential risks in the dossier. These are not discussed in the safety section of the clinical overview. There is brief discussion of the risk of pharmacodynamics interactions resulting in CNS and respiratory depression and a longer discussion of pharmacokinetic interactions with inhibitors or inducers of the CYP3A4 system in the summary of clinical safety. The following discussion is based on information extracted independently.

One of the main groups of drug-drug interactions is the co-administration of buprenorphine patch with other drugs that potentially have a sedating or respiratory depressant effect, as this may result in excessive sedation or serious respiratory depression. There were no reports of this occurring in the clinical studies. The PSURs, however, describe a number of patients in whom buprenorphine patch was co-administered with benzodiazepines, other opioids and other drugs with the potential to cause sedation. This resulted in hospitalisation of 16 patients and contributed to the death, due to hypoxic brain and organ injury, in one of these patients and respiratory arrest in another. These cases have occurred despite the risk of co-administration with other potentially sedating agents being clearly described in the SPC.

The other main group of possible drug interactions is with drugs that inhibit or induce the CYP3A4 or CYP2D6 enzymes that are involved in the metabolism of buprenorphine. Many drugs are known to inhibit or induce these enzymes systems with the potential to alter the metabolism of buprenorphine. This is regarded as a low risk in the clinical overview as the main route of excretion of buprenorphine is unchanged in the bile. There are no reports of such interactions occurring in the clinical trial programme but patients on such drugs were largely excluded from the clinical studies. There were two reports of these drug-drug interactions in the PSURs: one patient had reduced analgesic efficacy of buprenorphine when carbamazepine was co-administered; another patient had increased buprenorphine side effects when fluoxetine was co-administered. This latter patient required hospitalisation. Carbamazepine is commonly prescribed for neuropathic pain and is known to induce the cytochrome P450 system. Anti-
depressants such as fluoxetine are known to inhibit CYP3A4 and are commonly prescribed in chronic pain states. Anti-retroviral drugs are also known to alter the cytochrome P450 system; buprenorphine may be co-administered for chronic pain states related to HIV infection. Anti-fungal drugs such as voriconazole are also known to inhibit the CYP3A4 enzyme and are commonly used for prophylaxis and treatment of fungal infections in patients receiving chemotherapy who may also have chronic pain. The risk of interactions with these drugs is inadequately discussed in the clinical overview.

Two other concerns relate to the potential for buprenorphine to reduce the analgesic effect of other opioids during co-administration and a possible reaction with MAOIs. The summary of clinical safety states that there is sufficient evidence in the public domain to indicate that therapeutic doses of buprenorphine do not reduce the analgesic efficacy of standard doses of an opioid agonist and that when buprenorphine is employed within the normal therapeutic range, standard doses of opioid agonist may be administered before the effects of the former have ended without compromising analgesia. In support of this it refers to the SPC for the parenteral versions of buprenorphine. Articles referred to elsewhere in the dossier describe co-administration of morphine and buprenorphine patches without loss of the analgesic effect of morphine.

Life threatening reactions have occurred when pethidine has been administered with, or within 14 days of administration, of MAOIs. The summary of clinical safety states that this same interaction with buprenorphine cannot be ruled out.

8.13. Safety and the opioid naïve

Most of the clinical efficacy studies were performed on patients who had previously received opioids for the management of chronic pain. In study PB-TTC-01 that compared prolonged release tramadol and buprenorphine patches in the management of chronic, non cancer related pain, only one third of patients had been previously exposed to opioids. This study found that a disproportionate number of patients withdrew early from the buprenorphine arm (117 out of 284), compared to the prolonged release tramadol arm (71 out of 276). A subgroup analysis was performed to compare opioid naïve patients to patients who had previous opioid experience. This found that the rate of nausea and/or vomiting in both subgroups of the prolonged release tramadol group was about 30% (opioid naïve patients; 32%, opioid experienced patients; 29%). However in the buprenorphine group, 62% of opioid naïve patients reported nausea and/or vomiting compared to 32% of the opioid experienced patients. It was also reported that 57 out of 117 patients in the buprenorphine group who terminated the study early due to nausea and/or vomiting were opioid naïve compared to 27 out of 71 patients in the tramadol group.

8.14. Safety and switching from other opioids

Response to opioids in chronic pain states can be highly individual and it is not unusual for different opioids to be tried in sequence in order to obtain optimal pain control. This practice raises the difficulty of determining the most appropriate starting dose of the next opioid, if under or over dosing is to be avoided. Different equivalence tables are commonly provided but these, particularly in relation to transdermal buprenorphine, are based on little evidence. A systematic review published in 2011 provides estimated conversion rates of oral morphine to transdermal buprenorphine of 1:75 and transdermal fentanyl to transdermal buprenorphine of 1:0.7 to 1.3.

The issue of opioid switching and dose equivalence was not specifically dealt with in the clinical studies. The subset analysis of patients on high dose oral morphine (at least 120 mg/day) in the post marketing surveillance study AWB Transtec 2003/2, found that although equivalence tables indicated that the strongest strength patch (40 mg) was appropriate, 29 out of 42 patients were commenced on the 30 mg patch and that this apparently provided acceptable pain control. In PSUR 3 from 2002, it was noted that 'According to the current knowledge on equi-efficient dosages of opioids 100 µg/h fentanyl should roughly be equivalent to 140 µg/h buprenorphine (2 x 40 mg buprenorphine patches). In practice it has been shown that when switching from Durogesic to Transtec the amount of active substance should be halved (Transtec 52.5 µg/h, 30 mg patch) to achieve the most favourable side effect profile possible'. Opioid switching is also discussed in the pharmacodynamics section.

8.15. Safety and off-label use

Off-label use, such as use in children and use for indications such as restless legs syndrome, depression and acute pain, are apparent from the post-marketing surveillance studies and the PSURs and briefly discussed in the Risk Management Plan. These issues are not discussed in the clinical overview.

It also appears, from the post marketing surveillance studies and the PSURs, that the practice of advising patients to cut the patch into smaller pieces in order to reduce the dose is not infrequent. This practice is mentioned as a ‘medication error’ in the RMP.

8.16. Evaluator’s overall conclusions on clinical safety

The sponsor seeks to demonstrate safety of the buprenorphine transdermal delivery system through the reporting of adverse events for this route of administration and through the existing literature regarding the safety of buprenorphine administered by other routes. There were no studies using safety as the primary variable. The clinical pharmacokinetic studies looked at safety variables other than adverse events (vital signs and laboratory variables) but these short-term studies were performed in healthy volunteers. The summary of clinical safety comments: ‘The safety evaluation plan included ongoing routine collection and evaluation of case reports, signal detection and generation of periodic safety update reports. It was considered adequate, because the product is a new application form of an established compound with a well-known safety profile.’ This safety profile was not otherwise substantiated: there was no review or summary of the currently available literature provided to support the safety profile of buprenorphine administered by other routes. This is not adequate.47

8.16.1. Exposure

This buprenorphine patch was first registered in Switzerland in 2000, with the development programme occurring in the late 1990’s and early 2000’s. In the controlled clinical trials 1,053 patients were exposed to the patch, with another 370 exposed to placebo patches. Of the 1,053 patients, 546 continued into open follow-up phases. In the post-marketing surveillance studies from the early 2000’s that were included in the dossier, over 30,000 patients were exposed to the buprenorphine patch. According to the Risk Management Plan, the total cumulative post authorization patient exposure to this buprenorphine patch is 505.6 million Patient Treatment Days since first registration in Switzerland in June 2000.

The duration of exposure documented in the studies provided is short for a drug proposed for long term use. No patients in the controlled studies were treated with the patch for more than 3 months. Of all the patients in the open studies, including the post-marketing surveillance studies, only 238 patients were treated with the patch for longer than 6 months. The sponsor proposes a maximum dose of 140 µg/h (2 x 40 mg patch, 2 x 70 µg/h). No patients in the controlled studies received this dose. The number treated with this dose in the post-marketing surveillance studies could not be determined as only the dose range of 71 to 140 mg was provided. Ninety three patients were exposed to this dose range but only 2 of these for longer than 6 months. No separate analysis of patients exposed to the proposed maximum dose is provided in any of the studies or in the dossier.

8.16.2. Adverse events

Adverse events were common in the clinical studies and were typical of opioid analgesics acting as mu-opioid receptor agonists. They included nausea, vomiting, constipation, dizziness and fatigue in rough order of frequency. A common adverse effect that is specific to the patch was application site reaction, most commonly itch and redness. Application site reactions were common with both active and placebo patches.

The frequency with which these opioid type AEs were observed varied considerably across the studies provided. Rates, overall, tended to be highest in the healthy volunteers in the clinical pharmacokinetic studies and in the two active controlled studies. Not surprisingly, the rates were lower in the post marketing surveillance studies where patients are less closely observed and there was a much higher discontinuation rate. Rates are lower again in the Company Core Data Sheet (CCDS), which is largely influenced by voluntary reporting.

Table 67: Frequency of adverse events according to type of trial

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo Controlled</th>
<th>Active controlled</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>WIS BUP 01, 02, 03</td>
<td>PR TTC 02</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17</td>
<td>13</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>Tiredness</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Constipation</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2</td>
<td>0.7</td>
</tr>
<tr>
<td>Headache</td>
<td>1.5</td>
<td>7</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>4</td>
<td>0.7</td>
</tr>
<tr>
<td>Application Site reaction</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

Occurrence of AES did not vary considerably between patients with tumour or non-tumour pain and patients aged more or less than 70 years. AEs were, however, observed to be more common in patients who had not previously been exposed to opioids (and a more common reason for discontinuation in these patients). In those studies that used prolonged release tramadol as a comparator, AEs were observed to occur considerably more frequently in the buprenorphine patch group.

The 6 month open follow-up phase of PB TTC 01 suggests that the rate of gastrointestinal AEs seemed to decrease over time (nausea from 12.5% to 7%; vomiting from 9 to 6% and
constipation from 9 to 2%) although it was not clear whether this was due to patients adjusting to these effects or to the use of anti-emetics and laxatives, or from patients with these side effects dropping out of the study. This study also found that application site reactions increased over time (from 40 to 50%) and were a common reason for patients discontinuing patch treatment.

Deaths were common in most studies involving the target population, but this was to be expected given the number of patients with serious malignancies included in these studies. No deaths in the clinical studies were assessed as related to the study drug and review of the narratives provided did not reveal any anomalies. SAEs described in the studies, and assessed as related to the study drug, were severe forms of the AEs described above. These included:

- severe nausea and vomiting, with this resulting in severe dehydration in one patient and a Mallory-Weiss tear in another
- confusion and respiratory depression
- severe somnolence
- generalised pruritus
- severe constipation
- severe application site reaction.

AEs resulting in discontinuation from the study were also those opioid type AEs described above. Nausea and vomiting, dizziness and application site reactions were some of the common AEs causing discontinuation from the studies.

8.16.3. Laboratory testing and other variables

The summary of clinical safety stated: ‘Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine’. In support of this, the clinical overview refers to a general review article from 2002 (sponsored by [information redacted]), an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine, from 1994 and 2005 respectively. Evidence of a more substantive assessment, with this including the past 10 years, is essential to determining the risks associated with the use of this product.

Potential effects of the study drug on vital signs, ECG, as well as laboratory variables, were not tested in the target population and only for a short period of time (up to 15 days) in healthy volunteers. Other parameters such as respiratory function, skin absorption from different sites, factors affecting absorption (local and general) were not assessed. Safety in special populations was not assessed.

8.16.4. Post-marketing experience

Periodic Safety Update Reports (PSURs) covering the years 2000 to 2013 were provided. During this time, the buprenorphine patch has gone from being marketed in one country to twenty six countries. Unsurprisingly, the number of case reports received each year has increased from less than 200 per year to over 1,000 per year. As discussed in the section above, some of these case reports describe serious adverse events attributable to the buprenorphine patch. Of these the most concerning are:

- Multiple reports of overdose symptoms requiring hospitalisation but occurring with doses as small as ½ of the lowest strength patch

48 Data from the 7 day patch was made available where it was relevant in response to TGA questions
49 Many of the AE’s attributable were also related to either unknown of sublingual formulation
• Multiple reports of depressed conscious state and/or respiratory failure requiring hospitalisation and occurring with co-administration of buprenorphine patch and other sedating agents. These included one death

• Several concerning cardiac events including syncopal episodes and tachyarrhythmias.

There were, however, few reports of drug abuse and only a small number of case reports of physical dependence developing with prolonged administration.

It is important to remember that these case reports result from voluntary reporting. The number of reports received is likely to represent only a fraction of the actual number of cases that occur in clinical practice.

8.16.5. Safety issues with the potential for major regulatory impact

There are a number of real or possible adverse effects that are concerning. These are mainly derived from the PSURs and represent real world experience. The only information provided to counterbalance these reports is the adverse event reporting in a number of short term studies of select populations.

One concern is the potential for side effects to occur with such severity as to require hospitalisation with therapeutic dosing (even as low as half a 20 mg patch). As noted above, there are a number of case reports in the PSURs in which patients treated with therapeutic doses were hospitalised due to AEs such as: severe nausea and vomiting; respiratory failure and stupor requiring treatment with naloxone; and acute confusional states including one culminating in a suicide attempt. Similar hospitalisations occurred when excessive doses were taken inadvertently or through activities that increased absorption from the patch.

Another concern is the number of patients in whom co-administration with other potential sedating agents resulted in respiratory depression and unconsciousness requiring hospitalisation and resulting in death from hypoxic injury for one patient. These cases occurred despite clear warnings in the SmPc and consumer information leaflets. Unfortunately, patients with chronic pain are likely to be on a variety of agents to control pain, with these commonly including benzodiazepines, anti-depressants and anti-psychotics, all of which are potentially sedating.

Cardiovascular safety is another concern. The track record of buprenorphine over the decades of use would indicate that this is very low risk but it cannot be ignored. The nonclinical studies indicating inhibition of the HERG potassium channel together with the QT prolongation observed with the use of 2 x 20 mg patches (average dose 70 µg/h) in a 'thorough QT study' and the PPR (Proportional Reporting Rate for the combination of a particular drug and particular ADR) signal of disproportionate reporting for sudden death with buprenorphine require serious consideration and close ongoing monitoring. It is worrying that this risk would appear to have been dismissed to the extent that it is not mentioned in the clinical overview and relevant documents only provided in appendices in the PSURs.

It is not possible to assess the risk of coronary vasospasm with use of the buprenorphine patch on the information available ('two well documented individual case safety reports'). It is unclear why this risk should only have been mentioned in the Risk Management Program and not have been addressed in the clinical overview. Coronary vasospasm is of serious concern in that it may require hospitalisation with invasive investigations and may be a precursor to acute myocardial infarction.

There is also the potential for abuse of this opioid. There are reports of the active drug being extracted from the patch in a variety of ways (descriptions of techniques can be readily found with a simple internet search). How frequently this may occur cannot be determined. It would be unusual for this to be reported as an adverse event, although it was in 3 reports. The other way it can be suspected is through the routine toxicology in the investigation of unexpected
deaths. Detectable buprenorphine levels do not, however, indicate the source of the buprenorphine. Despite this concern, buprenorphine is a restricted drug that, together with the added difficulty of extracting it from the matrix, should make abuse a relatively low risk.

8.16.6. Other safety issues

No specific data is provided regarding the use in special populations, except the elderly. The high mean age in most of the clinical studies and a subgroup analysis in one of the large post marketing surveillance studies suggest that there is no difference in safety in the elderly. This may need to be interpreted with caution in the extreme elderly as they were over represented in the case reports in the PSURs.

There are concerns with administration of buprenorphine to pregnant or breastfeeding women, based on nonclinical studies. This has not been tested in clinical studies. The dossier refers to reported safe use in observational studies of pregnant women in opioid dependence programmes, but correctly advises against the use of the buprenorphine patch in the draft PI.

Children were excluded from the clinical studies. The PI appropriately states that the use of the buprenorphine patch in patients below 18 years of age not recommended. The post marketing surveillance studies and case reports in the PSURs indicates that the product is used in children. This is not surprising given the convenience of a transdermal preparation in this age group and such off-label use can be expected to continue. The Risk Management Plan refers to an article describing use in children but this article was not included and is not referred to elsewhere.

Reference is made to the existing literature to guide use in liver and renal failure. As discussed in the pharmacodynamic section above, studies of the use of buprenorphine in patients with severe renal failure have not indicated any accumulation of the drug or its active metabolite. The recommendation that the buprenorphine patch may be used with close observation in liver disorders is based on pharmacokinetic studies that indicate most of its clearance is by biliary excretion and only 30% via hepatic metabolism. The safety of use in patients with liver impairment was not demonstrated.

The high rate of adverse drug reactions and discontinuation of buprenorphine seen in opioid naïve patients would indicate that this medication should be used with care in this group. The need for lower dose preparations is also suggested by the use of patches cut into quarters and halves, as described in the post marketing surveillance studies and PSURs. It may be more appropriate for opioid naïve patients to be commenced on the lower strength 7 day patches where these are available.

Drug-drug interactions, in particular the potential for life threatening respiratory failure and unconsciousness with co-administration of other sedating agents, are of obvious concern. Standard measures such as advice against this practice in the SmPC and CMI have not eliminated the problem.

8.16.7. Conclusion

A limited presentation of the safety of buprenorphine is provided in the dossier. Reliance is placed on the existing literature regarding administration by other routes to demonstrate safety but a review and summary of this literature is not provided.

There are substantial safety concerns regarding the product.

- The response to even low doses is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter patient variability in absorption from the patch demonstrated in the pharmacokinetic studies.

- Potentially life threatening co-administration with other sedating drugs is likely given the target population and given that many co-analgesics may cause sedation. This is a particular concern with the buprenorphine patch given the long half-life even after patch removal.
• The still unknown risk of Torsades de Pointes and coronary vasospasm also indicate the possibility that life threatening cardiac complications may occur.

Tolerability of the buprenorphine patch is another issue. Adverse event reporting in the clinical studies indicate that side effects such as nausea and vomiting were extremely common and one of the main reasons for patients discontinuing from the studies. That these side effects could be serious is shown by the SAEs in the clinical studies and the reports of hospitalisations due to ADRs in the case reports of the PSURs, although this was infrequent. Application site reactions were also common and, although categorised as mild to moderate with itching and erythema, were also a common reason for patients discontinuing the medication.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The dossier does not provide sufficient evidence to convincingly establish efficacy of the buprenorphine patch in the management of moderate to severe chronic pain. Given this, the advantages associated with transdermal drug delivery such as avoidance of first pass metabolism, achievement of constant drug plasma levels, an improved patient compliance and improved pain control due to less variation in therapeutic plasma levels may not be realised.

The three randomised double blind placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) proposed as ‘pivotal’ by the sponsor were unable to show that the buprenorphine patch was significantly better than placebo for the primary efficacy outcome measure of response rate, with this defined by a combination of pain relief and use of rescue medication. Secondary efficacy measures in these three studies (including retrospective pain relief, pain intensity, sleep duration, use of rescue medication) were, in general, suggestive of efficacy for the 20 mg and 30 mg patches. The 40 mg patch did not perform as well in the two studies that included it (WIS-BUP01 and WIS-BUP02).

PB-TTC-02 used a withdrawal design and recruited patients with severe tumour related pain who had previously been receiving high dose opioids. Of the 289 patients entering the run-in phase only 189 were randomised to the withdrawal phase. The most common reason for not continuing was lack of efficacy. The results of the withdrawal phase demonstrated efficacy of the 40 mg buprenorphine patch in a very select group of patients (patients with cancer related pain who had previously required strong opioids and who had achieved adequate pain control using the buprenorphine patch in the run-in phase).

The two active controlled non inferiority studies, PB-TTC-01 and BUP4201, used the WHO Level 2 weak opioid, tramadol, as comparator although the proposed indication would class buprenorphine as a WHO level 3 analgesic. Both of these studies had high discontinuation rates, with this disproportionately affecting the buprenorphine patch group; the most common reasons for discontinuation were ADRs. Both of these studies showed that the buprenorphine patch was non inferior in efficacy to prolonged release tramadol in the treatment of chronic non-tumour pain but less well tolerated.

The post-hoc analysis, WIS-BUP123 combined the data of the three studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03. The separate analyses of pain intensity and use of rescue medication showed improvements in the buprenorphine patch groups over placebo, but these improvements showed some inconsistencies across the three studies and the three patch strengths. The combined outcome measures failed to show statistically significant improvement over placebo.
At best, efficacy has been shown to be non-inferior to the weak opioid, prolonged release tramadol, with this occurring at the cost of a higher rate of side effects resulting in discontinuation of the buprenorphine patch.

9.2. First round assessment of risks

Clinical safety was inadequately dealt with in the dossier. Reliance was placed on experience with buprenorphine administered by other routes but a current review and summary of the relevant literature to support this was not provided. Important risks described in the Risk Management Plan were not discussed in the clinical overview.

There is little information to guide some aspects of safety, in particular the use in special populations, pharmacokinetic drug interactions, safety of long-term exposure, the potential for overdose at therapeutic doses and the dose relationship of reversibility of life threatening effects with naloxone.

From the information available, the main risks of the buprenorphine patch in the proposed usage are:

- Safety Concerns
  - The response to even low doses is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter patient variability in absorption from the patch demonstrated in the pharmacokinetic studies
  - Potentially life threatening co-administration with other sedating drugs is likely to continue to occur, given that many co-analgesics may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  - The still unknown risk of Torsades de Pointes and coronary vasospasm also indicate the possibility that life threatening cardiac complications may occur
  - The potential for abuse and misuse also exists, although this is probably at low risk of occurrence.

- Tolerability Concerns
  - Use of the buprenorphine patch of these strengths is frequently associated with such side effects of nausea, vomiting, constipation, dizziness and fatigue. These were sufficiently distressing for many patients to discontinue use of the buprenorphine patch (discontinuation rates of 18 to 46% were described in the post marketing surveillance studies)
  - Application site reactions frequently occurred and were of sufficient severity to be a common reason for patients to discontinue use of the product, particularly with long-term use.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of the buprenorphine patch for the proposed usage is unfavourable. Given the uncertain efficacy, the risks outweigh any potential benefit. These risks range from potentially life threatening, although rare, adverse drug reactions to the less severe but very common and distressing opioid type side effects.

10. First round recommendation regarding authorisation

It is recommended that the submission be rejected on the grounds that:
• efficacy has not been satisfactorily demonstrated for the proposed indication of the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids
  – the placebo controlled studies failed to demonstrate efficacy, using current regulatory and study design standards
  – the active controlled studies demonstrated non-inferiority to prolonged release tramadol, a WHO level 2 opioid, although the buprenorphine patch is proposed as a WHO Level 3 opioid
  – if reliance is to be on other supportive studies, then a thorough and current literature review and summary should be provided
• safety has not been satisfactorily demonstrated
  – the clinical overview and summary of clinical safety need to be updated to include all of the risks identified in the Risk Management Plan
  – for those aspects of safety that the submission relied upon the ‘well known’ safety profile of buprenorphine administered by other routes, a summary of the relevant literature should be provided
  – the risk of Torsades de Pointes needs to be reviewed. The scientific evaluation from 2006 (currently available only in the Appendix to a PSUR) should be included in the main part of the dossier and updated
  – the risk of coronary vasospasm needs to be discussed within the clinical overview and summary of clinical safety. More information regarding this risk should be provided.

11. Clinical questions

11.1. Pharmacokinetics

1. The PI describes buprenorphine as poorly soluble in water. It is elsewhere described as soluble and highly soluble in water. The major review by Budd, frequently referred to in the clinical overview, describes it as highly soluble. Could the water solubility of buprenorphine be better quantified?

2. Inspection of individual patient data in PK1599 appears to show considerable inter-patient variability. The plasma concentrations achieved during the wearing of a patch (HP5303/01, HP5303/02 and HP5303/04) also seem to show similar inter-patient variability. The inter-individual coefficient of variation is described as ‘relatively low (about 40% at the plateau level)’ for HP5303/01. Inter-patient variability is an important factor to consider in determining appropriate dosing recommendations and the expectation of response during patient counselling. It would be helpful to have a more comprehensive description of inter-patient variability with respect to release rates and plasma concentration with, for example:
  • Frequency histogram of calculated release rates from PK1599
  • Inclusion of median with min, max in the residual amounts and release rates in the summary table for PK1599
  • Inclusion of median with min, max for Cmax and AUC in the table of pharmacokinetic parameters of buprenorphine for HP5303/01 and HP5303/02.

An assessment of intra-patient variability in the crossover studies HP303/01 and HP303/04 would be useful as visual inspection of the individual patient concentration time...
graphs for HP5303/01 shows considerable variation in the amount of rise going from the 20 mg to the 40 mg patch.

3. The Transtec PI recommends that a skin site be left for at least one week before another patch is applied there. Study HP5303/02 demonstrated that re use of a site at 3 days resulted in increased absorption. The Australian PI for the sponsor’s product Norspan, a buprenorphine patch that is structurally almost identical to Transtec (although worn for 7 days not 4) states that 'In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events’ and that 'A new patch should not be applied to the same skin site for 3 to 4 weeks'.

Norspan and Transtec are structurally almost identical. Could the study of the effect of re using skin sites on absorption from the Norspan patch be provided? What is the evidence/rationale for the recommendation that it is appropriate to re-use a skin site after one week for Transtec?

4. The PI for the sponsor’s product Norspan provides additional important information of the effect of local application of heat on absorption: In another study in healthy subjects, application of a heating pad directly on the Norspan patch caused a transient, 26 to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. This is not consistent with the draft Transtec PI advice that: ‘Fever and the presence of heat may increase the permeability of the skin. Theoretically in such situations buprenorphine serum concentrations may be raised during Transtec treatment.’ Could the study of the effect of heat on absorption from the Norspan patch be provided and the effect of locally applied heat on the absorption of buprenorphine from the patch be clarified?

5. Bioequivalence of the 72 h and 96 h application times was demonstrated in healthy volunteers. Could the following study be provided to enable evaluation of the bioequivalence in the target population: Likar R et al., Transdermal Buprenorphine Patches Applied in a 4 Day Regimen Versus a 3 Day Regimen: A Single Site, Phase III, Randomized, Open label, Crossover Comparison. Clin Ther 2007; 29: 1591-1606.

6. The information provided by the National Library of Medicine on the sponsor’s product Butrans (a trademark clone of Norspan) provides additional important information regarding drug interactions: certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine and naloxone were administered sublingually. Cmax and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and Cmax and AUC for norbuprenorphine increased by up to 1.6 and 2.0 fold respectively, when sublingual buprenorphine was administered with these PIs. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor. The evaluator was unable to find any reference to these studies in the dossier. Could the effects of protease inhibitors on buprenorphine metabolism be clarified and a current review of pharmacokinetic interactions of buprenorphine be provided?

7. The draft Transtec PI states ‘There is evidence of enterohepatic recirculation’. This pharmacokinetic property was not described in the nonclinical overview or the clinical overview of pharmacokinetic properties of buprenorphine. Could this be clarified?

11.2. Pharmacodynamics

8. The potential for naloxone to reverse the unwanted effects of buprenorphine, especially in overdose, is problematic. The study by van Dorp\textsuperscript{29} showed that doses of 2 to 4 mg followed by an infusion rate of 4 mg/h were required to reverse the respiratory depressant effects of a therapeutic dose of intravenous buprenorphine. The Transtec PI recommends an initial bolus of 1 to 2 mg intravenously with this followed by an infusion. This initial dose may be inadequate and an initial bolus dose of 2 to 4 mg more appropriate, with a similarly high dose infusion rate (4 mg/h) to follow. The Naloxone PI that is referred to in the Transtec PI section on overdose does not allow for this high infusion rate, except at inordinately high intravenous fluid rate of 1 L/h given the recommendation: \textit{For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9\% or glucose 5\% injection to produce a solution containing 4 micrograms/mL.}\textsuperscript{51} Could advice be provided regarding the safety of a more concentrated solution of naloxone?

9. The references provided for pharmacodynamics interactions are over 10 years old. Could an updated review be provided?

11.3. Efficacy

10. In the protocol violations section of each of the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 it was noted that skin site assessments had occurred earlier than required by the protocol. The statement is then made that the patients were checked for skin reactions and that in all of the patients either no reaction was observed or the skin reaction lasted \textit{for longer than 30 minutes}. No further information is provided. Is this an error and should it read \textit{the skin reaction lasted for no longer than 30 minutes}?

11. In WIS-BUP02, the study report provides an estimate of the amount of opioids (as an average daily dose of \textit{buprenorphine equivalent}) being taken by the patients prior to entry into the study. No detail is provided regarding how the buprenorphine equivalent doses were determined. Could the method of determining the \textit{buprenorphine equivalents} be described?

12. The inclusion criteria for study PB-TTC-02 includes:

- \textit{Patients pre-treated with opioids and requiring an equi-analgesic dose range equivalent to 90 to 150 mg morphine per oral (p.o.) per day.}

Could the method of determining equi-analgesic doses be provided?

13. A number of the post-marketing observational studies, in which prescription of buprenorphine patches was said to be in accordance with the SPC, describe patients using \(\frac{1}{2}\) or \(\frac{1}{4}\) (and even \(\frac{1}{8}\)) of the 20 mg patch. Does cutting a patch into smaller pieces change its properties (for example, release rates, adhesion) and is this a recommended practice?

14. The post marketing surveillance study, AWB Transtec Pro 2005/2, describes Transtec Pro as a \textit{more advanced form of Transtec} and a \textit{new form with an application period of up to 96 hours}. From the pharmacokinetic studies it appeared that the patch used for 96 hours was identical to the patch used for 72 hours. Could this be clarified?

11.4. Safety

15. The summary of clinical safety states: \textit{Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine}. \textsuperscript{51}

\textsuperscript{51} DBL Naloxone hydrochloride injection product information.
In support of this, the clinical overview refers to a review article from 2002 (sponsored by [information redacted]), an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine, from 1994\textsuperscript{52} and 2005\textsuperscript{53} respectively. Could a substantive review of the safety of buprenorphine as evidenced in the literature, with this including the past 10 years, be provided?

16. The Risk Management Plan states in the section on local tolerability and sensitization that: ‘Two types of skin reactions can be observed in general: Irritative/toxic reactions or allergic skin reactions. Long term occlusion of the skin increases the risk for skin sensitisation and development of an allergic skin reaction.’ These effects of transdermal drug delivery systems are not elsewhere discussed. Could a review of the interaction between human skin and the buprenorphine patch be provided?

17. Pre-clinical data show that buprenorphine inhibits the Human Ether-a-Go-Go-Related Gene (HERG) channel in in vitro models. The potential for Torsades de Pointes, using the surrogate marker of QT prolongation, was investigated in the Phase I study BUP1011. The report of this is provided in PSUR10 and the conclusion of the study is that the dose of 2 x BTDS 20 mg (40 mg) prolongs QTci to an extent comparable to 400 mg of moxifloxacin. A maximal dose of 140 mg of transdermal buprenorphine is proposed in this submission. The risk of Torsades de Pointes is not discussed in the clinical overview or the summary of clinical safety. It is briefly addressed in the Risk Management Plan. With regard to the results of study BUP1011, this concluded that: ‘Several limitations around study design and data recording, which possibly confounded the results, were identified during an independent re-assessment of the electrocardiographic data’ and that ‘Aside from the trends of mean QTci values, no QTci outlier was identified which could be considered a concern with regard to pro-arrhythmic potential’. Despite this conclusion, the Australian PI for the sponsor’s closely related product Norspan includes:

\begin{quote}
In a study of the effect of Norspan patches on the QTc interval in 131 healthy males, therapeutic dosages (10 micrograms/h) had no effect on the QTc interval. Higher dosages (40 micrograms/h) and the active control (moxifloxacin 400 mg) each produced increases of 5.9 ms in the QTc interval. This observation should be considered when prescribing Norspan patches for patients with congenital QT prolongation and for patients taking antiarrhythmic medications in either Class 1A (for example quinidine, procainamide) or in Class III (for example amiodarone, sotalol) or any other medication which prolongs the QT interval.
\end{quote}

Could a more comprehensive scientific evaluation of the risk of Torsades de Pointes (including for the proposed maximum dose of transdermal buprenorphine 140 µg/h) be provided? Could the rationale for not including a warning regarding QT prolongation in the draft PI be provided?

18. According to the Risk Management Plan, two well documented individual case safety reports were received during post marketing surveillance that were suggestive of vasospastic angina induced by buprenorphine. Both cases were reported as serious, requiring hospitalisation, and both recovered. No further information was able to be located in the dossier. This risk is not addressed in the clinical overview or the summary of clinical safety. Could further information regarding these case reports be provided?

19. Re exposure during the clinical trial programme: According to the summary of clinical safety: ‘More than 1,250 patients were exposed to any buprenorphine transdermal patch during controlled clinical studies’. According to the Risk Management Plan: In total 1,318


subjects have been exposed in interventional clinical trials with buprenorphine transdermal patch. The Risk Management Plan also states that: ‘48 subjects in the clinical trial program were exposed to a 17.5 µg/h patch’; this dose was not used in any of the studies provided (except as ‘medication errors’ in some of the Post Marketing Surveillance Studies). Please clarify: have additional studies been included in the Risk Management Plan that have not been provided or discussed in the dossier?

20. Could the following documents that are in the Appendix of PSUR10 Volume 2 be provided as separate electronic copies:

- BUP1011 Study Report
- Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006
- EMA document ‘Points to Consider: The Assessment Of The Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products
- International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use ICH Harmonised Tripartite Guideline: The Clinical Evaluation Of Qt/Qtc Interval Prolongation And Pro-arrhythmic Potential For Non-antiarrhythmic Drugs E14 from 2005

12. Second round evaluation of clinical data submitted in response to questions

12.1. Norspan versus Transtec patches

As discussed in the clinical evaluation report (above), the proposed Transtec patch is the second buprenorphine patch proposed for the Australian market by the sponsor.

The sponsor sought to clarify this in the document ‘errors of fact/omission; clinical evaluation report’. In this document the sponsor provides the information that:

- Transtec is owned by [information redacted], manufactured by [information redacted] and the Australian sponsor is Mundipharma Pty Limited
- Norspan and Transtec share the same Australian sponsor (Mundipharma Pty Limited) and same manufacturer [information redacted] but had separate developments [information redacted]
- The studies AWB Transtec 2003/3 and AWB Transtec ONCO 2003/2 were included in the dossier.

Evaluation of response:

This response regarding the two patch types is incomplete. It is true that Transtec [information redacted] and Norspan had separate developments and the two brands of patches have the same manufacturer and the same sponsor in Australia. However, it is also important to appreciate that the two patches are virtually identical, both structurally and functionally.

The (clinical) evaluator has been provided with the TGA quality summary for ACPM for the Transtec patch. The summary contains information that is not publically available regarding the patches and that provides additional information regarding the Transtec and Norspan patch:
• The design of the Transtec and Norspan products are identical (this was noted by the evaluator in the comments in clinical rationale section above). The summary also notes that when comparing one strength of Norspan (as defined by mg of buprenorphine contained by the patch, for example 20 mg patch) to the same strength of Transtec, there is only a very slight difference in the amount of [information redacted] (the excipient that imparts the modified release and adhesive properties) and that the amounts of the other excipients and the surface area are the same.

• The difference in ‘release rates’ for the Norspan patch and the Transtec patch of the same strength in mg is due to the pattern of absorption from the patch, with a higher absorption rate seen during the first few days of wear. When an average is calculated for the first 3 to 4 days, the result is higher than the release rate calculated from an average over seven days. This accounts for the higher ‘release rate’ described for 4 day Transtec patch compared to the 7 day Norspan patch (see also evaluator comments in Clinical Rationale section above, the PK profile for the Transtec product in the description of Study HP5303-01 and the PK profile for the Norspan product in the Summary).

The importance of this information is that any safety concerns related to the Norspan product, as documented in the Norspan PI, must also be considered to apply to the Transtec product. Efficacy information, however, is not generalisable from the Norspan patch to the Transtec patch as the Norspan patch has not been investigated for the proposed Transtec indication. According to the current Norspan PI, the Norspan patch has been investigated in patients with moderate to severe chronic pain of osteoarthritis, low back and non-cancer pain requiring opioid analgesia and has not been investigated in patients with cancer related pain.

12.2. Clinical questions, the sponsor’s response and the evaluator’s comments

Clinical concerns were raised as clinical questions posed by the evaluator and clinical issues were also raised by the Delegate. Given the number of concerns and the overlap with some responses and comments, the following table is provided:

Table 68: Clinical concerns and associated questions

<table>
<thead>
<tr>
<th>Clinical Concern</th>
<th>Clinical Question</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interpatient variability in absorption from the patch</td>
<td>Pharmacokinetic Question 2</td>
</tr>
<tr>
<td>Intra-patient variability with change in patch strength</td>
<td>Pharmacokinetic Question 2</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 4</td>
</tr>
<tr>
<td>Appropriate interval before re-application of a patch to the same site</td>
<td>Pharmacokinetic Question 3</td>
</tr>
<tr>
<td>Patch-human skin interaction</td>
<td>Pharmacokinetic Question 3</td>
</tr>
<tr>
<td></td>
<td>Also: Safety Question 16</td>
</tr>
<tr>
<td>Effect of heat (endogenous and exogenous) on absorption from the patch</td>
<td>Pharmacokinetic Question 4</td>
</tr>
<tr>
<td>Bioequivalence of 72 hour and 96 hour application time in the target population</td>
<td>Pharmacokinetic Question 5</td>
</tr>
<tr>
<td>No demonstrated minimum effective plasma concentration</td>
<td>Clinical Issue 1</td>
</tr>
<tr>
<td>Clinical Concern</td>
<td>Clinical Question</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Drug-Drug Interactions, including range of estimated daily dose from Transtec patch</td>
<td>Pharmacokinetic Question 6</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Pharmacodynamics Question 9</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetic Question 6</td>
</tr>
<tr>
<td>Ceiling effect on respiratory depression</td>
<td>Clinical Issue Question 5</td>
</tr>
<tr>
<td>Naloxone in the management of buprenorphine overdose</td>
<td>Pharmacodynamics question 8</td>
</tr>
<tr>
<td>Pharmacodynamics drug-drug interactions</td>
<td>Pharmacodynamics Question 9</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Pharmacokinetic Question 6</td>
</tr>
<tr>
<td>Opioid equivalences in relation to transdermal buprenorphine and prolonged release tramadol</td>
<td>Efficacy Questions 11 and 12</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Clinical Issue Question 2</td>
</tr>
<tr>
<td>Potential for QT prolongation and Torsades de pointes</td>
<td>Safety Question 17</td>
</tr>
<tr>
<td>Potential for vasospastic angina</td>
<td>Safety Question 18</td>
</tr>
<tr>
<td>Clinical Study programme and current regulatory standards, including gaps in clinical study programme and failure to demonstrate efficacy</td>
<td>Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Also: Pharmacokinetic questions 2, 3, 4, 5, 6</td>
</tr>
<tr>
<td></td>
<td>Pharmacodynamics Question 9</td>
</tr>
<tr>
<td></td>
<td>Efficacy Questions 11 and 12</td>
</tr>
<tr>
<td></td>
<td>Clinical Issue Question 4</td>
</tr>
<tr>
<td>Appropriateness of prolonged release tramadol as a comparator in the non-inferiority studies</td>
<td>Clinical Issue Question 2</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td></td>
<td>Efficacy Questions 11 and 12</td>
</tr>
<tr>
<td>Equivalence interval in the non-inferiority studies</td>
<td>Clinical Issue Question 2</td>
</tr>
<tr>
<td>Enrichment study design for supporting study</td>
<td>Clinical Issue Question 3</td>
</tr>
<tr>
<td></td>
<td>Also: Clinical Issue Question 1</td>
</tr>
<tr>
<td>Dose dependent response</td>
<td>Clinical Issue Question 4</td>
</tr>
<tr>
<td></td>
<td>Also: Pharmacokinetic Question 2</td>
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<tr>
<td>Proposed dose range</td>
<td>Clinical Issue Question 5</td>
</tr>
<tr>
<td></td>
<td>Also: Efficacy Question 13</td>
</tr>
<tr>
<td></td>
<td>Clinical Issue Question 6 and 9</td>
</tr>
<tr>
<td>Proposed maximum dose</td>
<td>Clinical Issue Question 6</td>
</tr>
</tbody>
</table>
### 12.2.1. Evaluation of the response to issues raised

1. The PI describes buprenorphine as poorly soluble in water. It is elsewhere described as soluble and highly soluble in water. The major review by Budd, frequently referred to in the clinical overview, describes it as highly soluble. Could the water solubility of buprenorphine be better quantified?

**Sponsor’s response:**

Whilst it is the case that the review by Budd does refer to buprenorphine as highly soluble, it is our understanding that this reference relates to the actual in vivo performance and therefore relates to the finished drug product rather than buprenorphine API. The finished drug product does exhibit enhanced solubility due to the mixing with oleyl oleate. It remains the case that buprenorphine drug substance is poorly soluble in water.

**Evaluation of response:**

It is not clear to the evaluator what is meant by the distinctions ‘finished drug product’, ‘buprenorphine active pharmaceutical ingredient’ and ‘buprenorphine drug substance’. The solubility of buprenorphine both in in water and lipids is an important factor for transdermal absorption.

2. Inspection of individual patient data in PK1599 appears to show considerable inter-patient variability. The plasma concentrations achieved during the wearing of a patch (HP5303/01, HP5303/02 and HP5303/04) also seem to show similar inter-patient variability. The inter-individual coefficient of variation (CV) is described as ‘relatively low (about 40% at the plateau level)’ for HP5303/01. Inter-patient variability is an important factor to consider in determining appropriate dosing recommendations and the expectation of response during patient counselling. It would be helpful to have a more comprehensive description of inter-patient variability with respect to release rates and plasma concentration with, for example

- **Frequency histogram of calculated release rates from PK1599**
- **Inclusion of median with min, max in the residual amounts and release rates in the summary table for PK1599**
- **Inclusion of median with min, max for C_{max} and AUC in the table of pharmacokinetic parameters of buprenorphine for HP5303/01 and HP5303/02.**
– An assessment of intra-patient variability in the crossover studies HP303/01 and HP303/04 would be useful as visual inspection of the individual patient concentration-time graphs for HP5303/01 shows considerable variation in the amount of rise going from the 20 mg to the 40 mg patch.

**Sponsor’s response:**

The inter-individual variation in PK1599 was revisited. This report details the in vivo release rates for BTDS and lists and summarises the residual buprenorphine in BTDS patches from two studies; HP5503/01 and HP5503/02. The coefficients of variation associated with residual buprenorphine in HP5503/01 were between 8 and 10% and between 5 and 6.5% for HP5303/02.

The variability mentioned in the request above is in relation to the individual patch in vivo release (flux) rates that were calculated from the residual buprenorphine data. The following have been compiled to address the request for a more comprehensive description of inter-patient variability.

*Frequency histograms*

Frequency histograms of calculated release rates from the data in PK1599 have been requested and are presented below.
Figure 32: HP5303/01 frequency histograms of calculated release rates from the data in PK1599

Evaluator comment: Note that the ‘release rates’ provided for the Transtec patches in the PI are:
• 20 mg patch = 35 µg/h
• 30 mg patch = 52.5 µg/h
• 40 mg patch = 70 µg/h

This suggests a far more consistent and predictable absorption of the drug than is shown by the display of the results of Study 1599 provided here (above).

Additional summary statistics for PK1599

Residual buprenorphine patch content data were used to calculate the individual flux rate for each patch. These data were used to generate median values for the residual content and the release rates, which have been added to the summary table for HP5303/01 and HP5303/02

Table 69: Median values for the residual content and release rates

<table>
<thead>
<tr>
<th></th>
<th>Study HP5303/01</th>
<th>Study HP5303/02</th>
</tr>
</thead>
<tbody>
<tr>
<td>Content of patch (µg)</td>
<td>19840</td>
<td>21000</td>
</tr>
<tr>
<td>20 mg patch</td>
<td>20000</td>
<td>20000</td>
</tr>
<tr>
<td>40 mg patch</td>
<td>20000</td>
<td>20000</td>
</tr>
<tr>
<td>Residual amount of buprenorphine (µg)</td>
<td>17621 ± 1440</td>
<td>16000 ± 170</td>
</tr>
<tr>
<td>Mean</td>
<td>14088</td>
<td>16000</td>
</tr>
<tr>
<td>(CV%)</td>
<td>13640 ± 1540</td>
<td>16000</td>
</tr>
<tr>
<td>Median</td>
<td>18041</td>
<td>17560</td>
</tr>
<tr>
<td>Max</td>
<td>19698</td>
<td>20770</td>
</tr>
<tr>
<td>Amount of buprenorphine released (µg)</td>
<td>2219 ± 6718</td>
<td>2750 ± 3100</td>
</tr>
<tr>
<td>Mean</td>
<td>2219</td>
<td>2750</td>
</tr>
<tr>
<td>Min</td>
<td>2219</td>
<td>2750</td>
</tr>
<tr>
<td>Median</td>
<td>2219</td>
<td>2750</td>
</tr>
<tr>
<td>Max</td>
<td>2219</td>
<td>2750</td>
</tr>
<tr>
<td>Calculated buprenorphine release rate over 72 hours (Flux, µg/h)</td>
<td>30.6 ± 9.14</td>
<td>38.2 ± 43.1</td>
</tr>
<tr>
<td>Mean</td>
<td>30.6 ± 9.14</td>
<td>38.2 ± 43.1</td>
</tr>
<tr>
<td>Min</td>
<td>29.0</td>
<td>37.0</td>
</tr>
<tr>
<td>Median</td>
<td>25.0</td>
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</tr>
<tr>
<td>Max</td>
<td>38.6</td>
<td>56.8</td>
</tr>
</tbody>
</table>

Additional summary statistics for pharmacokinetic parameters for HP5303/01 and HP5303/02

For Study HP5303/02, AUC summaries were for 3 patch applications, and C_max summaries were for the 3rd patch application.

Table 70: Study HP5303/02, AUC summaries for 3 patch applications, and C_max summaries for the 3rd patch application

<table>
<thead>
<tr>
<th></th>
<th>Study HP5303/01</th>
<th>Study HP5303/02</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC0-INF (k·µg/mL)</td>
<td>20028</td>
<td>64596</td>
</tr>
<tr>
<td>Mean</td>
<td>20028</td>
<td>64596</td>
</tr>
<tr>
<td>Min</td>
<td>6629</td>
<td>31250</td>
</tr>
<tr>
<td>Median</td>
<td>19761</td>
<td>40837</td>
</tr>
<tr>
<td>Max</td>
<td>42759</td>
<td>163137</td>
</tr>
<tr>
<td>C_max (µg/mL)</td>
<td>20028</td>
<td>64596</td>
</tr>
<tr>
<td>Mean</td>
<td>20028</td>
<td>64596</td>
</tr>
<tr>
<td>Min</td>
<td>102.6</td>
<td>172.0</td>
</tr>
<tr>
<td>Median</td>
<td>314.2</td>
<td>499.0</td>
</tr>
<tr>
<td>Max</td>
<td>515.3</td>
<td>890.0</td>
</tr>
</tbody>
</table>

Intra-patient variability

The assessor has requested an assessment of intra patient variability in the crossover studies HP5303/01 and HP5303/04. However, the study HP5303/04 compares Transtec patches given...
over two different time periods of 72 and 96 hours therefore the sponsor believes that any comparison between treatments within an individual for this study will not be a true reflection of intra-patient variability. The response therefore focuses on the data gathered in HP5303/01.

The pharmacokinetic parameters $C_{\text{max}}$ and AUC recorded in Study HP5303/01 for the 20 mg patch were scaled to represent the parameters expected from a 40 mg patch, or an application of 2 x 20 mg patches. For those subjects who received both the 20 mg patch and the 40 mg patch, a ratio of the AUCs or the $C_{\text{max}}$ values was calculated and expressed as a percentage. The data are presented below.

**Table 71: Pharmacokinetic parameters $C_{\text{max}}$ and AUC recorded in Study HP5303/01 for the 20 mg scaled to represent the parameters form a 40 mg patch**

<table>
<thead>
<tr>
<th>Subject</th>
<th>$C_{\text{max}}$ TTS50</th>
<th>$C_{\text{max}}$ TTS50 x 2</th>
<th>$C_{\text{max}}$ TTS100</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>242.4</td>
<td>484.8</td>
<td>452.1</td>
<td>93.3</td>
</tr>
<tr>
<td>3</td>
<td>316.5</td>
<td>633</td>
<td>776</td>
<td>122.6</td>
</tr>
<tr>
<td>8</td>
<td>515.3</td>
<td>1030.6</td>
<td>711.1</td>
<td>69.0</td>
</tr>
<tr>
<td>10</td>
<td>102.6</td>
<td>205.2</td>
<td>346</td>
<td>168.6</td>
</tr>
<tr>
<td>15</td>
<td>356.1</td>
<td>712.2</td>
<td>778.1</td>
<td>109.3</td>
</tr>
<tr>
<td>20</td>
<td>232.7</td>
<td>465.4</td>
<td>616.3</td>
<td>132.4</td>
</tr>
<tr>
<td>21</td>
<td>192.2</td>
<td>384.4</td>
<td>420.6</td>
<td>109.4</td>
</tr>
<tr>
<td>22</td>
<td>333.2</td>
<td>666.4</td>
<td>519.5</td>
<td>78.0</td>
</tr>
<tr>
<td>24</td>
<td>447</td>
<td>894</td>
<td>808.6</td>
<td>96.4</td>
</tr>
<tr>
<td>25</td>
<td>472.4</td>
<td>944.8</td>
<td>609.7</td>
<td>64.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>AUC TTS50</th>
<th>AUC TTS50 x 2</th>
<th>AUC TTS100</th>
<th>Ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>14723</td>
<td>29446</td>
<td>31820</td>
<td>108.1</td>
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<tr>
<td>3</td>
<td>22206</td>
<td>44412</td>
<td>53036</td>
<td>119.4</td>
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<tr>
<td>8</td>
<td>34859</td>
<td>69718</td>
<td>63123</td>
<td>96.5</td>
</tr>
<tr>
<td>10</td>
<td>7670</td>
<td>15340</td>
<td>24151</td>
<td>157.4</td>
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<tr>
<td>15</td>
<td>20848</td>
<td>41696</td>
<td>46187</td>
<td>110.8</td>
</tr>
<tr>
<td>20</td>
<td>16216</td>
<td>32432</td>
<td>48455</td>
<td>149.4</td>
</tr>
<tr>
<td>21</td>
<td>16214</td>
<td>32428</td>
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<td>24</td>
<td>24560</td>
<td>49120</td>
<td>55176</td>
<td>112.3</td>
</tr>
<tr>
<td>25</td>
<td>42759</td>
<td>85518</td>
<td>44524</td>
<td>82.1</td>
</tr>
</tbody>
</table>

**Evaluation of response:**

The sponsor’s response confirms the wide range of inter-patient variability with respect to release rates and plasma concentration that was not apparent from the previous display of average values. This may provide some insight into the failure of the clinical efficacy studies to demonstrate efficacy with the buprenorphine patch. If it is assumed that there is a critical plasma concentration of buprenorphine that must be achieved for analgesia to occur, then the widely ranging absorption, and resulting plasma concentrations, would contribute to low response rates and inconsistent response across the patch strengths. Note that in some subjects, the plasma concentration achieved with the 20 mg patch was similar to the median plasma concentration achieved with the 40 mg patch in other subjects. This variability was even more marked with the obverse, with the plasma concentration achieved in some subjects with the
40 mg patch considerably lower than the median plasma concentration achieved with the 20 mg patch in other subjects. This overlapping spread of plasma concentrations seen with the different strength patches would also result in considerable difficulties in demonstrating any dose dependent response.

The display of intra-patient variability is also of interest as it confirms that changing from one strength patch to another higher strength patch will also have an unpredictable effect. This may be best appreciated by examining the difference between the maximum concentration achieved with the 20 mg patch and the 40 mg patch in each individual.

**Table 72: Change in plasma concentration with change to higher strength patch**

<table>
<thead>
<tr>
<th>Subject</th>
<th>20 mg patch</th>
<th>40 mg patch</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>242.2</td>
<td>452.1</td>
<td>209.9</td>
</tr>
<tr>
<td>3</td>
<td>316.5</td>
<td>776.1</td>
<td>459.5</td>
</tr>
<tr>
<td>8</td>
<td>515.3</td>
<td>711.1</td>
<td>195.8</td>
</tr>
<tr>
<td>10</td>
<td>102.6</td>
<td>346</td>
<td>243.4</td>
</tr>
<tr>
<td>13</td>
<td>366.1</td>
<td>780.1</td>
<td>412.1</td>
</tr>
<tr>
<td>20</td>
<td>232.1</td>
<td>615.3</td>
<td>382.6</td>
</tr>
<tr>
<td>21</td>
<td>192.2</td>
<td>420.6</td>
<td>228.4</td>
</tr>
<tr>
<td>22</td>
<td>333.2</td>
<td>519.5</td>
<td>186.3</td>
</tr>
<tr>
<td>23</td>
<td>447</td>
<td>808.6</td>
<td>361.5</td>
</tr>
<tr>
<td>34</td>
<td>472.4</td>
<td>609.7</td>
<td>137.3</td>
</tr>
<tr>
<td>25</td>
<td>266.4</td>
<td>642.6</td>
<td>376.2</td>
</tr>
</tbody>
</table>

It is reassuring that the change to from a 20 mg patch to a 40 mg patch resulted in an increase in plasma concentration for all subjects. However, the amount of increase varied from an increase of 137 pcg/mL to 460 pcg/mL. This non-linear and unpredictable response could account for some of the reports of serious adverse events reported by post-marketing sources with a change to higher strength patch.

This inter-patient and intra-patient variability raises the question as to whether the patches are best described by their putative release rates. It may be more accurate to describe them by the amount of buprenorphine contained within the patch and the application time.

It is very important that this individual variability is highlighted in the product information as it is relevant to an individual’s analgesic response and also relevant when switching from another opioid to buprenorphine patches, and from one buprenorphine patch to another. The inter-patien variability would indicate that it is most prudent to commence on the lowest available patch strength for all patients (with this including the range of Norspan patches) and that increasing the patch strength should also be done with care.

3. **The Transtec PI recommends that a skin site be left for at least one week before another patch is applied there.** Study HP5303/02 demonstrated that re-use of a site at 3 days resulted in increased absorption. The Australian PI for the sponsor’s product Norspan, a buprenorphine patch that is structurally similar to Transtec (although worn for 7 days not 4) states that ‘In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reappllication caused increased absorption, without clinical adverse events’ and that ‘A new patch should not be applied to the same skin site for 3 to 4 weeks’.

Norspan and Transtec are structurally identical. Could the study of the effect of re-using skin sites on absorption from the Norspan patch be provided? What is the evidence/rationale for the recommendation that it is appropriate to re-use a skin site after one week for Transtec?
**Sponsor’s response:**

The period between applying patches to the same skin site is different for Transtec compared with Norspan, as the development programmes for the two products were completely distinct and undertaken by separate companies. Therefore, each product’s posology is informed by its own data set.

The study examining the reapplication of Norspan after variable rest periods was BUP1002, (provided in the response). The objective of the study was to determine the minimum application site rest period necessary before reapplication of a subsequent patch, to ensure consistency in the PK profiles. Norspan was administered with, no rest, or 1, 2, 3 or 4 weeks rest in between applications. The study concluded that for maximal PK consistency, a minimum of 3 weeks rest is needed.

The rationale for a different recommendation for the period between applying patches to the same skin site for Transtec is based on the application regimen for Transtec, time taken for repair of the stratum corneum, literature information on transdermal patch application and post-marketing experience of Transtec in the European market.

The rationale is discussed in detail and is summarised here. Unlike Norspan, Transtec is a 4 day patch to be applied for up to 96 hours. Because of the difference in application regimen, it is not implausible to assume that the effect of continuous occlusion for the two products is different, and that skin regeneration (including the recovery of skin barrier properties) may occur faster for the 4 day Transtec application regimen.

The minimum period of at least 7 days of no reapplication to the same skin site, as recommended for Transtec, is generally consistent with literature on transdermal patches (Ale et al, 200955, Wohlrab et al, 201156). The minimum period of at least 7 days recommended for Transtec also appears reasonable in the context of dermatological considerations of epidermal regeneration and turnover.

The full turnover time of the human stratum corneum (the outermost layer which mainly provides for the skin barrier function) is estimated in the literature to be on average about 14 days (Hoath and Leahy 2003). However, only upper levels of the stratum corneum are typically removed as a result of the stripping effect. This supports a recovery time lower than 14 days between patch applications at the same skin area. The recommendation in the Transtec PI to ensure a minimum of 7 days patch free interval therefore appears adequate and in consistency with dermatological considerations on epidermal regeneration and turnover.

In addition, Transtec has been marketed for more than 10 years in the European Union with the recommended patch free interval of a minimum of 7 days. There is no evidence from post-marketing experience that this minimum interval of 7 days between two applications to the same skin site (resulting in a rotation including at least 3 different skin sites) would not be sufficient.

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54 BUP1002 CSR. A parallel, open label study to examine plasma concentrations of buprenorphine following reapplication of 10 mg buprenorphine transdermal system (BTDS) after variable application site rest periods in healthy subjects
Evaluation of response:

The issue of appropriate application time and the interaction between human skin and the Transtec patch is also addressed in the document response to other questions. The comments below addresses the issues raised in both locations.

The sponsor indicates that both the development program and the structure of the Norspan patch and the Transtec patch are different. Reading of descriptions of the two patches, as summarised in the clinical evaluation report, indicates that both are ‘matrix patches’ with near identical structure; this has been confirmed by the TGA quality evaluation section (summary for ACPM for the Transtec patch). It is therefore appropriate that information from one development programme be used to inform clinical use of the other patch.

Study BUP 1002 was performed as part of the clinical development programme for the Norspan patch. The stated objective was to: ‘determine the minimum application site rest period that ensured that reapplication of 10 mg BTDS to the same site in the deltoid region would not result in increased absorption of drug in normal healthy subjects’. The method used was to apply one Norspan 10 mg patch for seven days to the deltoid region of healthy subjects, aged 18 to 45 years. This patch was removed and a second patch applied to the same site 0 days, 1 week, 2 weeks, three weeks or four weeks later. Plasma concentrations were measured to determine AUC, Cmax, Tmax, Cmin parameters and to determine the time for absorption to return to normal. Subjects also took naltrexone to minimise adverse consequences. This study found that ‘Reapplication of BTDS 10 to the same site resulted in increased plasma concentrations and consequently higher mean AUC and Cmax values in the no rest, 7 day rest, and 14 day rest groups’. This is shown in the graphs below shows plasma concentration against time plots for the first patch application compared to patch application 7 and 14 days later.

Figure 33. Study BP1002. Mean plasma concentration versus time for 7 day interval between patch application and 14 day interval between patch applications

The clinical development programme for Transtec, as provided by the sponsor, has included little investigation of the factors that may affect absorption from the patch. There was no investigation of the appropriate interval between re-use of an application site.

The sponsor recommends a seven day interval between patch applications to the same site. The supporting documents provided in response to this question include two reviews of transdermal drug delivery and one review of human skin. These reviews were provided. Neither of the reviews of transdermal drug delivery systems specifically addresses the buprenorphine patch. The main focus of each review is the relationship between application time and the occurrence of skin reactions, both irritant and allergic. Neither review addresses the issue of increased absorption with too early re-use of an application site. Both reviews refer to skin stripping with removal of the patch and suggest that this can vary with the method of patch removal and also with the nature of the skin, with skin stripping and injury more severe in the fragile inelastic skin of the elderly. In the review by Ale55, an unreferenced statement is made: ‘Do not reapply the patch to the exact same area of skin for at least 7 days (or longer dependent on
manufacturer’s guidelines). The review by Wohlrab\textsuperscript{56} seems to be heavily dependent on the earlier review by Ale. This review makes the statement that ‘Transdermal patch application should be regularly rotated between body areas recommended in the product information that demonstrate the greatest tolerability, with no reapplication of the patch to the same area of skin within a period of at least 7 (preferably 14) days’. In support of this statement, the article refers only to the review by Ale. The review of the structure of the human epidermis discusses the structure of the human skin and the timeframe over which different components of skin regenerate and turn over. This review describes a 14 day turnover of the stratum corneum under normal circumstances. The review does not address the response of the stratum corneum to ‘skin stripping’ and the time taken for skin to repair following such an injury. These reviews do not support the sponsor’s contention that an interval of 7 days is sufficient between re-use of an application site.

The response provided by the sponsor suggests that the minimum interval of 7 days is based on ‘expert opinion’ and extrapolation from the behaviour of human skin under normal conditions. An inappropriately early interval between re-application at the same site puts the patients at risk of increased absorption of buprenorphine, with the potential for more adverse effects, and also at higher risk of skin reactions, both irritant and allergic.

The sponsor also comments that Transtec has been safely marketed for more than 10 years with the recommendation for a 7 day interval between patch applications. Reliance on spontaneous post-marketing reports may not be adequate to inform this basic property of absorption from the patch, for example the information related to patch site and interval between patch applications is not reported for the case reports of overdose at therapeutic doses provided in the PSURs. Nor is this information available in relation to skin reactions observed with patch application.

This is a significant gap in the development programme for the Transtec patch and the advice provided in the PI is insufficient. Study BUP 1002, performed with the Norspan patch, provides the only evidence of the effect of the interval time on absorption from a buprenorphine patch. In the absence of any evidence that the duration of application affects absorption with subsequent re-use of an application site, the same interval should be recommended for both the 7 day patch and the 4 day patch. The Transtec PI should recommend an interval of 3 to 4 weeks before re-use of an application site and the patient should also be advised that the skin site should not be re-used while any skin changes persist, in particular any reddening or broken skin. Note that there was a post-marketing report of hospitalisation due to overdose resulting from application of the patch to an area of damaged skin.

The CMI should include detailed instructions as to the method of patch removal as provided in the review by Wohlrab:\textsuperscript{56}

\begin{quote}
“Following the treatment period with a particular patch, patients should carefully remove the system to minimise damage to the stratum corneum. The patch should be removed in a careful manner by mobilising one patch corner and moving this slowly and horizontally across the skin surface at a flat angle. This is particularly important in elderly patients who have more fragile skin.”
\end{quote}

4. The PI for the sponsor’s product Norspan provides additional important information of the effect of local application of heat on absorption: In another study in healthy subjects, application of a heating pad directly on the Norspan patch caused a transient, 26 to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed. This is not consistent with the draft Transtec PI advice that: ‘Fever and the presence of heat may increase the permeability of the skin. Theoretically in such situations buprenorphine serum concentrations may be raised during Transtec treatment’. Could the study of the effect of heat on absorption from the Norspan patch be
provided and the effect of locally applied heat on the absorption of buprenorphine from the patch be clarified?

Sponsor’s response:

For Norspan 7 day patch, there are two studies that are applicable to the effect of heat on buprenorphine absorption; BP96-1102 and BP98-1204.

BP96-1102 looked at the effect of increased core body temperature on buprenorphine absorption, in response to an endotoxin challenge. The data showed that there was a significant correlation between plasma buprenorphine concentration and change in body temperature, however, the increase in plasma buprenorphine concentration in the endotoxin treatment was not statistically significant. Fever did not result in significant changes in plasma buprenorphine concentrations during BTDS wear. The study concluded that BTDS poses no special safety concerns during fever and the accompanying sequelae of the acute phase response to infection.

BP98-1204 examined the effect of external heat application on plasma buprenorphine concentrations. An external heating pad was applied for three 2 hour periods on days 2 and 4. During the hours of intermittent heating pad application and up to 5 hours later, the average plasma buprenorphine concentration was higher than it was without heat. The mean AUC, for buprenorphine over 7 days was similar for BTDS 10 and BTDS10 with a heating pad, therefore total exposure was not affected. An increase in opioid related adverse events was associated with the heating pad application; these events were judged not to be clinically important.

In summary, whilst the results of the studies showed that fever and external heat did transiently increase concentrations, these increases were not deemed to be clinically significant. However, because some increase was observed in both cases, this resulted in a note of caution being added to the Norspan PI in relation to avoiding exposing the application site to external heat sources, and in relation to patients who are febrile. It is reasonable that the wording in the Transtec PI should be consistent with the Norspan PI in relation to the effects of heat.

Supporting documents:

- BP96-1102; A pharmacokinetic study to determine the effect of increased core body temperature on buprenorphine absorption from the buprenorphine 25 µg/h TDS in normal volunteers
- BP98-1204; Evaluation of effect of external heat application on the plasma concentration time course of buprenorphine from BTDS in healthy subjects (BTDS 10)
- Norspan PI
- Updated Transtec PI.

Evaluation of response:

The study reports of BP96-1102 and BP98-1204 were reviewed and are described below:

BP96-1102; In this crossover study, healthy subjects wearing a Norspan 10 patch were exposed to an endotoxin challenge on Day 2 of patch application. This was repeated after a 10 day washout period but with placebo administered instead of endotoxin. Oral temperature and plasma concentrations were measured frequently throughout patch application. The definition of fever proposed in the original protocol for this study was body temperature > 38.3°C. As this body temperature was not achieved in most subjects after the endotoxin challenge, the definition was changed post-hoc to a body temperature of 0.56°C above a baseline of 36.38°C for endotoxin treatment and a baseline of 36.33°C for placebo treatment. According to the latter definition, 19 out of 20 healthy subjects had a 'fever' in response to the endotoxin challenge. Note that this 'fever' equates to a body temperature of 36.94°C which would commonly be regarded as normal. Unsurprisingly, this study did not find significantly elevated plasma concentrations of buprenorphine with endotoxin challenge. Of interest and as another indicator...
of individual variability in absorption, one subject was found to have plasma concentrations of buprenorphine that were 3 to 12 times higher than the population mean in both phases of the study.

BP98-1204; in this crossover study, healthy subjects wore a Norspan 10 patch for seven days. After a 10 day washout period, a second patch was applied. During one of the treatment periods, a heating pad was placed over the patch for several 2 hour periods on Day 2 and Day 4. Plasma concentrations of buprenorphine were measured at frequent interval during each patch application. The temperature under the heating pad was measured and recorded at the onset, midpoint, and end of each 2 hour heating period. Mean plasma buprenorphine concentrations were found to increase within a half hour of heating pad administration and to remain high throughout heating pad application. The heat effect remained evident for 5 hours after the heating pad was removed.

**Figure 34: Study BP98-1204 Effect of heat application on plasma concentration of buprenorphine**

Adverse event reporting was noted to increase during the treatment period with heat application (from 84 to 133 reported adverse events). The most frequent adverse events for both treatment groups included headache, pruritus, nausea, vomiting, dizziness, somnolence, asthenia, and other known pharmacological effects of opioids. Adverse events that occurred with higher frequency during the heat treatment period (nausea, dizziness, vomiting, somnolence), occurred at those times when the heating pad was being administered. Hypotension (defined as a simultaneous decrease of 20 mmHg in systolic BP and 10 mmHg
A decrease in diastolic BP was observed in 20% of subjects during the heat treatment period but no subjects during the control treatment period.

Absorption from a buprenorphine patch is clearly increased by the exogenous application of heat. The resulting nausea, dizziness, vomiting and somnolence was not adjudged to be clinically relevant by the sponsor. Note, however, that these distressing symptoms were observed with the low dose 10 mg Norspan patch. It is not known if the application of heat to the higher strength Transtec patches (20 mg, 30 mg and 40 mg), with their larger drug amount and surface area, would result in even more severe adverse effects. The effect of endogenous increases in heat (as with fever or activity or exposure to hot weather) on absorption has not been clarified. The post-marketing reports of hospitalisations due to overdose resulting from increased absorption (from working outside on a hot day, application of TENs) indicate that this is a realistic concern.

The lack of knowledge regarding the effect of heat, exogenous and endogenous, is a concerning gap in the clinical development programme of the Transtec patch. Given this, it may be appropriate to considerably strengthen the warning in the PI beyond that which is provided for the low strength Norspan patch.

5. Bioequivalence of the 72 h and 96 h application times was demonstrated in healthy volunteers. Could the following study be provided to enable evaluation of the bioequivalence in the target population: Likar R et al., Transdermal Buprenorphine Patches Applied in a 4-Day Regimen Versus a 3-Day Regimen: A Single-Site, Phase III, Randomized, Open label, Crossover Comparison. Clin Ther 2007; 29 (8): 1591-1606.

Sponsor’s response:
The study conducted by Likar et al. was an investigator led study for which [information redacted] only provided an unrestricted grant as detailed in the acknowledgements. As such there is no access to the study data beyond the published paper.

Evaluation of response:
The clinical question requested that the study be provided as the published article not the study report. This important article was not included in and was not referred to in the original submission. A major concern of the original submission was to show that the application times of 96 hours and 72 hours were equivalent. The dossier provided a pharmacokinetic study in healthy volunteers and a population PK study. It was not demonstrated in the target population and all of the clinical studies included in the original submission used an application time of 72 hours (except for one post-marketing surveillance study that was not discussed in the clinical overview). Demonstrating the equivalence of 72 hour and 96 hour application times in the target population is clearly important as the submission proposes an application time of 96 hours.

6. The information provided by the National Library of Medicine on the sponsor’s product Butrans (a trademark clone of Norspan) provides additional important information regarding drug interactions: ‘certain protease inhibitors (PIs) with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine and naloxone were administered sublingually. C_{max} and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and C_{max} and AUC for norbuprenorphine increased by up to 1.6 and 2.0 fold respectively, when sublingual buprenorphine was administered with these PIs. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that atazanavir is both a CYP3A4 and UGT1A1 inhibitor.’58 The evaluator

was unable to find any reference to these studies in the dossier. Could the effects of protease inhibitors on buprenorphine metabolism be clarified and a current review of pharmacokinetic interactions of buprenorphine be provided?

**Sponsor’s response:**

A full analysis regarding the association of buprenorphine and interaction with protease inhibitors has been performed by the applicant. Following an initial analysis in 2007 the topic was placed under ongoing monitoring for a 12 month period and was then analysed further following which the applicant concluded that there was insufficient evidence for an association. Both analyses have been provided for your reference. As part of the MAH’s ongoing pharmacovigilance system, reports of buprenorphine and interaction with protease inhibitors will be continually evaluated to ensure that the current conclusion remains accurate.

Supporting documents:

- Buprenorphine-protease inhibitor interaction review June 2008.

**Evaluation of response:**

No formal drug-drug interaction studies were provided in the sponsor's dossier. The supporting documents are a safety evaluation; interaction between buprenorphine and protease inhibitors that was conducted in 2007 and an update to this review made in 2008 after 12 months of ongoing monitoring. These reviews were written in relation to the Norspan patches.

**Summary of reviews:**

Three case reports of adverse events associated with the combined use of buprenorphine and protease inhibitors were described. In each of these, the patient experienced increased sedation. From the descriptions provided in two of the cases, the patients were taking sublingual buprenorphine in doses of 8 to 12 mg daily. In the other case, the route of administration was not clear. The safety evaluation refers to a clinical trial that found increased buprenorphine levels in participants receiving the protease inhibitors ritonavir whilst also taking buprenorphine/naloxone for opioid dependence, although no pharmacodynamic sequelae were described. A further study by the same group is referred to in the 12 month update. This study examined the pharmacokinetic and pharmacodynamic interactions between buprenorphine and the protease inhibitors Atazanavir and Atazanavir/Ritonavir in forty control and opioid dependant, buprenorphine/naloxone maintained, HIV negative subjects. This found that the co-administration of protease inhibitors significantly increased buprenorphine serum concentrations and its metabolites. This pharmacokinetic interaction was associated with a mild to moderate increase in daytime drowsiness in 30% of the opioid dependant patients. The buprenorphine doses administered in the clinical trial were 15 to 16 mg per day.

A third article by the same group was identified by the evaluator. This article reviews clinically important drug interactions with regard to the high doses used in the maintenance of opioid dependent patients.

These reviews were written in relation to the low dose Norspan patches as is clear from the reference to the Butrans/Norspan patch (20 µg/h) in the discussion section of the 12 month

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60 McCance-Katz E F, et al. Interaction between Buprenorphine and Atazanavir or Atazanavir/Ritonavir; *Drug and Alcohol Dependence* 2007; 91; 269-278
update. This states that the daily dose of buprenorphine achievable by the highest Butrans/Norspan patch strength (20 µg/h) is 0.48 mg/day. No reference is made to the daily doses achievable with the much higher strength Transtec patches. A range of approximate doses in healthy volunteers can be calculated from the pharmacokinetic data provided in Question 2 above:

Table 73: Approximate daily dose of buprenorphine from Transtec patch (calculated from residual buprenorphine in used patches)

<table>
<thead>
<tr>
<th>Study HP5303/01</th>
<th>20mg patch</th>
<th>40mg patch</th>
<th>Study HP5303/02</th>
<th>20mg patch</th>
<th>30mg patch</th>
<th>40mg patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated release rate over 72 hours (mcg/h)</td>
<td>2</td>
<td>21</td>
<td>3.2</td>
<td>5</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Approximate 24 hour dose (mg)</td>
<td>0.0</td>
<td>0.5</td>
<td>0.1</td>
<td>0.1</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Note that the range of daily dose estimated for the 40 mg patch was 0.04 to 5.0 mg. If the proposed maximum of 2 x 40 mg patches is used, the daily dose may be as high as 10 mg in some patients. This suggests that the average daily doses of 15 to 16 mg seen with maintenance therapy in opioid dependent patients in whom the pharmacodynamics interaction was observed are unlikely to be achieved transdermal delivery systems. The lowest daily dose of buprenorphine at which a drug-drug interaction with protease inhibitors may be seen is, however, unknown. The possibility of interactions with protease inhibitors remains and it is appropriate that a warning to this effect be included in the PI.

7. The draft Transtec PI states ‘There is evidence of enterohepatic recirculation’. This pharmacokinetic property was not described in the Non-clinical overview or the clinical overview of pharmacokinetic properties of buprenorphine. Could this be clarified?

Sponsor’s response:
The BNF, section 4.7.2 (2006) and Martindale (2010) both state that after parenteral and sublingual administration, buprenorphine is excreted mainly unchanged in the faeces and there is some evidence for enterohepatic recirculation.

In addition, the presence of buprenorphine and metabolite in human faeces at times when there was very little urinary excretion of conjugated buprenorphine was described by Cone et al. (1984), indicating an enterohepatic circulation of buprenorphine in humans.

Supporting documents:

Evaluation of response:
This is acceptable
8. The potential for naloxone to reverse the unwanted effects of buprenorphine, especially in overdose, is problematic. The study by van Dorp29 showed that doses of 2 to 4 mg followed by an infusion rate of 4 mg/h were required to reverse the respiratory depressant effects of a therapeutic dose of intravenous buprenorphine. The Transtec PI recommends an initial bolus of 1 to 2 mg intravenously with this followed by an infusion. This initial dose may be inadequate and an initial bolus dose of 2 to 4 mg more appropriate, with a similarly high dose infusion rate (4 mg/h) to follow. The Naloxone PI that is referred to in the Transtec PI section on overdose does not allow for this high infusion rate, except at inordinately high intravenous fluid rate of 1L/h given the recommendation: ‘For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9% or glucose 5% injection to produce a solution containing 4 micrograms/mL’. Could advice be provided regarding the safety of a more concentrated solution of naloxone?

Sponsor’s response:

Naloxone is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by opioids. In the mentioned study by van Dorp and co-workers (van Dorp et al., 2006), it was shown that naloxone doses of 2 to 3 mg, followed by a continuous infusion of 4 mg/h, caused a full reversal of 0.2 and 0.4 mg buprenorphine induced respiratory depression. They concluded that the reversal ‘depends on the buprenorphine dose and the correct naloxone dose window. Because respiratory depression from buprenorphine may outlast the effects of naloxone boluses or short infusions, a continuous infusion of naloxone may be required to maintain reversal of respiratory depression.’ This approach is in general in line with the recommendations given in the Transtec PI, however the initial doses of naloxone are lower than those recommended by van Dorp et al. (2006).

The dose recommendation of IV naloxone in the overdose section of the Transtec PI is based on experiences from clinical daily work and the recommendations given in the respective PI of Narcan (naloxone hydrochloride solution). As stated in the latter, initial boluses of 1 to 2 mg in 2 to 3 minute intervals should be given until the balance of optimum respiratory response and adequate analgesia is reached. If this level is attained, continuous infusion to maintain constant naloxone plasma levels is recommended. Additional doses may be necessary depending on the individual patient’s response.

At this point, we are unable to provide evidence for the safety for higher concentrated naloxone solutions (as for example stated by van Dorp et al., 2006). However, the sponsor appreciates further thoughts and discussions about a potential adaption of the Transtec PI with respect to an increase of the dose recommendation for the initial naloxone dose to treat respiratory depression caused by buprenorphine.

Supporting documents:


Evaluation of response:

Widely ranging doses of naloxone are used in clinical daily practice, according to the nature of the opioid overdose and response to initial doses of naloxone. The important information for the prescriber in relation to reversing the respiratory depression, and other side effects, that may occur with transdermal buprenorphine overdose includes the need to remove the patch, that higher doses of naloxone may be required compared to other opioids and that the duration of effect of the buprenorphine patch may outlast the effect of bolus doses of naloxone, even with patch removal.

Clarification of the appropriate dose of naloxone may require examining clinical reports. From the case reports of buprenorphine overdoses in the PSURs that were treated with naloxone, doses of 0.2 mg to 2.5 mg were described as effective. Closer examination of these cases by the
sponsor, and any others subsequently reported, may provide further information. The article by van Dorp does not describe the concentration of the naloxone infusion used. The sponsor may also find it useful to perform a literature search for the use of naloxone infusions in the management of opioid overdose. If descriptions of more concentrated infusions are described as having been used without adverse consequences then this information could be added to the PI as ‘described in clinical practice’ and reference made to the relevant article(s). For example the review article provided to another question describes the use of ‘1 mg in 50 mL of normal saline over 30 minutes’ (page 434) although the source of this data is described as ‘(data on file, Langford)’ with Langford being one of the authors.

9. The references provided for pharmacodynamics interactions are over 10 years old. Could an updated review be provided?

Sponsor’s response:

An ongoing review of literature is undertaken by the Marketing Authorisation Holder in the EU for pharmacovigilance activities. This review is based on the following 3 search strategies:

- Buprenorphine is searched as major focus in the database Embase.com (EMBASE+MEDLINE) combined with the term transdermal drug administration as well as major focus with the route subheadings transdermal drug administration.
- PubMed is searched with the string 'buprenorphine transdermal [Title/Abstract]'
- The Cochrane Library is searched using the keyword 'transdermal buprenorphine'.

No new references relating to pharmacodynamics interactions of the 4 day Transtec patch have been identified.

Evaluation of response:

The discussion of pharmacodynamics interactions provided in the clinical overview, refers to possible interactions with MAOIs and agents that cause depression of the central nervous system. Three articles are cited, from 1990, 1991, and 1993. Of note, is that no reference is made to the potential loss of the protective ‘ceiling effect’ regarding respiratory depression with buprenorphine when co-administered with other sedating agents.

The potential from pharmacodynamics interactions with protease inhibitors (as discussed above in Question 6) is also not described. The possible interactions with other CYP3A4 inhibitors and inducers resulting in pharmacodynamics effects that were the subject of case reports in the PSURs (decreased efficacy with carbamazepine, increased side effects with fluoxetine) are not discussed.

Pharmacodynamic interactions develop following absorption of the drug. Given this, drug interactions described with buprenorphine administered by routes other than transdermal may be relevant, for example the pharmacodynamics interaction described with protease inhibitors above. Drug interactions described with other transdermal preparations of buprenorphine would also be generalisable to the 4 day Transtec patch. It would appear from the sponsor’s response that the search strategy only includes transdermal buprenorphine.

The sponsor’s response is insufficient.

10. In the protocol violations section of each of the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 it was noted that skin site assessments had occurred earlier than required by the protocol. The statement is then made that the patients were checked for skin reactions and that in all of the patients either no reaction was observed or the skin reaction lasted ‘for

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longer than 30 minutes'. No further information is provided. Is this an error and should it read 'the skin reaction lasted for no longer than 30 minutes'?

**Sponsor’s response:**

The WIS-BUP02 clinical study report states that the skin assessment should not have been carried out within 15 minutes after patch removal. This was to avoid recording skin reddening owing to the removal of the patch as an adverse event. The underlying assumption was that skin reddening owing to patch removal disappears within 15 minutes and that in contrast erythema from other causes will not disappear within 15 minutes from patch removal.

The protocol violations section explains that in some cases the skin assessment was made within 15 minutes after patch removal. The skin reactions observed did not disappear within 30 minutes and thus were not ascribed to patch removal. In other words, the skin reactions were adverse events and were not artefacts due to patch removal. Therefore, the current text is correct.

**Evaluation of response:**

This is acceptable

11. In WIS-BUP02, the study report provides an estimate of the amount of opioids (as an average daily dose of ‘buprenorphine equivalent’) being taken by the patients prior to entry into the study. No detail is provided regarding how the buprenorphine equivalent doses were determined. Could the method of determining the ‘buprenorphine equivalents’ be described?

**Sponsor’s response:**

At the time of this study it was common practice to convert between opioid doses. This conversion was based on widely used and well accepted knowledge that was published by Kathleen Foley in the New England Journal of Medicine (Foley 1985) and in a handbook about experimental pharmacology (Foley 1993). Therein, the concept and details about relative analgesic potency and estimates to allow conversion of equi-analgesic doses of different opioids is described. For the commonly used opioid drugs, the relative potency estimate was based on clinical experience (Foley 1985) and later on also upon investigations in studies mostly done in comparison to morphine in acute and chronic pain patients (Foley 1993).

However, if an individual product’s PI contained conversion information different from Kathleen Foley’s information, the information in the PI prevailed and was used in study WIS-BUP02.

The use of the Foley table was acknowledged by a review published by Pereira et al. (2001). This publication critically reviewed and discussed equi-analgesic dose ratios for opioids and confirmed the use of the Foley data. In addition, also the results of study WIS-BUP02 further confirmed the use of the Foley conversion table (Sittl et al., 2003).

Altogether, it was shown that the right choice was taken to determine the equivalent doses of buprenorphine when the study was initiated.

(Note: please also see our response to request 3).

Supporting documents:


**Evaluation of response:**

The evaluator accepts the use of opioid equivalence tables to determine equi-analgesic doses when switching between opioids and accepts that these tables can be used to determine equi-analgesic doses when assessing patients for inclusion in the study. The evaluator also accepts that the tables used were appropriate to that time and place. The evaluator’s question was more specific; how were the buprenorphine equivalent doses as shown for example in Figure 8.3.1.1 and Table 8.4.2.2 of the study report determined?

**Figure 35: Figure 8.3.1.1 of study report WIS-BUP02**

![Figure 8.3.1.1](image)

**Figure 8.3.1.1**

**Average daily dose of opioid medication (buprenorphine equivalents [mg]) taken before study entry**

At the time and place of the study, equivalence estimates for transdermally administered buprenorphine were not available (this information is still difficult to find).

The article by Sittl et al,\(^{38}\) which is provided in the supporting documents and which describes Study WIS-BUP02, states that:

'**dosages of pre study analgesics were converted to buprenorphine equivalents, as described previously.**\(^{34}\) Using this method, mean consumption of opioid analgesics overall prior to the study was equivalent to oral buprenorphine 0.8 mg/d.'

The article cited for the method is the article by Pereira et al\(^{63}\) provided by the sponsor in response to this question. This article does not discuss buprenorphine by any route. The articles by Foley provide dosing equivalence estimates for intra-muscular and sub-lingual buprenorphine only, no information is provided regarding transdermal buprenorphine.

The question has not been answered by the sponsor. It is not clear what the x-axis of the above graph refers to, oral or sub-lingual administration or transdermal administration of buprenorphine, nor is it clear how these ‘buprenorphine equivalents’ were determined.

12. The inclusion criteria for study PB-TTC-02 includes: Patients pre-treated with opioids and requiring an equi-analgesic dose range equivalent to 90 to 150 mg morphine p.o. per day. Could the method of determining equi-analgesic doses be provided?

**Sponsor’s response:**

To determine the respective equi-analgesic doses of the pre-study analgesic treatment (and thereby if a patient fulfilled this inclusion criteria), a conversion table was used. This conversion table was based on the respective information in the SmPCs of the individual opioids. Please find the respective conversion table used for study PBTTC-02 below. (Note: please also see our response to request 2).

**Table 74: Clinical study PB-TTC02. Conversion table**

![Table 74: Clinical study PB-TTC02. Conversion table](image)

* If tolerance suspected please clarify with sponsor’s contact person

**Evaluation of response:**

This is satisfactory except for the lack of information regarding tramadol. The study report for WIS-BUP02 provides an estimate of 30 mg oral morphine being equivalent to 100 to 150 mg tramadol. The source of this is not apparent; the table above and the supporting articles provided by the sponsor to Question 2 do not contain any estimates of dose equivalences for tramadol.

13. A number of the post-marketing observational studies, in which prescription of buprenorphine patches was said to be in accordance with the SPC, describe patients using ½ or ¼ (and even...
% of the 20 mg patch. Does cutting a patch into smaller pieces change its properties (for example release rates, adhesion) and is this a recommended practice?

Sponsor’s response:
It is noted that some prescribers have been known to cut patches at their own discretion. Where this occurred, it was felt important that this be reported in the CSR for completeness. No information on cutting patches is available and this is therefore not recommended practice.

Evaluation of response:
This practice of cutting a patch into two or more pieces reported in the post-marketing observational studies occurred relatively commonly despite advice to the contrary in the SmPC. It suggests that there is a clinical need for lower strength patches than those included in this submission. This is supported by the Risk Management Plan in its discussion of medication errors which includes the statement:

‘by far most commonly reported medication error was ‘dividing the patch into pieces’ with the intention to achieve the prescribed dose or in some cases to reduce side effects’

14. The post marketing surveillance study, AWB Transtec Pro 2005/2, describes Transtec Pro as a ‘more advanced form of Transtec’ and a ‘new form with an application period of up to 96 hours’. From the pharmacokinetic studies it appeared that the patch used for 96 hours was identical to the patch used for 72 hours. Could this be clarified?

Sponsor’s Response:
Transtec and Transtec Pro are exactly the same product. In Germany the name of the product was changed from Transtec to Transtec Pro with the extension of the application time to 96 hours.

Evaluation of response:
This is acceptable

15. The Summary of Clinical Safety states: ‘Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine’. In support of this, the clinical overview refers to a review article from 2002 (sponsored by [information redacted]), an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine, from 1994 and 2005 respectively. Could a substantive review of the safety of buprenorphine as evidenced in the literature, with this including the past 10 years, be provided?

Sponsor’s response:
The MAH presents two articles by Kress (2009) and Pergolizzi (2010) which detail the most recent reviews in literature on the safety profile of buprenorphine to date.

Supporting documents:

Evaluation of response:
These comprehensive reviews provide important information regarding pharmacokinetics (including enterohepatic circulation, pharmacokinetics with hepatic impairment, CYP3A4 interactions), pharmacodynamics (including hyperalgesia, immune effects, effects on the HPG
axis, pharmacodynamics interactions with CNS depressing drugs and CYP3A4 inhibitors),
lengthy discussions of the use of naloxone in buprenorphine overdose, an assessment of the
effect of transdermal buprenorphine administration on driving ability, discussions of the use
in special populations (renal and hepatic impairment, the elderly) and discussions of the range of
lower dose 7 day patches. The safety discussion in the review provides a useful discussion of the
safety profile of buprenorphine patches in relation to oral morphine and transdermal morphine.

It would have been extremely helpful if these reviews had been included in the submission, both
to better inform the discussion provided in the clinical overview and to improve the overall
quality of the submission through evidence of a recent consideration of the available literature
(the most recent reference cited in the submission was 2005).

16. The Risk Management Plan states in the section on Local Tolerability and Sensitization that:
'Two types of skin reactions can be observed in general: Irritative /toxic reactions or allergic
skin reactions. Long term occlusion of the skin increases the risk for skin sensitisation and
development of an allergic skin reaction.' These effects of transdermal drug delivery systems
are not elsewhere discussed. Could a review of the interaction between human skin and the
buprenorphine patch be provided?

Sponsor's response:
The dossier provides an analysis of the local tolerability of buprenorphine transdermal patch
from clinical trials.

Since the product has been on the market the MAH of Transtec has performed a detailed
evaluation of the effect of Transtec on human skin in 2005. It was concluded from this analysis
that 'based on all evaluated data it can be summarized that skin reactions under treatment with
[information redacted]'s buprenorphine transdermal patch occur with a frequency and
intensity as indicated in the current SmPC.

AE reports from clinical trials as well as spontaneous ADR reporting do not suggest a signal that
Transtec may be associated with unexpected effects on skin reactions. From the data presented
in this evaluation it is concluded that no further amendments to the reference safety
information on Transtec are currently required. The risk/benefit ratio of Transtec remains
unchanged.'

Routine pharmacovigilance activities performed since 2005 did not provide evidence for a
signal or a new pattern regarding local skin reactions associated with the administration of
Transtec

Supporting documents:
- CTD Module 2.7.4 Section 3.4.1 Local tolerability

Evaluation of response:
This response does not address the question.

The dossier in Module 2.7.4 Section 3.4.1 Local Tolerability lists adverse skin reactions as
observed in the clinical trial programme. It does not provide background or discuss the
aetiology by which these reactions occur. The clinical overview provides minimal discussion of
the interaction between the patch and skin.

This seems to be a major gap in the information presented in the submission given that the
reaction between skin and patch determines bioavailability and given that skin reactions are a
significant issue; local reactions were reported in up to 30% of patients in the clinical
efficacy/safety studies. It was also found that skin reactions may worsen over time: 23 patients discontinued from the long-term study, WIS-BUP-LTS, due to worsening skin reactions over a period of 25 to 1,114 days. Discussion of the background and aetiology of skin reactions is warranted given that the likelihood of skin reactions is related to duration of application, method of removal and re-use of application sites.

Given the gap in information provided in the sponsor’s submission, the evaluator had hoped that the sponsor would provide a discussion of the interaction between the proposed transdermal drug delivery system and skin in response to this question. With regard to the supporting documents provided:

- The ‘Evaluation of the Effect of Transtec on the Human Skin’ was located in the appendices of PSUR 8 that was provided in the sponsor’s response. This review was not bookmarked or hyper-text linked and could not be located in the 1,000’s of pages of appendices.
- The review by Ale et al provides a brief overview of transdermal drug delivery systems in general and then specific discussions of a number of drugs (lignocaine, methylphenidate, rotigotine, rivostigmine, rotigotine, and selegiline). The buprenorphine transdermal delivery system is not discussed.

The interaction between human skin and the Transtec patch and the development of skin reactions has still to be clarified.

17. Pre-clinical data show that buprenorphine inhibits the Human Ether-a-Go-Go-Related Gene (HERG) channel in in vitro models. The potential for Torsades de Pointes, using the surrogate marker of QT prolongation, was investigated in the Phase I study BUP1011. The report of this is provided in PSUR10 and the conclusion of the study is that the dose of 2 x BTDS 20 mg (40 mg) prolongs QTci to an extent comparable to 400 mg of moxifloxacin. A maximal dose of 140 mg of transdermal buprenorphine is proposed in this submission. The risk of Torsades de Pointes is not discussed in the clinical overview or the Summary of Clinical Safety. It is briefly addressed in pages 22 and 23 of the Risk Management Plan. With regard to the results of study BUP1011, this concluded that: ‘Several limitations around study design and data recording, which possibly confounded the results, were identified during an independent re-assessment of the electrocardiographic data’ and that ‘Aside from the trends of mean QTci values, no QTci outlier was identified which could be considered a concern with regard to pro-arrhythmic potential’. Despite this conclusion, the Australian PI for the sponsor’s closely related product Norspan includes:

In a study of the effect of Norspan patches on the QTc interval in 131 healthy males, therapeutic dosages (10 µg/h) had no effect on the QTc interval. Higher dosages (40 µg/h) and the active control (moxifloxacin 400 mg) each produced increases of 5.9 ms in the QTc interval. This observation should be considered when prescribing Norspan patches for patients with congenital QT prolongation and for patients taking antiarrhythmic medications in either Class 1A (for example quinidine, procainamide) or in Class III (for example amiodarone, sotalol) or any other medication which prolongs the QT interval.

Could a more comprehensive scientific evaluation of the risk of Torsades de Pointes (including for the proposed maximum dose of transdermal buprenorphine 140 µg/h) be provided? Could the rationale for not including a warning regarding QT prolongation in the draft PI be provided?

Sponsor’s response:

The MAH of Transtec have performed several comprehensive scientific evaluations (including the Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006 provided in PSUR 10 Appendices) of buprenorphine transdermal patch and QT prolongation, the latest in Mar 2015, which considers all the data available for on this topic and concludes that there is no signal that buprenorphine may have a pro-arrhythmic effect in the
range of exposure achieved with transdermal systems or even the higher doses of oral buprenorphine used in opioid substitution therapy.

Supporting documents:


**Evaluation of response:**

Given the seriousness of this potential complication of the use of buprenorphine patches, it would have been appropriate that this risk be discussed in the clinical overview in the original submission. It is, however, reassuring to find that a recent evaluation has been performed. This evaluation:

- reviewed the pre-clinical data and confirms that although HERG channel inhibition occurs with buprenorphine, it does so only at concentrations of buprenorphine that are considerably higher than the ‘maximum therapeutic plasma concentration in humans’, with an estimated safety margin of 200

- performed a literature search and identified 11 articles. These describe the investigation for evidence of QT prolongation in patients receiving buprenorphine for maintenance therapy in opioid dependence, where daily doses of 5 to 30 mg buprenorphine (the estimated daily dose from a 40 mg patch is 1.7 mg). The abstracts of these studies, and a discussion of the results, are provided and indicate no evidence for clinically meaningful QT prolongation in patients receiving buprenorphine. The articles also include several case reports of patients who experienced methadone related QT prolongation and/or TdP, successfully transitioning to buprenorphine for ongoing maintenance therapy

- included the 2006 review of the Thorough QT study performed in the clinical development programme for Norspan. This contains a critique of the study design and conduct and the opinion of an independent expert. The conclusion of this review is confusingly phrased but the main point is that: ‘Even if the results were to be viewed as robust, solely based on the results of this study, the effect of BTDS 40 mg would be assessed as inconclusive’

- examined the [information redacted] clinical database and found that in 1,318 patients exposed for an equivalent of 245 subject years, found no adverse event reports of Torsade de pointes/QT prolongation

- queried the [information redacted] Global Safety database for the time period 23 June 2000 to 31 December 2014 using specific terms (QT prolongation, long QT syndrome, TdP), and less specific terms (including sudden death and ventricular tachyarrhythmias) and found one spontaneously reported case of ‘Electrocardiogram QT prolonged’. Limited information is available regarding this case. Of note is that the patient was hypokalaemic (2.8 mmol/L) and being treated with escitalopram, a drug known to cause QT prolongation. On the basis of these confounding factors, the case was assessed as unlikely to be related to buprenorphine

- queried the WHO vigibase using the specific terms of TdP/QT prolongation and found 13,107 reports concerning buprenorphine. Of these 10 were apparently considered relevant, within the confines of the limited information available in each Vigibase case. A summary of the review of these cases was provided and the conclusion was that there was ‘no signal of disproportionate reporting for buprenorphine and the SMQ ‘Torsade de pointes/QT prolongation’

- provided a summary of an evaluation of the FDA adverse event reporting system (FAERS) database for a signal of disproportionate reporting of cardiac arrhythmia associated with the buprenorphine transdermal system for the time period 1969 to the first quarter of 2013 performed by Purdue Pharma L P (the developers of the Norspan patch in the USA). The
conclusion provided is that: ‘The results of the analysis revealed no signal of disproportionate reporting for any of the buprenorphine subgroups while a clear signal was shown for methadone.’

This review is comprehensive but incomplete:

- It provides an estimate of the daily dose from a 40 mg patch as 1.7 mg. The possible range of the daily dose of buprenorphine seen with the Transtec patch is discussed in Question 6 above. This provides an estimated range of daily dose for the 40 mg patch of 0.04 to 5.0 mg. If the proposed maximum of 2 x 40 mg patches is used, the daily dose may be as high as 10 mg in some patients. The dose range referred to in the articles referring to buprenorphine maintenance in opioid dependent patients was 5 to 30 mg.

- There was a discrepancy compared to the review conducted in 2006. This review was described as a supporting document in the sponsor’s response but could not be located. It was, however, discussed by the evaluator in the clinical evaluation report. This review was largely similar in method to the one conducted in 2015. The difference was that in the 2006 review, the WHO Vigibase was searched for both the narrow terms of 'Torsades de Pointes' and 'QT prolonged' as well as the less specific terms of 'Cardiac Arrest', 'Cardio Respiratory Arrest', 'Fibrillation Cardiac', 'Fibrillation Ventricular', 'Sudden Death', 'Syncope', 'Tachycardia Ventricular', 'Unconsciousness', 'Ventricular Fibrillation paroxysmal' up to the third quarter of 2005. This search showed no reports of TdP or QT prolongation in association with buprenorphine (all routes of administration). However, there were 36 reports of cardiac arrest, 8 reports of sudden death, 82 of syncope and 3 of ventricular tachycardia. The PPR (proportional reporting rate for the combination of a particular drug and particular ADR) showed a signal of disproportionate reporting for sudden death. This signal was assessed in the 2006 review as weak and likely to be a false positive given the small number of cases. This signal was not mentioned in the 2015 review and a narrow search of the WHO Vigibase only was conducted in the 2015 review.

The further information provided in the sponsor’s response to this question suggests that the risk of QT prolongation/TdP with transdermal buprenorphine at therapeutic doses is very low. However, the evaluator does not believe that the risk does not exist, particularly in the patients with unpredictably high rates of absorption from the patch and who may have other risk factors for the development of Qt prolongation, including agents (for example protease inhibitors), that would cause increased plasma levels of free buprenorphine.

It is appropriate that a warning similar to that in the Norspan PI be included in the Transtec PI.

18. According to the Risk Management Plan, two well documented individual case safety reports were received during post marketing surveillance that were suggestive of vasospastic angina induced by buprenorphine. Both cases were reported as serious, requiring hospitalisation, and both recovered. No further information was able to be located in the dossier. This risk is not addressed in the clinical overview or the summary of clinical safety. Could further information regarding these case reports be provided?

**Sponsor’s response:**

The following two cases were considered suggestive of vasospastic angina induced by buprenorphine:

Cracowski et al. reported a case of a myocardial infarction in a 22 year male who snorted a crushed 8 mg buprenorphine tablet. Full details are provided in the literature article.

The CIOMS Report TTC-001981 details a case of angina pectoris and ST elevated in a 48 year old male patient 14 days after using the Transtec patch. This case was rated serious due to hospitalisation. The patient recovered but the same symptoms recurred following rechallenge with Transtec. The full CIOMS is provided.
Supporting documents:


CIOMS Report TTC-001981

**Evaluation of response:**

This is a serious safety concern with buprenorphine that was described in the Risk Management Plan but not in the clinical overview of the original submission. In both cases symptoms recurred with re-challenge with buprenorphine and myocardial ischaemia was considered to be related to buprenorphine.

The first case is described in a letter to the editor of the Annals of Internal Medicine. In this 1998 case, a patient snorted a crushed 8 mg tablet of buprenorphine and developed chest pain two hours later that resolved spontaneously. Three weeks later, similar pain developed following another inhalation of buprenorphine. On this occasion the patient sought medical attention and was found to have ST elevation on ECG. The patient was admitted to hospital. Subsequent investigations showed an elevation in CKMB and normal coronary arteries at angiogram. Coronary vasospasm was unable to be induced using intravenous methylergotamine. No cocaine was detectable and the myocardial infarction was considered to be related to buprenorphine.

In the second case, reported in 2003, severe angina occurred after the patient had been treated with transdermal buprenorphine for 14 days. As this was associated with ECG changes consistent with an acute myocardial infarction, the patient was investigated with an emergency coronary angiogram that was reported as normal. Transdermal buprenorphine was ceased during hospitalisation and the patient was discharged with no apparent diagnosis. Two to three weeks later, transdermal buprenorphine was recommenced. After the second patch application, the patient developed chest pain and removed the patch with resolution of symptoms. The patient was reviewed medically the next day and was noted to have ST elevation on ECG. Review of the case by [information redacted], as documented in the CIOMS Report, found no confounding factors.

This risk would appear to be very low given that only two spontaneous case reports have been received, although no cumulative review has been presented. The risk is very serious and will require careful follow-up. It may be appropriate for it to be mentioned in the PI.

19. Re exposure during the clinical trial programme - According to the Summary of Clinical Safety: ‘More than 1,250 patients were exposed to any buprenorphine transdermal patch during controlled clinical studies’. According to the Risk Management Plan: In total 1,318 subjects have been exposed in interventional clinical trials with buprenorphine transdermal patch. The Risk Management Plan also states that: ‘48 subjects in the clinical trial program were exposed to a 17.5 µg/h patch'; this dose was not used in any of the studies provided (except as ‘medication errors’ in some of the Post Marketing Surveillance Studies). Please clarify: have additional studies been included in the Risk Management Plan that have not been provided or discussed in the dossier?

**Sponsor’s response**

The RMP exposure information includes data from the initial stages of a development for a patch that could be divided. The study treated patients with a cut patch as a precursor to the potential development of this dividable patch. Development of this patch was not ultimately pursued, however this was included in RMP for completeness of exposure numbers, but not included in the dossier itself as it was development that was not developed further or commercialised.
Evaluation of response:

This is acceptable

20. Could the following documents that are in the Appendix of PSUR10 Volume 2 be provided as separate electronic copies:

- BUP1011 Study Report
- Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006
- EMA document 'Points to Consider: The Assessment Of The Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products
- International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use ICH Harmonised Tripartite Guideline: The Clinical Evaluation Of Qt/Qtc Interval Prolongation And Proarrhythmic Potential For Nonantiarrhythmic Drugs E14 from 2005

Sponsor’s response

All documents are provided.

Evaluation of response:

The request was that these documents be provided as separate electronic documents as they were only available in the approximately 6,000 page appendix in a PSUR in the submission. The absence of a table of contents and bookmarks made accessing the documents and referring back to them extremely difficult. The sponsor has not provided all requested documents; the Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27 February 2006 has not been provided. The other documents have not been provided as separate electronic copies. They have been provided in the 6,182 page document response to the TGA request for information; Clinical Evaluation, Safety. This document has bookmarks that have facilitated accessing the documents.

12.3. Clinical issues

The sponsor was asked to address a number of additional clinical issues. These issues, together with the sponsor’s response and the evaluator’s comments, are provided below. Where appropriate, the evaluator has inserted detailed comments within the sponsor’s response and a summary at the end.

Clinical issue question 1

The pivotal studies were designed more than 20 years ago and do not conform with current recommendations. The supportive studies are at least 12 years old and have similar, though less serious design flaws that limit the usefulness of their results.

Sponsor’s response:

Guidelines and recommendations for clinical trials

There are a number of well accepted guidelines for dealing with clinical trials. Some of today’s most relevant international recommendations for conducting trials in humans for the investigation of pain medications are for example the

- EU612 CPMP nociceptive pain guideline
• EMA pain draft guideline CHMP970057/2001 or
• FDA 2014 draft guidance for Industry: Analgesic Indication.

These guidelines give recommendations regarding the conduct and methodology of clinical studies including study design, study population, pain models, and methods to assess and evaluate efficacy and safety, statistical methods, etcetera.

The existence of such guidelines is the result of a long history of attempts to improve clinical trials for drug development. They focus on both ethical and scientific reasons, to ensure a high quality standard of research and study results. In addition, another important purpose of these guidelines is to maximize the safety of subjects involved in trials, as well as for the target patients after drug approval.

Since 1945, the ethical impact of clinical trials has become increasingly important, resulting in strict regulation of medical experiments on human subjects. These regulations have been enshrined in documents such as the Nuremburg Codex (1947) and the Declaration of Helsinki (1964; latest amendment in 2013).

Studies within the clinical development program of Transtec

For Transtec, the original clinical development program was a complete program for a new formulation (transdermal patch) of a known active substance (buprenorphine) and included both pharmacokinetic and clinical studies. All clinical studies performed within this development program were carried out according to the ICH Guideline for Good Clinical Practice as well as the ethical standards as laid down in the Declaration of Helsinki.

At the time of conducting the relevant placebo controlled studies and later on the other Transtec studies, most of the current important guidelines for clinical trials in pain treatment that are mentioned above did yet not exist; at least, not in the current and comprehensive versions. However, the studies were compliant with the respective standards at the time of the development and furthermore also fulfil key recommendations of today's guidelines.

Placebo controlled studies

The efficacy studies were designed to support the target indication 'moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics'. Three placebo controlled studies were the original basis for the proof of efficacy and showed the following key characteristics:

Table 75: Design of placebo controlled studies

<table>
<thead>
<tr>
<th>DESIGN</th>
<th>WIS – BUP01</th>
<th>WIS – BUP02</th>
<th>WIS – BUP03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised, placebo, double-blind (DB), parallel group</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Duration</td>
<td>6 days DB</td>
<td>15 days DB</td>
<td>9 days DB</td>
</tr>
<tr>
<td>Study population</td>
<td>Cancer and non-cancer patients suffering from moderate to severe pain</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>WIS – BUP01</th>
<th>WIS – BUP02</th>
<th>WIS – BUP03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study medication</td>
<td>BUP 20-40 mg</td>
<td>BUP 20-40 mg</td>
<td>BUP 40 mg</td>
</tr>
<tr>
<td>Rescue medication (buprenorphine SL)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>OBJECTIVES</th>
<th>WIS – BUP01</th>
<th>WIS – BUP02</th>
<th>WIS – BUP03</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder rate: VRS pain/rescue medication</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>QoL (by assessing Sleep quality)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Taken together, these key characteristics are those recommended in the guidelines listed above for placebo controlled efficacy studies:

- Adequate blinding and randomisation; randomised controlled parallel group trial as required design for confirmatory evidence of efficacy and safety
- Parallel group design (preferred design for confirmatory trials)
- Appropriate provision of rescue medication
- Need for rescue medication as appropriate measure of efficacy
- Study population representing the target population and therapeutic setting
- Primary and secondary endpoints in accordance with target indication
- Objectives include assessment of pain but also on quality of life (important when assessing chronic pain)
- Pre-defined responder criteria, preferably change from baseline.

**Evaluation of response:**

The evaluator agrees that the clinical studies provided met many of the characteristics described above (although it is arguable that sleep duration is a validated quality of life measure). The sponsor refers to the guidelines Note for Guidance on Clinical Investigation of Medicinal Products for Treatment of Nociceptive Pain and the Guideline on Clinical Medicinal Products Intended For The Treatment Of Neuropathic Pain, both of which have been adopted by the TGA. These guidelines provide considerable additional advice:

- Appropriate studies should be conducted according to the intended indications, treatment duration, administration route, delivery system and target population
- Efficacy and safety implications of concomitant use of drugs likely to be administered in clinical practice should be evaluated and that 'Particular attention should be focussed on. ..... The use of co-analgesic drugs [that is antidepressants, neuroleptics, anticonvulsants, antihistamines]'
- Well planned dose response studies should be carried out with a dose-response curve analysis
- Efficacy assessment should be through pain measurement, using time specific pain scores or pain intensity difference. The more recent guideline advocates the use of visual analogue scale (10 cm scale) or 11 point Likert numerical rating scale. Avoiding bias due to 'recall pain' is recommended
- Duration of studies should be in keeping with the type of pain that is to be treated

**Table 76: Type of pain to be treated**

<table>
<thead>
<tr>
<th>Type of Pain</th>
<th>Duration</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Mild</td>
<td>≥ 3 months</td>
<td>Osteoarthritis, rheumatoid arthritis, low back pain</td>
</tr>
<tr>
<td>Chronic Moderate/severe</td>
<td>≥ 1 month</td>
<td>Cancer, skeletal metastasis with movement related pain</td>
</tr>
</tbody>
</table>

The development programme of the Transtec patch has not been consistent with all of these recommendations.
• The patch application time used in all the clinical studies was 72 hours. The application time proposed by the sponsor is 96 hours. The equivalence of the two application times has not been established in the target population

• No drug interaction studies have been performed despite involvement of CYP3A4 in the metabolism of buprenorphine and in vitro evidence of inhibition of CYP3A4 by buprenorphine and its metabolites

• No formal dose response studies have been performed. WIS-BUP01 and WIS-BUP02 compared the three patch strengths. Inconsistent results were found across the two studies such that dose dependent responses cannot be established

• The minimum effective concentration (MEC) of buprenorphine has not been established in the target population. Only expert opinion is provided for an estimate of MEC

• Efficacy assessment in the ‘pivotal’ studies for the primary end point was the response rate with responders defined by the combination of the patient’s retrospective perception of pain relief as being ‘at least satisfactory’ on a four point scale and the use of rescue medication being less than a pre specified level. Use of retrospective recollection of pain introduces recall bias. The four point scale to assess pain provides too little discrimination. Also of note is the ‘at least satisfactory’ is only one step above the worst pain relief on the scale (unsatisfactory pain relief, satisfactory pain relief, good pain relief, complete pain relief)

• Efficacy was not established in the pivotal studies: these did not show that the buprenorphine patch was significantly better than placebo for the primary efficacy outcome measure

• The duration of the ‘pivotal’ efficacy/safety studies was 6 to 15 days.

Other concerning gaps in the clinical development include the effect of heat and activity on absorption from the patch, a comparison of absorption from different sites and different skin types and determination of the appropriate time between re-use of an application site.

Sponsor response (continued):

Another placebo controlled trial (study PB-TTC-02) with a randomised withdrawal design was performed in cancer and non-cancer pain patients suffering from moderate to severe pain. This type of study ‘enrichment’ design is discussed and even recommended in the guidelines if necessary and useful (please also see the response to the clinical issue 3 dealing with the cancer study PB-TTC-02). The EMA pain draft guideline CHMP970057/2001 states that ‘strategies such as unbalanced randomisation to maximize the number of patients enrolled in the test treatment arm are acceptable’. Furthermore, the FDA enrichment strategy guideline draft from 2012 comprehensively discusses options and details for the strategy of designing trials with enrichment strategies.

In the placebo controlled trials, the duration of treatment was not longer than 30 days, to exclude bias caused by mortality of cancer patients. However, large data regarding long-term efficacy and safety were derived from the other supportive studies (for example observational study AWB Transtec 2001) and will be discussed further below.

Evaluation of response (continued):

As stated above, three of the four placebo controlled studies were 16 days or less in duration; only one had a duration of thirty days. The rationale for the short duration of the studies is inadequate. Many cancer patients have a life expectancy much greater than 30 days. Appropriate inclusion/exclusion criteria and randomisation (including stratification) would ensure that both the placebo and active arms would have similar predicted mortality.
Sponsor response (continued):

Upon authority request from the UK authority (MHRA, 2001/2002), an additional responder analysis was requested. Therefore, a post-hoc analysis of baseline corrected secondary parameters was also performed. This additional strategy of analysis further substantiated the evidence of efficacy and dose dependency.

Active controlled and uncontrolled studies

Besides the placebo controlled studies, active controlled studies and uncontrolled studies were carried out.

Additional evidence for the efficacy of Transtec was derived from a combined efficacy analysis of the placebo controlled studies, two active controlled, double blind studies, one uncontrolled extension study and five non interventional studies.

Evaluation of response (continued):

Efficacy of Transtec in the target population of patients with moderate to severe cancer pain and severe pain that does not respond to non-opioids has not been established. This failure to demonstrate efficacy has been extensively discussed in the clinical evaluation report above and is summarised here. In the three placebo controlled studies described as 'pivotal' in the sponsor’s submission, there was no statistically significant difference to placebo for the pre-defined primary outcome measure. Secondary efficacy measures in these three studies were suggestive of efficacy but this was limited due to inconsistencies across the patch strengths and across the studies. A post hoc pooled analysis of these studies, requiring some adjustments of the primary end-point and time-points of evaluation, was also provided in support of efficacy. This analysis was also suggestive of efficacy but, again, limited due to inconsistent results across the three studies and the three patch strengths. The supporting placebo controlled study established efficacy in a sub group of the proposed population (patients with severe tumour related pain who achieved acceptable analgesia with Transtec during the run-in phase). Two other supportive studies, performed in the sub-group of patients with non-tumour pain, showed that Transtec was 'non-inferior' to the weak opioid tramadol.

A regulatory guideline that was developed by the European Medicines Agency, and adopted by the TGA in 2005, expresses the opinion that: 'In pivotal clinical trials where pre-defined primary variable analysis has failed to demonstrate efficacy, favourable results on secondary variables will not be enough to grant a marketing authorisation'

Sponsor response (continued):

Although there is no 3 months double blind data from the placebo controlled studies (for the reasons mentioned above) long term follow up safety and efficacy data are available for almost all controlled clinical studies.

In study PB-TTC-01, a 6 month open label period was conducted following the 4 weeks of double blind treatment. The follow up involved 307 patients. Results of the study provided strong confirmation that efficacy of buprenorphine is maintained during long term treatment without development of tolerance for buprenorphine.

Evaluation of response (continued):

'Long term follow-up' safety and efficacy data was available for the follow-up study for the three 'pivotal' placebo controlled studies (WIS-BUP-LTS) and for PB-TTC-01. Both follow up studies were notable for the rapid drop-out rate of study participants. In WIS-BUP-LTS, 241 patients were enrolled for a planned follow up of 24 months; only 37 patients continued for longer than 12 months and 19 patients completed 24 months. In PB-TTC-01, 307 patients entered in the 6 month follow up phase and 145 completed the planned six months. Assessment of efficacy is obviously limited by these high discontinuation rates but, for those patients who continued in these studies, there seemed to be no development of tolerance.

Sponsor response (continued):
**Sponsor response (continued):**

Furthermore, additional non-interventional trials have been performed. These can’t be used for an official proof of efficacy, but do reflect the use of Transtec in daily clinical practice in a large number of patients, and thus provide valuable information on its routine use in the target population. The largest non-interventional study (AWB Transtec 2001) included over 13,000 patients, and investigated therapy with Transtec for 10 weeks. About 70% of all patients were willing to continue therapy with Transtec after 10 weeks of treatment and were followed up for up to 9 months.

**Evaluation of response (continued):**

Most of the post-marketing studies had planned durations of 8 to 12 weeks. The study AWB Transtec 2001 had a planned duration of 10 weeks and 25% of the 13,179 recruited patients discontinued use of the patch. The mean duration of the observation period was 61 days. Of the patients who continued with the patch, over 70% of the patients described their pain relief as good or very good and 70% chose to continue with this form of analgesia after the end-of-study visit.

**Sponsor response (continued):**

The data of the just mentioned supportive studies gave further significant evidence for the usefulness of Transtec for long-term treatment of chronic pain and showed that the established efficacy is also maintained over time without development of tolerance or differences in the safety profile.

**Extensive post-marketing studies and experience**

Since approval of Transtec in several countries, there is also additional data available from non-interventional (observational) studies, post-marketing surveillance (such as Periodic Safety Update Reports (PSURs)), as well as from published literature.

**Conclusion**

The sponsor hopes this gives a satisfactory explanation about the validity of the Transtec studies and respective study results. As discussed above, all studies are consistent with international current guidelines and followed today’s recommendation for clinical trials for analgesic products in moderate to severe chronic pain. Therefore, the sponsor sees their data to be valid and adequate for granting approval.

**Supporting documents:**


**Evaluation of response (continued):**

In summary, the sponsor has provided no new information and no new insights beyond those presented in the dossier; these have been extensively discussed in the first round clinical evaluation report.

**Clinical issue question 2**

*In the 2 non cancer pain studies designed to demonstrate equivalence used inappropriate comparators given the dose of buprenorphine. A high dose of a strong opioid compared with a moderate and maximum doses of a weak opioid. This strongly suggests that lower doses of*
buprenorphine would also be effective. Lower doses would also be safer. No justification for the equivalence interval in these studies was presented.

**Sponsor’s response:**

Oral tramadol was used as a comparator to Transtec in studies PB-TTC-01 and BUP4201 as it was anticipated that Transtec would be used in place of oral tramadol in future. The studies followed accepted practice at the time, which was to use an equipotency table to determine the equivalent opioid dose. Doses lower than 35 µg/h of Transtec would have been inappropriate for the indications of the patients in these studies, and inappropriate for the proposed Transtec indication. The equivalence intervals used in these studies were less than the published clinically meaningful difference, while in study PB-TTC-01 the equivalence interval used was also conservative by the ‘half of the standard deviation’ approach to determining the minimal relevant change. These justifications are described further in the next few paragraphs.

**Comparators were selected using a dose equivalence method**

In the treatment of chronic pain, patients frequently have to be switched from one opioid to another due to therapeutic necessity (Skaer, 2004; Gonzalez-Escalada, 2004; Sittl et al, 2005). When switching patients from one opioid to another, it was accepted practice at the time of studies PB-TTC-01 and BUP4201 to use a conversion or ‘equipotency’ table (Transtec SPC, 2006). Such equipotency tables had the consent of regulatory authorities and were (still are) included in the SPC for other products, such as Durogesic transdermal patch (Durogesic SPC, 2015). Removal of the equipotency table from the Transtec SPC was approved by the BfArM (as RMS) and accepted by regulatory authorities in other countries.

Opioid equipotency tables used in daily clinical practice were generally based on a single publication (Foley, 1985). In this publication, the calculation of equi analgesic doses between different opioids was based on clinical experience. When compiling the equipotency table in the Transtec SPC (2006), the above-mentioned publication and its subsequent adaptations in standard text books were used, taking into account the release rates of the transdermal patches and the corresponding daily doses of buprenorphine. The dose equipotency in the Transtec SPC (2006) was therefore the basis of choosing a comparator for studies PB-TTC-01 and BUP4201. The relevant dose equivalences on page 2 of the Transtec SPC (2006) are reproduced below:

**Table 77: Relevant dose equivalences for oral tramadol and Transtec.**

<table>
<thead>
<tr>
<th>Opioid treatment</th>
<th>Dose strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tramadol</td>
<td>150 to 300 mg/day</td>
</tr>
<tr>
<td>TRANSTEC</td>
<td>35 µg/h</td>
</tr>
<tr>
<td></td>
<td>Up to 450 mg/day</td>
</tr>
<tr>
<td></td>
<td>52.5 µg/h</td>
</tr>
<tr>
<td></td>
<td>Up to 600 mg/day</td>
</tr>
<tr>
<td></td>
<td>70 µg/h</td>
</tr>
</tbody>
</table>

Hence, in both the PB-TTC-01 and BUP4201 studies, 200 mg/day oral tramadol (100 mg twice daily) was an appropriate comparator for 35 µg/h Transtec. Likewise, in study BUP4201, 300 mg/day oral tramadol (150 mg twice-daily) was an appropriate comparator for 52.5 µg/h Transtec and 400 mg tramadol (200 mg twice daily) was an appropriate comparator for 70 µg/h Transtec.

**Evaluation of response:**

The Notes for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96), adopted by the TGA in 1999, states that a ‘suitable active comparator would be a widely used therapy whose efficacy in the relevant indication has been clearly established and quantified in well designed and well documented superiority trial(s)’.

The indication for sustained release tramadol provided in the current Australian PI is for ‘Relief of moderate to severe pain’, with a recommended dose of 100 to 200 mg twice daily. Despite this, the Therapeutic Guidelines; Analgesic advises that ‘Tramadol may not be suitable as the
sole analgesic for patients with moderate to severe pain' and that 'Tramadol has a limited role in chronic pain. It has limited analgesic activity'.

The source of the proposed equivalences for the different strength patches and tramadol dose provided by the sponsor from 'page 2 of the Transtec SPC (2006)' is unclear. The opioid equivalence tables developed by Foley and, according to the sponsor, widely used at the time of the studies are discussed in relation to Questions 11 and 12 above. Of note is that these opioid equivalence tables, and the cited references, do not include tramadol or transdermal buprenorphine.

Therapeutic Guidelines; Analgesic provides an approximate potency for tramadol:

- 150 mg oral tramadol approximately 30 mg oral morphine approximately 0.8 mg sublingual buprenorphine
- And that the 7 day 20 µg/h (20 mg) buprenorphine patch is approximately equipotent to 50 mg oral morphine per day

A recent systematic review of opioid equivalences by Mercante et al suggests that there is some limited evidence that the 4 day 35 µg/h patch (20 mg) is equivalent to 60 mg of oral morphine and 25 µg/h of transdermal fentanyl

The 1986 WHO cancer pain ladder for adults is frequently referred to in the dossier, with transdermal buprenorphine positioned as a means of transitioning from level two to level three and as a level three analgesic. Neither tramadol nor transdermal buprenorphine were available at the time of the development of the pain ladder. A review of the analgesic ladder in 2010 positioned tramadol as a weak opioid at level 2 and transdermal buprenorphine as level 3. The table of opioids according to WHO levels provided in the post-marketing surveillance study AWB Transtec 2003 also describes tramadol as a level 2 'weak opioid'.

With regard to the supporting documents provided by the sponsor:

- Foley KM (1985). The treatment of cancer pain. N. Engl. J. Med. 313: 84–95. This article has been discussed above in Questions 11 and 12. It provides no dose equivalence information for tramadol or buprenorphine
- Gonzalez-Escalada J (2004) Use of buprenorphine and oral morphine in patients with chronic pain. Rev Soc Esp Dolor 11 suppl V: 3–10. The abstract of this article describes a clinical audit in which an equianalgesic table for oral morphine and TD buprenorphine was developed. The body of the article was in Spanish so this could not be substantiated
- Sittl R, Likar R & Nautrup BP (2005) Equipotent doses of transdermal fentanyl and transdermal buprenorphine in patients with cancer and noncancer pain: results of a retrospective cohort study. Clin. Ther. 27: 225–237. A different article by these authors was provided
- Skaer TL (2004) Practice guidelines for transdermal opioids in malignant pain. Drugs 64: 2629–2638. This is a review article that only briefly refers to transdermal buprenorphine. It offers dose equivalencies of 20 mg patch approximately 60 mg oral morphine; 30 mg patch approximately 90 mg oral morphine and 40 mg patch approximately 120 mg oral morphine. In support of this, the article cites three review articles.

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In summary, dose equivalency between tramadol and transdermal buprenorphine has not been established. The clinical use of tramadol in Australian practice is predominantly for acute pain and its use in chronic pain is recommended against. Therefore, tramadol is not an appropriate comparator for the Transtec patch.

**Sponsor response (continued):**

Lower doses were inappropriate for the patient population in these studies or the proposed indication of Transtec

The 150 to 200 mg/day tramadol dose is the typical starting dose indicated for moderate to severe pain. The recommendations for are either 10 to 200 mg twice daily (SPC ZydolR tablets) or 150 mg once daily (SPC ZyrtramR tablets). These studies were carried out in patients experiencing moderate to severe pain (PB-TTC-01) or exclusively severe pain (BUP4201). Therefore, it would have been unethical for these patients to receive a dose of Transtec equivalent to less than 200 mg/day tramadol. Likewise, the proposed Transtec indication is for severe pain in non cancer patients. The investigation of buprenorphine doses equivalent to less than 200 mg/day Tramadol would be appropriate for drugs of a different indication.

**Evaluation of response (continued):**

The relative equivalence of tramadol and buprenorphine patches has not been established. This, together with the high inter-patient variability of absorption from the buprenorphine patch means that the appropriate starting strength of buprenorphine patch in an individual patient is unpredictable. Commencing on the lowest available strength patch (with this including the range of 7 day Norspan patches) may provide adequate pain control with the least side effects. Commencing on a high strength patch may provide adequate pain control but such distressing side effects that the therapy is discontinued. High discontinuation rates were observed in both of the non-inferiority studies (see also Clinical Issue Question 8 below). The use of 'part patches'(patches cut into 2, 4 and even 8 pieces, with the small pieces used instead of the full size patch) as described in the post-marketing surveillance studies suggests a clinical need for lower strength patches. Note also that the opioid equivalence tables was removed from the Transtec SPC in 2007, and replaced by the statement: 'In general it is advisable to titrate the dose individually, starting with the lowest transdermal patch strength

**Sponsor response (continued):**

**Justification of the equivalence interval**

The change in pain intensity that represents a clinically important difference has been reported (Farrar et al, 2001). Farrar and colleagues related pain intensity reported on an 11 point numerical rating scale (NRS) and the then standard 7 point patient global impression of change scale. They assessed data for 2,724 subjects from 10 different clinical trials. They determined that a change in pain intensity less than 2 points on the 11 point NRS is not clinically important. Therefore, in studies BUP4201 and PB-TTC-01, a difference of less than 2 units of pain intensity (on an 11 point NRS) might be considered clinically equivalent. In fact, more conservative values than suggested by Farrar and colleagues (2001) were used: in study BUP4201 a difference of 1.5 units or less was considered clinically equivalent, while in study PB-TTC-01 a difference of 1.0 units or less was considered clinically equivalent; in both studies units were pain intensity on an 11 point NRS. In these situations Transtec was considered as efficacious as Tramadol.

An alternative method of determining the equivalence interval is based on using half of the standard deviation (SD). This method is based on a systematic review of 83 studies, which showed that if patients with a chronic disease are asked to identify a minimal relevant change in health related patient reported outcomes, the estimates fall very close to half of the SD (Norman et al, 2003). Therefore it can be concluded that the threshold of discrimination for changes in health related patient reported outcomes is approximately half of the SD. This approach is
supported by the FDA Draft Guidance for Industry on Patient Reported Outcome Measures, which states that for defining a minimum important difference, a distribution based approach (for example defining the minimal important difference as 0.5 times the SD) is acceptable as long as this result is not used in isolation (FDA, 2009). In study PB-TTC-01, half of the SD was 1.35 units of pain intensity (on an 11 point NRS). Therefore, the difference of 1.0 unit or less that was considered clinically equivalent in this study was also conservative by this alternative method of determining the equivalence interval.

**Evaluation of response (continued):**

This justification of the equivalence interval is acceptable

**Sponsor response (continued):**

**Conclusion**

Studies PB-TTC-01 and BUP4201 followed accepted practice at the time, which was to use an equipotency table to determine the equivalent opioid dose. Doses lower than 35 µg/h Transtec would have been inappropriate for the indications of the patients in these studies, and inappropriate for the proposed Transtec indication. The equivalence intervals used in these studies were less than the published clinically meaningful difference and the equivalence interval used in study PB-TTC-01 was also conservative according to an alternative approach. Therefore, the equivalence intervals were valid, and indeed slightly conservative, in both studies.

**Supporting documents:**

- Transtec SPC (2006) [information redacted]
- Zydol PIL (2012) [information redacted]
- Zyrtram XL Monograph (2014) Purdue Pharma

**Evaluation of response (continued):**

The sponsor’s response has not established that tramadol is an appropriate comparator for the buprenorphine patch. The issue of establishing that a proposed level 3 analgesic is non-inferior
to a level 2 analgesic remains. The possible effectiveness of lower strength patches in these patients also remains. An acceptable justification for the equivalence interval in these studies has been presented.

**Clinical issue question 3**

*Cancer pain study; only responders to the 70 µg/h buprenorphine patch were included in the ITT population of a randomised withdrawal study. Thus assessment was limited to a limited population already assessed as responding to treatment.*

*Sponsor's response:*

Transtec is intended for severe cancer pain patients, and in this study this population were in focus. Trials in this indication and population require careful design; also as there is a high and variable placebo effect in pain trials. In order to minimize inadequate pain treatment of patients for ethical reasons, an appropriate study design was selected. Both of these enrichment strategies are supported by FDA and ICH guidelines. Furthermore, this is only one study in the larger Transtec development plan. These points are elaborated in the following paragraphs.

*The severe cancer pain patient population in this study was extremely relevant*

The proposed Transtec indication specifically mentions ‘severe cancer pain’. The aim of study PB-TTC-02 was to investigate the analgesic efficacy and safety of 70 µg/h Transtec in patients with severe chronic tumour related pain. Therefore severe cancer pain patients were in focus in this study. The limitation of the patient population to severe pain patients allowed the study to provide results more relevant to the study aim.

*The placebo effect in pain studies is large and unpredictable*

The placebo effect describes apparent response to treatment in patients who have not received active drug. The placebo effect is known to be large and unpredictable in pain studies, and so it was required to show superiority of Transtec to placebo in the placebo controlled study (PB-TTC-02).

*Inclusion of non-responders in study PB-TTC-02 would have been unethical*

The company believes that in study PB-TTC-02 it would have been unethical to retain severe pain patients who did not respond to Transtec treatment during the run-in phase. Although the study design required a placebo group in order to show superiority of Transtec, the aim was to minimise the chance that a patient retained in the study did not receive adequate pain treatment. Randomization of patients who were not responding to Transtec was not essential for the study design, and would have made it very likely that those patients would be denied adequate pain treatment during the study.

*Enrichment is an approved aspect of study design and is statistically acceptable if applied prior to randomization*

Enrichment guidance provided by the FDA as well as the ICH E8 statistical guidelines and ICH E9 clinical trial guidelines all support the use of the PB-TTC-02 study design.

FDA guidance states that enrichment is a valuable tool in study design that facilitates increased study power for ‘proof of principle’ studies (FDA, 2012). Both prognostic enrichment (choosing patients that have the indication of interest; such as severe cancer pain patients in study PB-TTC-02) and predictive enrichment (choosing patients more likely to respond to treatment; in study PB-TTC-02 this equates to excluding non-responders) are acceptable. As stated on pages 2 to 3 of this FDA guidance (2012), enrichment strategies applied before randomization ‘do not compromise the statistical validity of the trials or the meaningfulness of the conclusions reached with respect to the population actually studied’. On pages 11 and 17 of this FDA guidance (2012), study designs extremely similar or identical to study PB-TTC-02 are described.
as acceptable. The FDA guidance (2012) also states that enrichment studies are best if they comprise only part of the body of evidence, as is the case for Transtec.

The ICH E9 statistical principles guidelines make no statement that enrichment is forbidden (ICH, 1998a). However, these ICH guidelines do recommend on page 6 that subjects in trials should closely mirror the target population. This supports the use of a severe cancer pain patient population in the PB-TTC-02 study, as severe cancer pain is a substantial part of the proposed Transtec indication. The ICH E8 guidelines for clinical trials also support the use of enrichment in study PB-TTC-02, recommending on page 10 that ‘Some groups … may require special study because they have unique risk/benefit considerations that need to be taken into account during drug development’, while page 11 states that ‘The appropriate study design should be chosen to provide the desired information’ and ‘the indication to be studied … should be taken into account in selecting the subject population’ (ICH, 1998b).

**Conclusion**

Severe cancer pain is a substantial part of the proposed Transtec indication. Study PB-TTC-02 was designed to assess the analgesic efficacy and safety of Transtec in patients with this indication. The inclusion of non-responding patients in this trial would have been unethical. FDA and ICH guidelines support the use of enrichment in studies such as PB-TTC-02, both in terms of the patient population matching the indication, and the exclusion of non-responders.

**Supporting documents**

- ICH (1998b) E8 Note For Guidance On General Considerations For Clinical Trials.

**Evaluation of response:**

The evaluator agrees that enrichment can be an appropriate study design in some circumstances. The point at issue here is that this study was the only placebo controlled study presented in the dossier in which efficacy of the patch over placebo, as shown by a significant difference in the primary end-point, was demonstrated. The evaluator also agrees with the sponsor’s description of the opinion expressed by the FDA: ‘The FDA guidance (2012) also states that enrichment studies are best if they comprise only part of the body of evidence, as is the case for Transtec.’ An enrichment study may be necessary and appropriate in some circumstances but it provides only weak evidence for efficacy by itself. Of note is that the two ‘pivotal studies’ WIS-BUP01 and WIS-BUP03 can also be considered ‘enrichment’ studies as only those patients who had at least satisfactory pain relief on a regimen of sublingual buprenorphine tablets were able to be enrolled in the double blind assessment phase. This would select out those patients who were responders to buprenorphine for inclusion in the double blind phase.

**Clinical issue question 4**

_Dose response was not demonstrated_

**Sponsor’s response:**

A dose dependent difference between treatment and placebo can be seen when the datasets from 3 placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) were combined. Dose proportionality was also supported by a large non interventional study. These points are described further in the following paragraphs.
A dose response was demonstrated in the pooled analysis: WIS-BUP01/02/03

Dose response of Transtec was demonstrated in the retrospective combined analysis of 3 placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 (WIS-BUP123).

The response criteria were harmonised to improve the comparability of the three studies. The variables pain relief; pain intensity and rescue medication were combined, as they are co-dependent. High pain intensity could, for instance, be a reason for a high use of rescue medication. Two response criteria were defined being 'pain relief response', combining pain relief and rescue medication, and 'pain intensity response', combining pain intensity and rescue medication. In the 'pain relief response', the overall pooled treatment groups showed a distinct difference to placebo.

The analysis demonstrates that each of the underlying individual studies was insufficiently powered to demonstrate a clear dose response-relationship. Using the combined data set, however a clear dose response relationship could be determined for the response rates based on pain intensity and on mean consumption of rescue medication.

Dose proportionality was demonstrated in the single study: AWB Transtec 2001/1

The demonstration of dose proportionality is important as it provides evidence that in clinical practice a patient without sufficient pain relief at a certain dose level may benefit from being given a higher dose.

Demonstration in daily clinical practice of this important consequence of dose proportionality in response to Transtec was provided by the large non interventional study AWB Transtec 2001/1. Increases in patch strength were in general associated with a remarkable improvement of pain relief, regardless of the underlying pain cause, for patients whose dose of the buprenorphine transdermal patch was increased from 35 µg/h to 52.5 µg/h.

Conclusion

Although a dose response was not demonstrated in individual studies, this was due to the fact that they were not sufficiently powered to demonstrate clear dose response. However, by combining the datasets from 3 placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03), a dose dependent difference between treatment and placebo can be seen. Dose proportionality was also supported by the large non interventional study AWB Transtec 2001/1.

Evaluation of response:

The placebo controlled studies, WIS-BUP01 and WIS-BUP02 compared the three patch strengths. Efficacy according to the primary outcome measure was not established for any patch strength. Secondary outcome measures were described as exploratory and showed inconsistent results across the two studies and across patch strengths such that dose dependent responses cannot be established. The graphs below are copied from the results of WIS-BUP02 as shown in the clinical evaluation report above (in section WIS-BUP02) as an example of the lack of clear difference between the three dose strengths:
Figure 35: Study WIS-BUP02. Responses to different dose strengths

WIS-BUP123 was a post-hoc analysis of the pooled results of three under-powered studies each with a different design. Timeframes and end points were manipulated to enable the results to be pooled. The results did not show a clear and consistent dose response for all groups and all patch strengths (see also the clinical evaluation report above). The parameter ‘Combined response of pain intensity and rescue medication’ was said to provide evidence for dose-dependent effect:
The very wide and overlapping confidence intervals limit the interpretation of this result.

It is unusual to suggest that the results of a post-marketing surveillance study can be used to establish dose response. In AWB Transtec 2001, around 16% had an increase in dose (to a maximum of one 70 µg/h patch). Evaluation of the effectiveness of this was by pain evaluation at the follow-up visits. This showed that changing to a higher strength patch in these patients resulted in more patients describing their pain as ‘good’ or ‘very good’ compared to before the patch change. This result can only be interpreted with caution given the discontinuation rate of 25% reported for the study.

If the pharmacodynamics effect of analgesia occurs at a particular plasma concentration of buprenorphine, then the difficulty in demonstrating dose responsiveness is not surprising. Wide and overlapping ranges of plasma concentrations with the different strength patches were observed in the pharmacokinetic studies (see Question 2 above). This is, however, speculation as the effective concentration of buprenorphine was not demonstrated in the clinical study programme.

In summary, dose responsiveness of this buprenorphine patch has not been demonstrated.

**Clinical issue question 5**

There was no exploration of the comparative effectiveness of a lower dose of buprenorphine. This is particularly of concern given the lowest dose in the proposed dose recommendations is 75% higher than the maximum transdermal buprenorphine dose recommendations of the Australian Therapeutic Guidelines; Analgesics. The highest proposed dose (2 x 70 µg/h) is 7 fold higher than the currently recommended maximum dose.

**Sponsor’s response:**

The proposed Transtec doses are acceptable according to the Australian Therapeutic Guidelines in the likely scenarios that either Transtec is not first line opioid therapy or specialist advice is sought. We believe that lower buprenorphine doses are inappropriate for the proposed
Therapeutic Goods Administration

Transtec indication, which encompasses moderate to severe cancer pain and severe pain that does not respond to non-opioids. At lower doses, an alternative transdermal buprenorphine patch could be prescribed, such as Norspan. Transtec has a wide safety margin, but the risk-benefit ratio for Transtec may be better at higher doses, and there is extensive clinical evidence for the safety and efficacy of the proposed Transtec doses. These responses are elaborated in the following paragraphs.

The proposed Transtec doses are appropriate for the proposed indication

The proposed Transtec indication is for the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids. As a general treatment principle for chronic pain patients receiving opioids, the dose administered by the prescribing physician is titrated to the patient’s needs. Moderate to severe pain patients typically need opioid doses equivalent to between 30 mg and 240 mg oral morphine each day, which equates to between 35 µg/h and 140 µg/h Transtec (Transtec SPC, 2006).

Evaluation of response:
The efficacy of Transtec in treatment of moderate to severe cancer pain and severe pain that does not respond to non-opioids has not been established. The relative equivalence of morphine and buprenorphine patches has not been established; see Clinical Issue Question 2 and Questions 11 and 12 above.

Sponsor response (continued):
The investigation of buprenorphine doses less than 35 µg/h would be appropriate for clinical situations with pain that responds to the equivalent of less than 30 mg oral morphine. Norspan, which is also a buprenorphine transdermal delivery system, has been investigated in these situations. There is already overlap between the proposed Transtec doses and the available Norspan doses in Australia. The maximum Norspan dose approved in Australia has an average buprenorphine flux rate of 40 µg/h (over 7 days), which is greater than the lowest proposed Transtec dose, which has an average buprenorphine flux rate of 35 µg/h (over 4 days). Therefore, rather than explore the comparable effectiveness of lower doses of buprenorphine for Transtec, it was instead considered that patients requiring a lower buprenorphine dose should be prescribed Norspan.

Evaluation of response (continued):
Response to any opioid analgesic in chronic pain may be unpredictable, due to psychosocial overlays, differing aetiologies and the placebo effect. This is compounded in the case of Transtec patches due to the wide inter-patient variability in absorption and resulting plasma concentrations. Given the common and distressing side effects that may accompany the patches, it would be reasonable to test the patient with the lowest suitable patch strength, with this including the range of Norspan patches.

Sponsor response (continued):
The Australian Therapeutic Guidelines do not exclude the proposed Transtec doses

The Australian Therapeutic Guidelines (ATG) recommend that in first line opioid treatment, specialist advice should be sought when prescribing buprenorphine transdermal patch doses above 20 µg/h (ATG, 2015). The proposed Transtec indication encompasses moderate to severe cancer pain and severe pain that does not respond to non-opioids which means that for the majority of patients it is unlikely that Transtec will be used for first line treatment. Even where Transtec is used as first line opioid treatment, the proposed Transtec doses are acceptable according to the ATG when specialist advice is sought, which is a likely scenario for patients with moderate to severe pain.
The ATG also include several disclaimers, indicating that these guidelines should not be treated as unbreakable rules. The following statements are found on page 1 of the ATG Key Information on therapeutic Guidelines:

**Dosing Regimens**

The dosing regimens in the text generally apply to non-pregnant adults of average size; higher or lower doses are appropriate for some patients.

**Disclaimer**

These guidelines are an acceptable basis for management of patients, but there may be sound reasons for modifying therapy in certain patients or specific institutions. The complexity of clinical practice requires that users understand the individual clinical situation and exercise independent professional judgment when basing therapy on these guidelines. Particularly in complicated situations, these guidelines are not a substitute for expert advice.

Therefore, as indicated by the disclaimers contained within the ATG, these guidelines should not prevent the proposed Transtec doses from being made available.

**Evaluation of response (continued):**

The Therapeutic Guideline series is intended to provide recommendations for the management of patients within Australia and are updated every 3 to 4 years. As such, only those medications that are available in Australia at the time of writing of each version. Therefore, the most recent version (updated in 2012) would not include the range of Transtec patches. The recommendation for a maximum dose of 20 µg/h for the buprenorphine transdermal patch provided would be based on the evidence around the range of Norspan patches available at the time.

The discussion regarding chronic pain provided in the Therapeutic Guidelines: Analgesic largely refers to chronic non-malignant pain and is very cautious regarding the use of opioids in these patients, warning that ‘Evidence suggests that opioids work in only one in three patients and that they reduce pain intensity by 30 to 50% at best in patients taking opioids for chronic non-malignant pain, about 80% have at least one adverse effect and only 44% remain on opioids long term.’ A lengthy process of assessment, trialling of ‘all other treatment options, both physical and psychological’, and discussion with informed consent, is advised prior to commencement of opioids.

If opioids are to be used for the management of chronic pain, the Therapeutic Guidelines advise that oral morphine, oxycodone and buprenorphine patches are suitable first line agents. The recommended starting dose for the buprenorphine patch is 5 µg/h and the recommendation of ‘start low, go slow’ is made. The Guideline advises that the more potent fentanyl patches ‘should never be commenced in opioid naïve patients unless in a monitored setting’. Given the possible increase in potency with the higher strength Transtec patches, it is likely that similar advice would be provided regarding these. With regard to the recommended maximum dose for the first line agents, the Guidelines recommend that, if higher doses are required, specialist advice should be sought. This does not preclude higher doses but seeks to ensure that the circumstances of the individual patient are carefully considered and the patient is fully informed.

**Sponsor response (continued):**

*Transtec is relatively safe, especially at high doses*

Buprenorphine has a wide safety margin (Davis, 2013). Due to the rate controlled delivery of small amounts of buprenorphine into the blood circulation by Transtec treatment, high or toxic buprenorphine concentrations in the blood are unlikely (Kress, 2009). The maximum serum concentration of buprenorphine after application of the 70 µg/h Transtec transdermal patch is...
about six times less than after the intravenous administration of the therapeutic dose of 0.3 mg buprenorphine. Buprenorphine has a ceiling effect on respiratory depression but not analgesia, making it an excellent choice of opioid for use at medium to high doses (Davis, 2013; Dahan et al, 2005).

**Evaluation of response (continued):**

Absorption from the patch is a passive process that is affected by many factors: area of skin exposed to the drug containing matrix of the patch, effectiveness of patch adhesion, thickness of the stratum corneum of the skin, blood supply to the area, local heat and physical activity. Absorption is highly variable between patients; minimum and maximum daily doses can be calculated using the absorption rates calculated for individual patients (see discussion of PK Study 1599 and Question 2 above). This shows that the daily dose delivered from a 20 mg patch could range from 0.048 mg to 1.92 mg and the range for a 40 mg patch could be 0.036 mg to 5.0 mg. If the proposed maximum dose of 2 x 70 mg patches is used, the daily dose could be as high as 10 mg in some patients.

Administration of an intravenous dose of 0.3mg of buprenorphine in a small number of healthy volunteers did achieve a higher maximum serum concentration compared to that achieved with transdermal delivery (the C<sub>max</sub> observed in healthy volunteers wearing a 40 mg patch was 624 pg/mL (SD ± 185) and the C<sub>max</sub> following an intravenous dose of 0.3 mg of buprenorphine was 3,625 pg/mL (SD ± 1,315)). Whether this is true in the target population under all conditions has not been demonstrated. Of note is that in the pharmacokinetic arm of the placebo controlled study WIS-BUP02, plasma concentrations as high as 1,800 pg/mL were achieved in some patients with the Transtec patch.

The postulated ceiling effect on respiratory depression with buprenorphine was demonstrated by the administration of intravenous buprenorphine to healthy volunteers with an average age of 22 years. It has not been demonstrated in the target population, who will vary in age, co-morbidities and concomitant medication. Note that many of these patients will be taking co-analgesics that have sedating effects (for example antidepressant, carbamazepine). A number of case reports in the PSURs describe respiratory depression occurring in patients receiving other sedating agents and occurring in elderly patients.

**Sponsor response (continued):**

There is substantial evidence for safe and efficacious use of the proposed Transtec doses

The proposed Transtec doses have been safely and efficaciously used in many clinical studies, as documented in the Transtec dossier. Extensive evidence of the use of the proposed doses in clinical practice is also provided, as documented in the post marketing data (17 periodic safety update reports (PSURs) and 16 post-marketing studies).

Safe and efficacious use of the proposed Transtec doses and even higher doses have been reported in the medical literature (Pergolizzi et al, 2010; Clement et al, 2013; Mercadante et al, 2007; Menten et al, 2006; Camba & Opioid Study Group of the Spanish Pain Society, 2004). Reports describing the safe and efficacious use of the highest proposed Transtec dose (140 µg/h) are described further in the response to clinical issue 6.

**Evaluation of response (continued):**

See comments to clinical issue 6 which discusses the lack of evidence for the proposed maximum dose of Transtec.

**Sponsor response (continued):**

Conclusion

In light of the target indication for Transtec, the proposed Transtec doses are acceptable in accordance with the ATG, as it is likely that either Transtec is not first line opioid therapy
and/or specialist advice would generally be sought for patients experiencing moderate to severe cancer pain, or severe pain that does not respond to non-opioids. Lower buprenorphine doses are unlikely to be appropriate for the proposed Transtec indication, but Norspan could be prescribed instead at lower doses. The safety margin of Transtec is wide and there is also extensive clinical evidence for the safety and efficacy of the proposed (35 to 140 µg/h) Transtec doses.

**Evaluation of response (continued):**

The variable response to buprenorphine patches demonstrated in the clinical studies (for example the high proportion of non-responders in the enrichment study described above) may reflect the wide inter-patient variability in absorption from the patch, and wide variability in plasma concentrations (see Question 2 above). This inter-patient variability means that the response to even the lowest strength Transtec patch can be unpredictable. This is evident in the case reports described in the PSURs where some patients developed symptoms of overdose at less than the proposed dose range (using 'part patch': ½ and ¼ of the 20 mg patch).

The maximum dose proposed by the sponsor was not tested in any of the controlled efficacy studies. It was described as being used in a small number of patients in the post-marketing surveillance studies (134 patients of the total 33,673; see also comments to Clinical Issue Question 6 below). This would suggest that there is little clinical experience on which to base the assertion that this dose is safe and efficacious, and little clinical need for this dose.

The clinical need for lower strength patches seems stronger. It was not uncommon for patients to be advised to cut the patch into smaller pieces (into halves or quarters or even eighths in the post-marketing surveillance studies (545 of 33,673 patients), despite advice to the contrary in the SPC.

**Clinical issue question 6**

*The 140 µg/h dose was not tested in any of the clinical studies and no justification for this recommendation was provided.*

**Sponsor’s response:**

The 140 µg/h Transtec dose is a valuable option for prescribing physicians to manage severe pain patients. In order to titrate the Transtec dose up to a level that meets the patient’s needs, high doses such as 140 µg/h may be required. Arbitrary maximum dose limits are not recommend, but there is a practical limitation to 140 µg/h Transtec dose due to the number of patches required. This dose level has been safely used in clinical practice, as documented in the post marketing data and open label extension studies included in the Transtec submission and reported in the medical literature. However, for ethical reasons it was not deemed appropriate to carry out healthy volunteer studies including a 140 µg/h Transtec dose. These reasons are elaborated in the following paragraphs.

*Transtec is relatively safe, especially at high doses.*

Buprenorphine has a wide safety margin (Davis, 2012). Due to the rate-controlled delivery of small amounts of buprenorphine into the blood circulation by Transtec treatment, high or toxic buprenorphine concentrations in the blood are unlikely (Kress, 2009). The maximum serum concentration of buprenorphine after application of the 70 µg/h Transtec transdermal patch is about six times less than after the intravenous administration of the therapeutic dose of 0.3 mg buprenorphine. Buprenorphine has a ceiling effect on respiratory depression but not analgesia, making it an excellent choice of opioid for use at high doses (Davis, 2013; Dahan et al, 2005).

*High doses of Transtec may be required and maximum dose limits are not recommended, however there are practical limitations of a dose above 140 µg/h.*

As a general treatment principle for chronic pain patients receiving opioids, the dose administered by the prescribing physician is titrated to the patient’s needs, which means that
high doses may sometimes be required. Buprenorphine is as efficacious for analgesia as morphine (Raffa et al, 2014). Severe pain patients typically need opioid doses up to an equivalent of 240 mg oral morphine each day, which equates to 140 µg/h of Transtec (Transtec SPC, 2006). The American Academy of Pain Medicine have stated that arbitrary dose limits disregard differences between patients, while setting a ceiling dose could be dangerously misleading as it implies that lower doses are inherently safer (AAPM, 2013). This is corroborated by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists, who note that for opioid treatment of chronic pain the question of a ‘ceiling dose’ has not been settled (ANZCA, 2015).

The proposed indication for Transtec includes severe cancer pain and severe pain that does not respond to non-opioids. Therefore it is considered likely that severe pain patients requiring a high opioid dose will be prescribed Transtec, and so it should be recommended that the prescribing physician may provide up to 140 µg/h Transtec if appropriate.

Transtec doses higher than 140 µg/h might sometimes be valuable, for example in the case reported by Menten et al. (2006) described further below. However, the administration of more than 2 patches to new skin sites twice a week is considered a practical obstacle to recommending greater Transtec dose strengths, considering that the greatest single patch dose strength is 70 µg/h.

Extensive post marketing data and open label extension studies describe use of the 140 µg/h dose.

The dose of Transtec administered by the prescribing physician is titrated to the patient’s needs, including 140 µg/h doses, in both post-marketing use and open label extension studies. Extensive post-marketing data is described by 17 periodic safety update reports (PSURs) included in the Transtec dossier. In addition to this, 16 post-marketing studies describing the use of Transtec up to doses of at least 140 µg/h are reported.

The open label extension study WIS-BUP-LTS describes several cases in which dose increases due to disease progression led to daily doses greater than 4 mg buprenorphine. Even at these high doses, the treatment showed a constant level of full efficacy after a long period without any indication of a ceiling effect in analgesia or development of tolerance.

One example of a post marketing study that included a minority of patients who received the 140 µg/h dose is AWB Transtec Pro 2005. The number of patients receiving the 140 µg/h Transtec dose increased throughout the study:

Table 78: Study AWB Transtec Pro 2005. Number of patients receiving 140 µg/h Transtec

<table>
<thead>
<tr>
<th>Dose</th>
<th>Enrolment to 1st check-up</th>
<th>1st to final check-up</th>
<th>After final check-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>140 µg/h TRANSTEC</td>
<td>11 patients</td>
<td>18 patients</td>
<td>25 patients</td>
</tr>
</tbody>
</table>

Use of high doses, including 140 µg/h, are reported in the literature.

Reports of safe and efficacious use of 140 µg/h Transtec, in patients with cancer pain have been published (Clement et al, 2013; Mercadante et al, 2007; Menten et al, 2006). Clement and colleagues report two cases of palliative cancer patients who received Transtec doses up to 210 µg/h and 175 µg/h respectively. In both of these cases, Transtec titrated to doses greater than 140 µg/h was well tolerated. Mercadante and colleagues up titrated Transtec doses from 70 µg/h to achieve stable pain control at 140 µg/h in 3 of 10 cancer pain patients. Another 3 of the 10 patients achieved stable pain control at a dose of 105 µg/h Transtec, while 4 patients required stronger opioid treatment than 140 µg/h Transtec and were switched to other opioids in order to achieve higher doses. Menten and colleagues describe the case of a patient with cancer switched to 140 µg/h Transtec in combination with morphine and then, later dicofenac.
The Transtec dose was gradually increased to 280 µg/h without an increase in side effects nor the appearance of clinical toxicity.

The safe and efficacious use of Transtec, has been reported, in doses up to 105 µg/h in patients with chronic nociceptive non-oncological pain (Camba & Opioid Study Group of the Spanish Pain Society, 2004). As a result of up titration to meet patient needs, the number of patients receiving 105 µg/h Transtec increased during the study, from one of 276 patients (0.4%) at Week 2, to 2 of 219 patients (0.9%) at Week 4.

*High doses are unethical in healthy volunteer studies.*

The company believes that it would have been unethical to administer the highest recommended dose Transtec (140 µg/h buprenorphine) to healthy volunteers, even with naltrexone cover. It is considered unlikely that dose strengths of 140 µg/h buprenorphine or greater would be well tolerated in opioid naïve patients. Therefore, enrolling healthy volunteers in studies assessing Transtec at these higher doses would expose the subjects to an unacceptable level of risk. This is an attitude that was shared by [information redacted] during the development of Transtec, and it was a [information redacted] policy that doses of 140 µg/h buprenorphine or greater would not be included in healthy volunteer studies. As a result of this ethical decision, doses of 140 µg/h buprenorphine or greater were not tested in the following healthy volunteer studies: HP5303/01, HP5303/02, PK1599, WIS-BUP02PK, PP0017P, HP5303/04, PK761, and PK747.

**Conclusion**

Buprenorphine is a relatively safe opioid, especially at high doses, and high opioid doses are sometimes required for chronic severe pain patients. Arbitrary maximum dose limits are not recommended, however there is a practical limitation to 140 µg/h Transtec. There is extensive evidence of safe and efficacious use of the 140 µg/h Transtec dose in post-marketing data, open label extension studies and in the medical literature. However, this high dose was not administered in healthy volunteer studies for ethical reasons.

**Supporting documents:**


• Transtec SPC (2006) [information redacted]

**Evaluation of response:**

The maximum dose proposed by the sponsor was not tested in any of the controlled efficacy studies. The post marketing surveillance studies describe the use of multiple patches in some patients. The exact number who used 2 x 40 mg patches (dose 140 µg/h) was unable to be determined as dose description in the study reports was provided as a dose range only (> 70 µg/h and ≤ 140 µg/h). The number of patients receiving a dose within this range was 131 out of 33,673 (0.4%) and only 2 patients received this dose for longer than 6 months. Another two patients were described as receiving a dose of 175 µg/h and one was described as receiving a dose of 200 µg/h for one month.

The sponsor provides a number of publications supporting this ‘higher than normal’ dose:

1. Clement PMJ, et al (2013).67 This article provides two case studies:

   A 31 kg, 77 year old patient with locally spread malignancy was switched from transdermal fentanyl to Transtec, initially at a dose of 2 x 40 mg patches and then 3 x 40 mg patches. The total duration of use was 18 days. During this time the patient severe pain required co-administration of escalating doses of subcutaneous morphine and was switched to this only for the terminal phase of her illness.

   A 72 year old, 73 kg patient with metastatic malignancy was commenced on a 20 mg Transtec patch. The dose was progressively escalated over 6 weeks to 2 x 40 mg Transtec patches and then over three weeks to (2 x 40 mg + 1 x 20 mg) patches. In the terminal phase of the patient’s illness, subcutaneous morphine infusion was added.


   This poster presentation describes a cancer patient treated with 2 x 40 mg patches for a period of 14 days prior to death.


   This article describes a series of 10 patients with cancer pain whose pain was no longer controlled by 1 x 40 mg Transtec patch. The dose of Transtec was increased in each patient until a maximum of 2 x 40 mg patches was reached. In four patients, this dose was not effective and the patients were switched to oral opioids or transdermal fentanyl. Three of the patients achieved adequate pain control on (1 x 40 mg + 1 x 20 mg) patches. The other

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three were treated successfully with 2 x 40 mg patches; how long this dose was continued was not described.

The post marketing surveillance studies suggest that there is little clinical need for a dose of 140 µg/hour and the safety of this dose in the target population has not been established. For those rare patients who obtain pain relief from the buprenorphine patch and whose pain escalates to the point that a dose of 140 µg/h or more is required, as for the small number of patients described in the case reports, then this can still be prescribed. A proposed maximum limit of 70 µg/h in the PI does not prevent higher, or lower, doses than the recommendations provided being prescribed. ‘off label’ use is known to occur with many drugs, including transdermal buprenorphine. This has been clearly demonstrated in the post-marketing studies in which were described the use of doses greater than 140 µg/h, the use of doses less than 35 µg/h and the use in children. Providing the recommendation of a maximum dose of 70 µg/h (1 x 40 mg patch) does, however, indicate the limit of available evidence. The need for higher doses in an individual patient may prompt closer evaluation of the pain and/or referral to a pain specialist and/or switching to an alternative opioid. Note also that the advice provided on the TGA website regarding the PI is that it ‘informs medical practitioners, pharmacists and other health professionals about the safe and appropriate prescribing and dispensing of the medicine’.70

**Clinical issue question 7**

There were no long term data. While long term data for other lower buprenorphine dose regimens are available it is not clear that the safety of the much higher doses proposed would be similar. There is concern that this would not be the case.

**Sponsor’s response:**

The placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 all started between 23 August 1995 and 16 January 1996. At that time long term studies were not routinely carried out. Even so, many patients from these 3 studies entered into open label extension phases; described in the WIS-BUP-LTS clinical study report. Additional long term safety data for the use of Transtec is provided by 16 post-marketing studies and 17 periodic safety update reports (PSURs), which describe post-marketing safety data for this product over more than 10 years. These sources of substantial long term safety data for Transtec are described further in the next few paragraphs.

**Open label extension studies provide long term data.**

Two studies included in the Transtec dossier describe long term open label use of Transtec at doses up to 70 µg/h.

The WIS-BUP-LTS study describes patients who continued taking Transtec in open label extension phases of placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03. In total this study included 239 patients (62.9% of the 380 patients who completed the relevant placebo controlled studies). In the extension phases described by this study, patients received a dose of up to 70 µg/h buprenorphine via Transtec patches. 103 patients (43.1%) participated in the study for 6 months or longer, while 9 patients (3.8%) participated for 5 years or longer. This study assessed the long term safety and efficacy of one or two 35 µg/h Transtec patches, according to the requirements of each individual patient. In general, Transtec treatment over a long period was well tolerated in this study. The majority of the systemic adverse events (AEs) occurred in the main body systems (central nervous, gastrointestinal, body as a whole and skin), and were by their nature typical of opioids. The most frequently reported local AEs were erythema, pruritus and exanthema and were by their nature typical of patches.

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The PB TTC-01 study comprised a blinded phase for the first 4 weeks (28 days) followed by a 6 month (168 day) open label phase. The 307 patients who continued into the open label phase of this study received doses of up to 70 µg/h Transtec. One hundred and fifty five patients completed the 6 month extension phase of the study, providing data on 7 months of treatment in total. This study assessed the long term safety and efficacy of the following Transtec doses; one 35 µg/h patch, one 52.5 µg/h patch and two 35 µg/h patches, according to the requirements of each individual patient. Overall, in both the blinded and open label phases of study PB TTC-01, the majority of observed adverse drug reactions were of mild to moderate intensity and resolved without intervention by the investigator.

*Extensive post-marketing data is available.*

Approval for Transtec was initially received in Germany in 2001. To date, Transtec is approved in 27 countries and has been available in at least 9 countries for the last 13 years. The extensive post-marketing data available over the period 2002 to 2013 is described by 17 periodic safety update reports (PSURs) included in section 5.3.6 of the dossier. In addition to this, 16 post-marketing studies describing use of Transtec up to doses of 140 µg/h (in general the dose is set according to patient requirements by the prescribing physician) are reported. These include the following studies: AWB Transtec ONCO 2003-1, AWB Transtec 2003-0, AWB Transtec ONCO 2003-0, PMS Transtec 2001-2, BIJC-11-03-04, BUP4202, TTC-MATRIX-AWB-2003, AWB Transtec 2003-2, Special Insight AWB Transtec 2003-3, AWB Transtec 2003-1, Special Insight AWB Transtec ONCO 2003-2, AWB Transtec Pro 2005-2, AWB Transtec 2001-1, Report Cohort Study, GRU-BUP-2002-01, AWB Transtec 2003-1.

**Conclusion**

Extensive long-term safety data is available from both open label extension studies and post-marketing experience. Overall, the information available shows that Transtec is safe and effective during long term use.

**Evaluation of response:**

The lack of availability of long-term data is dealt with at length in the clinical evaluation report (above) and is best shown by Table 46 (above), 'Exposure to Buprenorphine Patch in clinical studies according to dose and duration.'

Of note is that the controlled clinical studies all had duration of exposure of less than three months. The open follow-up studies allowed for longer follow-up but relatively few patients continued in these studies for longer than 6 months. Most of the post-marketing studies also had duration of less than 3 months. In total, only 238 patients have continued on the Transtec patch for longer than 6 months in any of the studies provided in the dossier. The high rate of discontinuation of patch use in all studies limits interpretation.

**Clinical issue question 8**

*There were considerable issues with safety even in the short term studies especially the very high discontinuation rates.*

**Sponsor’s response:**

In these studies, the vast majority of related adverse events were known side effects of opioid use. The discontinuation rates in these studies do not relate directly to the safety of Transtec, for the following reasons: Discontinuations during the run-in phases of studies occurred before Transtec was administered. High discontinuation rates are common in opioid pain treatment studies such as these. The placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 occurred at a time when there was little clinical experience of transdermal buprenorphine formulations, which exacerbated the challenge of managing patient expectations to minimise discontinuation. The discontinuation rates among the treatment and placebo groups in these studies are similar. These explanations are elaborated in the next few paragraphs.
Screening failures before randomization

Patient discontinuations before randomization are considered to be screening failures. These discontinuations occurred under buprenorphine sublingual (SL) tablet treatment, before the patients had received Transtec, and so do not indicate safety issues with Transtec. In fact, in the studies WIS-BUP01 and WIS-BUP03, the rate of discontinuation due to adverse events (AEs) was higher under buprenorphine SL tablet treatment in the run-in phases than under Transtec treatment in the double blind phases.

Table 79: Discontinuations due to AEs in Studies WIS-BUP01 and WIS-BUP03

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Discontinuations due to AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Buprenorphine SL tablet</td>
</tr>
<tr>
<td>WIS BUP01</td>
<td>6.4% (12/187)</td>
</tr>
<tr>
<td>WIS BUP03</td>
<td>7.5% (13/174)</td>
</tr>
</tbody>
</table>

This suggests that Transtec has a better safety profile than buprenorphine SL tablets, as measured by discontinuation rates due to adverse events in these studies.

Evaluation of response:

The discontinuation rate due to opioid type adverse events would be expected to be lower in the double blind phase compared to the run-in phase as many of the patients who were intolerant of these effects were selected out; they had discontinued in the run-in phase.

Sponsor response (continued):

High discontinuation rates are not uncommon in opioid trials.

High discontinuation rates are not uncommon in clinical trials for opioid pain products (Noble et al, 2010, 2008). This can be explained by the unpleasant side effects that can accompany use of an opioid such as Transtec, including nausea, constipation, vomiting, dizziness, headache (Transtec SPC, 2015) and the duration of time before the opioid drug reaches a minimum effective concentration (MEC) within the patient's bloodstream. The transdermal delivery system utilized by Transtec is now known to result in a delay between application of the transdermal patch and the development of the desired MEC of opioid in the patient's systemic circulation, due to the time required for absorption of the drug through the patient's skin (Margetts and Sawyer, 2007). These two effects can result in a patient experiencing unpleasant side effects and higher levels of pain following first administration of the treatment, before the administered opioid reaches the MEC. Under these conditions many patients may choose to drop out of the trial and return to their previous pain management regimen.

Evaluation of response (continued):

High discontinuation rates in opioid trials for chronic pain have been recognised for many years; the studies referred to in the meta-analysis and Cochrane review by Noble et al ranged from 1987 to 2004. Appropriate sample size calculations, and use of appropriate comparators, in the study design should allow for this. The latency in analgesic effect of the transdermal patch was also well recognised at the time of the clinical studies for transdermal buprenorphine: all patients were instructed to continue with their previous analgesic regimen for the initial period of application of the first patch. Given this, delay in efficacy of the patch should not contribute to discontinuations.

Also of note is that a minimum effective concentration of buprenorphine has not been established. The sponsor’s submission provides an expert’s opinion only for this. The expert commented that ‘The opioids concentration range in the plasma required to obtain an analgesic effect remains a question for debate’ and that titration to analgesic effect is more important.
Despite this, his conclusion after a review of the available literature was that ‘data are consistent with a roughly estimated BUP minimal effective plasma concentration above 0.1 to 0.2 ng/mL.’

**Sponsor response (continued):**

*Managing expectations with a lack of clinical experience*

Managing the expectations of patients entering a pain trial is an important challenge. This is especially true considering the obstacles to a high completion rate in opioid trials that are described above. At the time when the placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 were carried out, transdermal patch formulations were new and so patients were unlikely to have any previous experience of transdermal patch use. Instead, patients likely had expectations based on oral opioid administration. Likewise, there was little or no clinical experience of what to expect when administering transdermal formulations among the clinical team. Without clinical experience of the formulation, effectively managing patient expectations to minimise discontinuation was an even greater challenge than for trials where use of the formulation is well understood.

**Evaluation of response (continued):**

This is an interesting speculation but it would be expected that in these clinical studies considerable effort would have been made to educate both the investigators and the patients regarding transdermal delivery of medications. Some awareness of transdermal drug delivery systems could be expected amongst the clinical investigators given that transdermal fentanyl has been available since the early 1990’s.

**Sponsor response (continued):**

*Discontinuation rates may be a feature of the study populations*

Discontinuation rates may be high in particular study populations. This can be investigated by comparing the discontinuation rate among patients receiving placebo as compared to study drug. The discontinuation rates for patients receiving Transtec in the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 were all less than or similar to the discontinuation rates among patients receiving placebo as shown in Table 80.

**Table 80: Discontinuations in Studies WIS-BUP01, WIS-BUP02 and WIS-BUP03**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>TRANSTEC (all doses except placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIS BUP01</td>
<td>8.1% (3/37)</td>
<td>8.8% (10/114)</td>
</tr>
<tr>
<td>WIS BUP02</td>
<td>42.1% (16/38)</td>
<td>23.5% (28/119)</td>
</tr>
<tr>
<td>WIS BUP03</td>
<td>4.3% (2/47)</td>
<td>6.6% (6/90)</td>
</tr>
</tbody>
</table>

This suggests that rather than a substance specific issue, the reported discontinuation rates are likely a feature of the study populations.

**Conclusion**

High discontinuation rates are not uncommon in clinical trials for opioid pain products, and were more likely in these studies due to the lack of clinical experience of transdermal patch formulations among patients or the clinical team. Furthermore, the comparable discontinuation rates in the placebo groups for each of the placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 indicate that discontinuations were likely unrelated to Transtec administration.

**Supporting documents:**


_Evaluation of response (continued):_

High discontinuation rates in clinical studies are important as they can indicate both the safety and the tolerability of the medication being studied.

The sponsor has discussed the discontinuation rates seen in three of the controlled clinical studies provided in the submission. More information can be obtained by considering all of the controlled studies and the two follow-up studies, together with the two main reasons for discontinuation in these studies: lack of efficacy and adverse events.

**Table 81: Discontinuation rates from the controlled studies**

<table>
<thead>
<tr>
<th>Study &amp; Duration</th>
<th>Participant number</th>
<th>Discontinuations, and most common reasons for discontinuations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo or active control arm</td>
<td>Transtec (all doses)</td>
<td>Placebo</td>
</tr>
<tr>
<td>All</td>
<td>Lack of efficacy</td>
<td>Adverse events</td>
</tr>
<tr>
<td>WIS BUP 01* 9 days</td>
<td>37</td>
<td>114</td>
</tr>
<tr>
<td>WIS BUP 02* 15 days</td>
<td>38</td>
<td>119</td>
</tr>
<tr>
<td>WIS BUP 03* 6 days Pb TTC 02* 15 days runin phase</td>
<td>47</td>
<td>90</td>
</tr>
<tr>
<td>PB TTC 02* 15 days double blind phase</td>
<td>289</td>
<td></td>
</tr>
<tr>
<td>BUP 4201 5-8 weeks</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>PB TTC 01 follow up</td>
<td>154</td>
<td>159</td>
</tr>
<tr>
<td>6 months</td>
<td>71</td>
<td>26</td>
</tr>
<tr>
<td>WIS BUP LTS 6 months**</td>
<td>241</td>
<td></td>
</tr>
</tbody>
</table>

Note that in all the placebo controlled studies, patients in both the placebo arm and the active arm were able to take sublingual buprenorphine for breakthrough pain, thereby exposing all study participants to the adverse effects of buprenorphine. Patients in the placebo arms were
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also potentially receiving less analgesic therapy, exposing them to discontinuations due to ‘lack of efficacy’. In the placebo controlled studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03, higher discontinuation rates were observed in the placebo arms. The most common reason for discontinuation in the placebo patients was ‘lack of efficacy’. This did not account for all of the difference: discontinuation rates due to adverse events for patients wearing the Transtec patch ranged from 1% to 9% and from 2 to 16% for patients in the placebo arms. This may suggest that the opioid type side effects of sublingual buprenorphine are less well tolerated than transdermal but this interpretation must be made with care given the small numbers of patients and the wide range of adverse event rates. In the ‘run-in’ phase of the other placebo controlled study, PB TTC 02, all patients were managed with Transtec patches and 7% withdrew due to adverse events. The placebo arm of the double blind phase of this withdrawal study had a considerably higher discontinuation rate. Much of this difference was due to discontinuation due to lack of efficacy.

In the longer duration, non-inferiority Studies (BUP 4201 and PB TTC 01) patients were exposed to prolonged release tramadol or Transtec patches. Both of these studies had high discontinuation rates, with this most commonly due to adverse events. The discontinuation rate in the Transtec arm in each study was considerably higher than the tramadol arm, suggesting that the patch was less well tolerated. This was also noted in the post-marketing surveillance Study BUP 4202 that compared the use of buprenorphine patch and prolonged release tramadol.

All opioid analgesics are commonly associated with adverse events. Whether opioid type adverse events are more or less common with the buprenorphine patch has not been established, except in comparison with tramadol as described above. One open post-marketing surveillance study, PMS Transtec versus Durogesic Cohort Study, compared buprenorphine and fentanyl patches and is described above in the clinical evaluation report. This found similar discontinuation rates for both patch types. The sponsor’s submission has provided little comparison of the buprenorphine patch to other opioids commonly used for chronic pain, such as transdermal fentanyl and oral morphine. As possible advantages it suggests a ‘ceiling effect’ on respiratory depression and the convenience of a patch.

Clinical Issue Question 9

The proposal to use these transdermal patches in opioid naive patients is completely unacceptable in any event.

Sponsor’s response:

We appreciate this comment and would like to give some further background information and justification for the use of transdermal patches in opioid naive patients.

Available Data

Substantial experience with Transtec exists, from both clinical trials and post marketing ‘in real life’. Transtec is already approved and marketed in 22 European countries, with first approval in Switzerland in June 2000. The dose range includes the 20 mg, 30 mg and 40 mg patches with the indication of ‘moderate to severe cancer pain and severe pain that does not respond to non-opioid analgesics’. As defined in the Transtec SPC (2015), opioid naïve patients are included in the target population and also in the dose recommendation. The SPC states: ‘Initial dose selection: patients who have previously not received any analgesics should start with the lowest transdermal patch strength (35 µg/h).’

A significant number of opioid naïve patients have already been treated with Transtec and as yet no specific safety signals occurred, as outlined in the submitted PSURs. Overall, a huge number of patients, including opioid naïve patients, have been treated with buprenorphine transdermal patches and included in the regular PSURs. For example, in the post marketing surveillance study AWB2001, more than 13,000 cancer and non-cancer patients with moderate
to severe pain requiring treatment with an opioid analgesic were investigated, and about ⅓ of all patients were opioid naive (more than 4,000 opioid naive patients). The starting doses of the buprenorphine transdermal patch were 35 µg/h (78%), 52.5 µg/h (16%), and 70 µg/h (5%) of all patients. Cancer patients tended to have higher starting doses.

**Evaluation of response:**

According to the study report of AWB 2001, 29.8% of patients were opioid naïve. There was a discontinuation rate of 25% in this study; unfortunately the report provides no breakdown of the representation of the opioid naïve in the discontinuations.

**Sponsor response (continued):**

**Beneficial pharmacological characteristics**

Buprenorphine is an opioid that has a complex and unique pharmacology which provides some advantages over other potent mu agonists.

Buprenorphine is unique in that it has a dose ceiling effect on respiratory depression, but not on analgesia. Therefore, the relative safety of buprenorphine treatment increases with dose up titration (Budd 1981, Dahan et al. 2005 and 2006, and Dahan 2006). Respiratory depression associated with buprenorphine is related to its metabolite, norbuprenorphine, and not to its parent drug. Furthermore, the serum concentration of buprenorphine only rises slowly after application of the first transdermal patch, both in opioid pre-treated and opioid naive patients (Transtec SPC, 2015). Buprenorphine is therefore seen as one of the safest analgesics to use in individuals who are at risk for respiratory depression (Davis 2013).

**Evaluation of response (continued):**

The ‘ceiling effect’ on respiration was found in healthy volunteers receiving intravenous buprenorphine. It has not been established in the target population and may not occur in elderly patients, patients receiving drugs with sedating effect and patients with respiratory disease (see also Clinical Issue Question 5)

**Sponsor response (continued):**

**WHO recommendations and treatment options in opioid naïve cancer pain**

For patients with moderate to severe pain who obtain insufficient pain relief from non opioids, the World Health Organization (WHO) recommends the use of Step 2 opioids first, switching to Step 3 opioids (3 step ladder) if there is still an insufficient analgesic effect. The evidence for this approach is covered by observational studies (Ventafridda et al. 1987; Azevedo Sao Leao Ferreira et al. 2006). However, the WHO approach was developed in the 1980's and the approach has been challenged in recent years. Randomized controlled trials confirmed that using a strong opioid receptor agonist first (two step strategy) is significantly more effective than using the three step strategy, in improving cancer pain (Marinangeli et al.2004; Maltoni et al. 2005). Based on the evidence and the clinical experience over many years in western countries, opioid naïve cancer patients suffering from moderate to severe pain are often initiated on substances like tramadol or codeine but likewise with buprenorphine, morphine, oxycodone and fentanyl.

In opioid naïve patients, the recommended starting dose of sustained release morphine is 30 mg/day (Klepstadt et al 2011; SPC MST Continus). If patients were already treated with Step II analgesics, a starting dose of 60 mg/day is recommended (Klepstadt et al 2011). An up titration of the daily dose of oral sustained release opioids (for example oxycodone) is done on a daily or up to every third day frequency. For transdermal opioids (for example fentanyl) a three daily up titration is established. Likewise, in patients treated with sustained release morphine, who require an increase of the baseline daily dose, an up titration could be done on a 1 to 3 days frequency, in titration steps of approximately 30 mg morphine per day. A dose range of 60 mg/day to 120 mg/day morphine sustained release covers the majority of patients with
respect to achieving appropriate pain relief. The daily dose range of 60 mg to 120 mg morphine is equipotent to the 20 mg to 40 mg Transtec patches.

**Conclusion**

There is substantial evidence for the efficacy and safety of the use of buprenorphine in opioid naïve patients. There is also a medical need for prompt and adequate analgesic treatment to relieve the pain burden of severe pain patients, even if they have not previously received opioid treatment. Together, we believe these facts justify the use of Transtec to treat opioid naïve patients when appropriate.

**Supporting documents:**


**Evaluation of response (continued):**

The issue of using the Transtec patch in opioid naïve patients was discussed in the clinical evaluation report. In most of the clinical studies provided in the dossier, most of the patients had been previously treated with opioids. In study PB TTC 01, in which patients with non-cancer pain were recruited, only about one third of the patients had been previously exposed to opioids. This found a disproportionately high incidence of opioid type side effects, in particular nausea and vomiting, and discontinuations due to adverse events in the opioid naïve patients.
In response to this issue, the sponsor has provided a number of articles that were not provided in the original dossier. Maltoni et al.\(^{71}\) and Marinangeli et al.\(^{72}\) describe the comparison of a two-step approach compared to a three step approach to pain control in chronic cancer pain patients, with the introduction of ‘strong opioids’ after the patient’s pain is not controlled by non-opioids. This found that the early use of ‘strong opioids’ was well tolerated. However, the articles do not describe which opioids were used or the dose in which they were used. The systematic review by Klepstad et al.\(^{73}\) of the use of opioids in patients with moderate to severe cancer related pain advises that starting oral morphine at 30 mg/24 hours or fentanyl patch at 12.5 to 25 µg/h in opioid naïve patients is ‘safe and efficient’ but also acknowledges that this is based on descriptive studies and expert opinion. No advice is provided regarding buprenorphine patches.

It is generally accepted that opioid naïve patients, and the elderly, are more vulnerable to opioid type adverse events, although this is largely based on expert opinion and case studies. It is also generally recognised that there is insufficient evidence to make strong recommendations regarding starting doses or a preferred opioid to commence. As a consequence, most guidelines regarding the commencement of opioids in the opioid naïve recommend commencing at low doses and titrating slowly.\(^{74,75,76}\) The use of strong opioids early in patients with chronic cancer related pain may be appropriate and provide simpler escalation as the disease and pain progresses. The starting dose of an opioid needs to be carefully judged, with the individual factors of the severity and aetiology of pain, co morbidities, concomitant medications, and patient size taken into account.

Buprenorphine patches are available in a wide range the 7 day Norspan patches provide estimated release rates of 5, 10, 20, 30 and 40 µg/h. The 4 day Transtec patches provide estimated release rates of 35, 52.5 and 70 µg/h. The indication for the Norspan patch is ‘moderate to severe pain’ and it is listed on the PBS for this indication but with the added limitation that the patient’s pain cannot be controlled with non-opioids. Commencing opioid naïve patients on a low dose Norspan patch would therefore be appropriate and may provide satisfactory pain control with a lower incidence of adverse events. If pain control is not adequate, titration to desired effect could then occur using the full range of buprenorphine patches. Titrating to desired effect would take a similar length of time for either the 7 day or the 4 day patch as the current PI for the 7 day Norspan patch recommends that during titration, ‘The dose of Norspan patch should not be increased at less than 3 day intervals when steady state levels are attained and the maximum effect of a given dose is established’. Given the marked inter-patient variability in absorption from transdermal drug delivery systems, particular caution is appropriate during the initiation of these drugs, if distressing adverse effects are to be minimised.

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\(^{75}\) McDonough M. Safe prescribing of opioids for persistent non-cancer pain. Aust Prescriber 2012; 35:20-4

\(^{76}\) Chou et al. Opioid Treatment Guidelines: Clinical Guidelines for the use of chronic opioid therapy in chronic non-cancer pain. The Journal of Pain, 2009; 10,
13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The responses provided to the clinical concerns by the sponsor provide no new information related to efficacy. The evaluator’s opinion is unchanged from the first round assessment that the sponsor does not provide sufficient evidence to convincingly establish efficacy of the Transtec patch in the management of moderate to severe chronic pain on the basis that:

- The three ‘pivotal’ placebo controlled studies failed to demonstrate efficacy, using current regulatory and study design standards
- The post hoc analysis of the three under powered placebo controlled studies found inconsistent results across the three patch strengths and three studies and also failed to demonstrate efficacy
- The fourth placebo controlled withdrawal study demonstrated efficacy but only in a sub group of the target population; those patients with severe cancer pain who had already demonstrated a response to the Transtec patch
- The active controlled studies demonstrated non-inferiority to prolonged release tramadol, a WHO Level 2 opioid, although the Transtec buprenorphine patch is proposed as a WHO Level 3 opioid. This is not consistent with the proposed indication.

Given this, the advantages associated with transdermal drug delivery such as avoidance of first pass metabolism, achievement of constant drug plasma levels, an improved patient compliance and improved pain control due to less variation in therapeutic plasma levels may not be realised.

In the responses to the clinical concerns, the sponsor has indicated that the ‘ceiling effect’ on respiratory depression should be considered a safety related advantage of the use of the buprenorphine patch. It is important to remember that this postulated ceiling effect on respiratory depression with buprenorphine was demonstrated by the administration of intravenous buprenorphine to healthy volunteers with an average age of 22 years. It has not been demonstrated in the target population, who will vary in age, co morbidities and concomitant medication. Note that many of these patients will be taking co analgesics that have sedating effects (for example antidepressant, carbamazepine).

The process of raising clinical concerns and evaluating the sponsor’s responses has highlighted a number of gaps in the clinical development programme of the Transtec patch with these including:

- establishing the minimum effective therapeutic concentration,
- establishing the equivalence of 72 hour and 96 hour application times in the target population
- establishing dose responsiveness
- investigating drug-drug interactions
- investigating the factors that affect absorption and inter-patient variability in absorption.

13.2. Second round assessment of risks

The responses provided by the sponsor, including a considerable number of publications that are more recent than 2005 and that were not included in the original submission, has provided a greater depth to the descriptions of aspects of the product. Access to the studies from the clinical development programme of the 7 day Norspan patch has also provided a greater
understanding of the performance characteristics of the transdermal buprenorphine delivery
system together with safety concerns related to the 7 day patch.

These concerns include the safety aspects of an appropriate interval before re-use of an
application site, the effect of heat on absorption and potential drug-drug interactions. The lack
of information regarding these factors in relation to the Transtec patch means that the
information available for the 7 day Norspan patch must be used as the best available guide. This
would suggest that the risks associated with re-use of an application site within 21 days,
application of heat to the patch and potential interactions with drugs such as protease inhibitors
need to be acknowledged in the PI for Transtec.

Additional information was also provided regarding the potential safety concerns of QT
prolongation and vasospastic angina. The 2015 review of the risk of QT prolongation with
transdermal buprenorphine was reasonably comprehensive and suggests that this risk is, at
most, extremely low. However, the 2015 review was not as thorough as the review performed in
2006 and failed to follow up on the safety signal of increased ‘sudden death’ that was identified
by a broad search of the WHO Vigibase in the earlier review.77

The safety and tolerability concerns identified in the first round evaluation remain and several
more have been added following the second round evaluation:

- **Safety concerns**
  - The response to even low doses is unpredictable and can result in symptoms requiring
    hospitalisation. This unpredictability is consistent with the considerable inter patient
    variability in absorption from the patch demonstrated in the pharmacokinetic studies
  - Potentially life threatening co-administration with other sedating drugs is likely to
    continue to occur, given that many co analgesics may cause sedation. This is a particular
    concern with the buprenorphine patch due to its long half-life even after patch removal
  - The evaluator’s concern regarding the risk of Torsades de Pointes is lower following the
    second round evaluation but this concern has not been eliminated
  - Coronary vasospasm remains a serious potential risk
  - The potential for abuse and misuse also exists, although this is probably at low risk of
    occurrence.

- **Tolerability Concerns**
  - Use of the buprenorphine patch of these strengths is frequently associated with such
    side effects of nausea, vomiting, constipation, dizziness and fatigue. These were
    sufficiently distressing for many patients to discontinue use of the buprenorphine patch
    (discontinuation rates of 18 to 46% were described in the post marketing surveillance
    studies)
  - Application site reactions frequently occurred and were of sufficient severity to be a
    common reason for patients to discontinue use of the product, particularly with long-
    term use.

- **Additional concerns identified through the second round evaluation:**

77 The MAH of Transtec have performed several comprehensive scientific evaluations (including the
Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006 provided
in PSUR 10 Appendices) of buprenorphine transdermal patch and QT prolongation, the latest in Mar
2015, which considers all the data available for on this topic and concludes that there is no signal that
buprenorphine may have a pro-arrhythmic effect in the range of exposure achieved with transdermal
systems or even the higher doses of oral buprenorphine used in opioid substitution therapy.
– Increased absorption from the patch, with resulting increase in opioid type adverse effects may occur with
  ▪ re-use of an application site between 7 and 21 days
  ▪ local application of heat to the patch
  ▪ external heat and physical activity
  ▪ application to an area of damaged skin
– Use in opioid naïve patients should be avoided due to the likely occurrence of distressing opioid type adverse effects. Use of one of the lower strength 7 day Norspan patches should be considered instead
– The proposed maximum dose of 2 x 40 mg patches (estimated dose of 140 µg/h) is not supported by the clinical study programme. Insufficient use of this dose has been described in the post-marketing surveillance studies and available literature to provide support for this proposed maximum dose.
– The possibility of drug-drug interactions with drugs that affect CYP3A4 (including protease inhibitors)
– Risk of medication errors through the availability of two buprenorphine patches with different application times. Patients may inadvertently apply the 7 day patch for 4 days and receive a higher than intended dose.

13.3. Second round assessment of benefit-risk balance
The evaluator’s assessment of the benefit-risk balance is unchanged: the benefit-risk balance of the buprenorphine patch for the proposed usage is unfavourable. Given the uncertain efficacy, the risks outweigh any potential benefit. These risks range from potentially life threatening, although rare, adverse drug reactions to the less severe but very common and distressing opioid type side effects.

14. Second round recommendation regarding authorisation
The evaluator’s recommendation regarding authorisation is unchanged from the first round. It is recommended that the submission be rejected on the grounds of:
• Efficacy has not been satisfactorily demonstrated for the proposed indication of the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids
• Safety concerns such as;
  – Unpredictable response to even low doses (including part patches) that can result in symptoms requiring hospitalisation
  – Potentially life threatening co administration with other sedating drugs is likely to continue to occur, given that many co analgesics used in the target population may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  – Poor tolerability with high rates of discontinuation due to adverse effects
  – Cardiac risk due to possible QT prolongation and coronary vasospasm.
15. References

Temgesic Product Information accessed February 2015


ACPM Minutes: Item 2.8 Buprenorphine Transdermal Patch, Mundipharma Pty Ltd and Item 3.4 Buprenorphine hydrochloride (Norspan TDS) – Mundipharma Pty Limited - Section 60 Appeal Guideline on quality of transdermal patches, EMA/CHMP/QWP/911254/2011


Budd K. Buprenorphine: a review. Evidence Based Medicine in Practice 2002, 1-24


CPMP/EWP/252/03 Guideline on clinical medicinal products intended for the treatment of neuropathic pain


DBL Naloxone hydrochloride injection product information. Accessed on February 2015

