Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Tapentadol

Proprietary Product Name: Palexia IR

Sponsor: CSL Pty Ltd

February 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	17 November 2010
Active ingredient(s):	Tapentadol
Product Name(s):	Palexia IR (Immediate Release)
Sponsor's Name and Address:	CSL Ltd 45 Poplar Road, Parkville VIC 3052
Dose form(s):	Tablets
Strength(s):	50, 75 & 100 mg [Tablets potency is expressed in terms of tapentadol free base]
Container(s):	PVC/PVDC/Al blister packs
Pack size(s):	5, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90 & 100
Approved Therapeutic use:	Relief of moderate to severe pain
Route(s) of administration:	Oral (PO)
Dosage:	Dosing to be individualised according to the severity of pain, previous treatment experience and the ability to monitor the patient. Palexia IR: 50 mg, 75 mg or 100 mg every 4 – 6 hours depending on the initial pain intensity. Dose may be adjusted on the first day of dose as needed. The usual recommended dose is 50 to 100 mg every 4 to 6 hours. Starting doses of more than 700 mg daily and maintenance doses of more than 600 mg daily have not been studied and are not recommended.
ARTG Number (s)	165 310, 165317 and 165318

Product Background

Tapentadol is a centrally acting analgesic that exerts its pharmacological effects by two mechanisms of action in a single molecule, that is, mu-opioid receptor agonism and noradrenaline re-uptake inhibition. Its binding affinity to mu-opioid receptors is approximately 18 times less than that of morphine. The indication for the IR form of tapentadol is the same as currently applies to both the immediate and sustained release forms of tramadol and oxycodone (Endone).

The sponsor has proposed that tapentadol be scheduled as S8. A pharmacology study demonstrated that tapentadol demonstrated abuse potential comparable to that of hydromorphone. In the USA tapentadol is a federally controlled substance (C-II).

Regulatory Status

Palexia IR has a marketing authorisation in the USA (2008) where it is marketed as Nucynta (since November 2008). The approved indication in the US is as follows:

"Nucynta™ is an opioid analgesic indicated for the relief of moderate to severe acute pain in patients 18 years of age and older".

Palexia IR has a marketing authorisation in the European Union (since August 2010). The approved indication in the EU is as follows:

"Palexia IR is indicated for the relief of moderate to severe acute pain in adults, which can be adequately managed only with opioid analgesics."

The proposed indication for Australia is aligned with the TGA approved indications for other strong analgesics including Endone (oxycodone).

Product Information

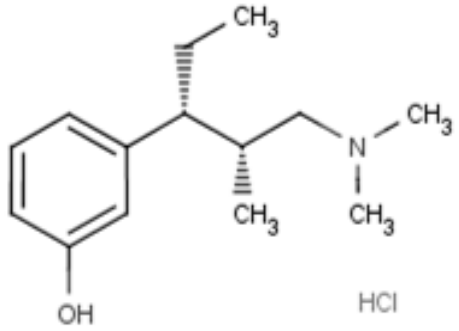
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Tapentadol shares a 3-(3-hydroxyphenyl)propylamino structural fragment with morphine and its analogues. It is isolated as the hydrochloride salt, the structure of which is shown below.

Figure 1. Chemical structure.



The drug substance has two chiral centres and is manufactured as a single (*R, R*) stereoisomer. All polymorphic forms are freely soluble within the physiological pH range. The drug substance is designated as BCS Class 1[1].

The drug substance specifications include appropriate limits for enantiomeric purity and for related substances.

Stability data have demonstrated that tapentadol hydrochloride is a stable substance. A retest period of 30 months with storage below 25°C has been approved.

Drug product

The product is a conventional, unscored, film-coated tablet, manufactured by a standard manufacturing process. The cores of the three different strength tablets are direct scales.

The drug product specifications are conventional. Individual degradation products are limited in accordance with ICH guidelines.

A shelf life of 3 years with storage below 30°C has been approved.

[1] The Biopharmaceutics Classification System (BCS) is a guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

Biopharmaceutics

Although tapentadol hydrochloride is both highly soluble and highly permeable (BCS Class 1), its absolute bioavailability is only 32% under fasting conditions (and 42% under fed conditions) due to a high first pass effect. Food increases both the area under the plasma concentration time curve (AUC) and maximal plasma concentration (C_{max}) (by 25% and 16%, respectively). The tablet used in clinical trials was shown to be bioequivalent to an earlier capsule formulation and it has been satisfactorily established, without the need for an *in vivo* study, that the clinical trial tablet is bioequivalent to the proposed registration formulation.

Quality Summary and Conclusions

The Palexia IR application was considered at the 132nd meeting of the Pharmaceutical Subcommittee of the ACPM on 24 May 2010. The subcommittee had no objections to registration on pharmaceutic grounds subject to satisfactory resolution of issues raised by the TGA following the initial evaluation of the application. All of those issues have since been satisfactorily resolved and there are now no objections to registration with respect to Chemistry, Manufacturing and Controls.

The subcommittee raised some additional, pharmacokinetic issues, which have been separately addressed by the company. The sponsor's responses have been referred to the Delegate for assessment (see below under *VI. Overall Conclusion and Risk/Benefit Assessment*).

III. Nonclinical Findings

Introduction

The submitted nonclinical data were extensive and generally adequate. The relevant studies were generally Good Laboratory practice (GLP) compliant, apart from some safety pharmacology studies (discussed under the relevant subheading below). Tapentadol was administered as a liquid solution in nonclinical studies, rather than as the proposed clinical tablet forms. Relative exposure to tapentadol in most toxicity studies was quite low, as dosage levels were limited by adverse effects on the central nervous system (CNS). The nonclinical findings were generally consistent with effects on the μ-opioid pathway. Most pharmacological effects were observed at dose levels between that of morphine and tramadol, on a dose per body weight basis.

A large series of primary pharmacology studies (>25 studies) was submitted, providing extensive data regarding the relative efficacy of tapentadol in various models of pain, by different routes in multiple species. In addition, the toxicity of tapentadol was investigated in a substantial number of repeat dose toxicity studies (including >20 non-pivotal studies). The value of such a large number of studies and the relatively large group sizes in pharmacodynamic studies is questioned, given the very clear, quantifiable efficacy and safety profile of tapentadol and ensuing ethical concerns.

Pharmacology

Primary pharmacodynamics

Mechanism of action

Mechanistic studies primarily consisted of *in vitro* competitive receptor binding assays. Tapentadol bound to the following receptors *in vitro* with half maximal inhibitory concentration (IC_{50}) values <1 μM: μ-opioid receptor (μOR; IC_{50} values 0.2-0.23 μM), noradrenaline uptake transporter (IC_{50} values 0.62-0.64 μM), β_1-adrenergic receptor, 5-HT_{2A} receptor, 5-HT uptake transporter, σ_2 opioid receptor (IC_{50} value 0.60 μM) glutamate phenycyclidine (PCP) receptor. Of these, greatest binding affinity (K_i values) was for the μOR (K_i 0.096 μM for the rat receptor and 0.164 μM for the human receptor, compared to

the clinical C_{max} at the MRHD[2] of 145 ng/mL[3] or 0.56 µM), followed by the σ_2 receptor (K_i 0.43 µM rat binding site) and noradrenaline uptake transporter (K_i 0.48 µM rat NA transporter. K_i values for the β_1-adrenergic receptor and 5-HT_{2A} receptor[4] were not reported. Tapentadol bound to the µOR with circa 10-fold greater affinity than to other opioid receptors, although with 18-fold lower affinity than morphine and 7-fold lower affinity than morphine-6-O-glucuronide.
Other receptors demonstrating some binding inhibition by tapentadol (that is, K_i values <1 µM) included the κ- and δ-opioid receptors and M_1 muscarinic receptor. An extensive panel of receptors, ion channels, transporters and enzymes was shown to exhibit low or no tapentadol binding *in vitro*. The primary metabolite of tapentadol (tapentadol-glucuronide; ≤ 10 µM) demonstrated only slight binding to the µ-OR, noradrenaline uptake transporter, α1- and β_2-adrenergic receptors, dopamine D_{2S} receptor and 5-HT transporter *in vitro* (7-20%). Other tapentadol metabolites (for example, N-desmethyl metabolites) demonstrated binding affinity compared to tapentadol to µ-Orland noradrenaline and serotonin uptake transporters, however these metabolites are considered minor human metabolites and any potential receptor binding was not considered toxicologically significant.

Tapentadol inhibited binding of noradrenaline by the noradrenaline uptake transporter *in vitro*, with an IC_{50} value of 0.6 µM. In an *in vivo* study, tapentadol administration (4.64 and 10 mg/kg via the intraperitoneal (IP) route) induced a dose-related increase in extracellular levels of noradrenaline and 5-HT in the ventral hippocampus of the rat (increases to ≤ 550% and ≤ 225% of baseline levels, respectively). These increases were not observed with morphine (1-10 mg/kg IP), indicative of non-opioid receptor-mediated effects of tapentadol.

Limited additional data investigating the mechanism of action of tapentadol were submitted. Several *in vivo* efficacy studies examined the extent to which the anti-nociceptive effects of tapentadol could be blocked by a µOR antagonist (naloxone), an α_2-adrenergic receptor antagonist (yohimbine) or a non-selective 5-HT receptor antagonist (ritanserin). Naloxone completely inhibited the effects of tapentadol in a phenylquinone writhing test in mice, a paw incision model of post-operative pain in rats and following injection of yeast in a rat model of inflammatory pain. In contrast, naloxone only partially inhibited the effects of tapentadol in tail flick assay, following spinal nerve ligation and following formalin injection in rats. Similarly, yohimbine abrogated the effects of tapentadol in tail flick assays, models of mono-neuropathic pain and a formalin test in rats, but had no effect in a phenylquinone writhing test in mice and in a rat model of inflammatory pain. Ritanserin had no effect in a tail flick assay or a model of inflammatory pain in rats. Thus, the actions of tapentadol in both opioid receptor and noradrenaline uptake pathways elicit anti-nociceptive effects, depending on the particular animal model under study. Despite the increase in extracellular CNS serotonin levels in rats, no effect of ritanserin was seen under the conditions tested and the role of 5-HT receptor pathways was unclear. The sponsor did not investigate the potential contribution of other receptor pathways (for example, σ_2, or M_1 muscarinic receptors) to tapentadol-induced analgesia *in vivo*.

Efficacy

Tapentadol demonstrated dose-related efficacy (generally at all doses tested) in mouse, rat and dog models of acute pain, rat models of neuropathic pain and mouse and rat models of inflammatory pain. Several routes of administration were generally tested; the majority did not use the intended clinical (oral) route of administration. The sponsor added the comment

[2] MRHD = maximum recommended human dose
[3] See **Relative exposure** below for a discussion of clinical C_{max}.
[4] 5-HT = serotonin

that this was due to the low (lower than in humans) oral bioavailability in rodents and dogs. The following table (Table 1) summarises the minimal efficacious doses observed in different experimental models in different species; efficacy in most models was observed with tapentadol exposure (AUC-based) lower than that at the minimum recommended clinical dose (calculated by comparison with dose-normalised, AUC-based clinical exposure at the lowest usual recommended dose of 100 mg/day Palexia IR; refer to '**Relative exposure**' below). This demonstrates that the animal pain models selected were sensitive to the analgesic effects of tapentadol.

Table 1: Minimal efficacious doses in various animal pain models

Experimental model	Species	Route	MED (mg/kg)	Exposure margin (AUC)[a]
Acute pain				
Tail flick assay	Mouse	PO	21.5	0.3
		IV	1	0.2
	Rat	PO	68.1	0.2
		IV	0.464	0.08
		IT	14.7 µg	NA
	Dog	PO	No effect at 215	1.4
		IV	4.64	1.1
Phenylquinone writhing test	Mouse	PO	21.5	0.3
		IV	0.215-1	0.03-0.2
Colorectal distension (visceral pain)	Rat	IV	2.15	0.4
Paw incision (post-operative pain)		IP	0.681	0.03
Hot plate test: weak pain	Mouse	IV	2.15	0.3
		IP	4.64	0.2
Hot plate test: strong pain	Mouse	IP	10	0.4
Formalin test: acute (chemical) effects	Rat	IP	2.15	0.1
Neuropathic pain				
Cold allodynia: chronic constriction injury	Rat	IP	0.464	0.02
Tactile allodynia: chronic constriction injury		IP	0.316	0.01
Tactile allodynia: spinal nerve ligation		IV	0.1	0.02
Cold allodynia: cytostatic agent-induced polyneuropathy		IP	1	0.05
Paw pressure test: diabetic polyneuropathy		IP	3.16	0.1
		IV	0.326	0.05
Inflammatory pain				
Mustard oil-induced colitis: curative	Mouse	IV	10	2
Mustard oil-induced colitis: prophylactic			2.15	0.3
Paw pressure test: yeast injection	Rat	IV	1	0.2
		IP	4.64	0.2
		IT	10 µg	NA
Anti-nociceptive effects				
Formalin test: chronic effects	Rat	IP	2.15	0.1
Tooth pulp stimulation	Rabbit	IV	2.15	NA

[a]Extrapolated from pharmacokinetic and toxicokinetic data; calculated by comparison with dose-normalised, AUC-based clinical exposure at minimum recommended dose (417 ng.h/mL at 100 mg/day Palexia IR; refer to '**Relative exposure**' below)

IT = intrathecal; IV=intravenous; IP=intraperitoneal; MED = minimal efficacious dose; NA = no available pharmacokinetic data for this route

Efficacy was relatively lower in dogs compared to other species; it was unclear whether this was due to insensitivity of the pain models in this species or whether it represented a general species specific insensitivity to tapentadol. However, exaggerated pharmacological effects observed in toxicity studies are indicative of some response in this species. The efficacious IV dose range of tapentadol (that is, with 100% bioavailability) was generally between that of tramadol and morphine; efficacious tapentadol doses were generally 2-3x greater than morphine, on a mg dose per body weight basis.

Tapentadol-glucuronide showed no effect in tail-flick assays in mice and rats and in a phenylquinone writhing test in mice at respective exposures (AUC-based, extrapolated from pharmacokinetic data obtained following a single IV dose) 25, 4 and 11 times greater than the lowest usual recommended clinical dose. Thus, the glucuronide was considered to be an inactive metabolite of tapentadol. The effect of several other tapentadol metabolites in a phenylquinone writhing test was examined; significant effects were observed for the dihydroxy HCl, 3-OH, 4-methoxy (racemic), 3-methoxy, 4-OH HCl, N-desmethyl and N,N-Di-desmethyl metabolites. As these were minor metabolites in humans, these findings were not considered pharmacologically or toxicologically significant.

Secondary pharmacodynamics

A dose-related increase in emetic episodes was observed with tapentadol IP dosing (≥10 mg/kg) in ferrets, although the incidence and frequency was less than that of morphine (0.125 – 0.5 mg/kg subcutaneously (SC) and 0.4 mg/kg IP). Intravenous (IV) administration of tapentadol (10 - 21.5 mg/kg) resulted in reduced incidence and frequency of morphine-induced emesis in ferrets. Nausea and vomiting are noted as 'very common' adverse reactions in the Product Information.

Tapentadol demonstrated a dose-related antitussive effect following exposure to ammonia in rats with IV dosing (0.215 - 21.5 mg/kg), similar to that observed with codeine (≤ 21.5 mg/kg IV). A dose-related local anaesthetic effect, measured as an increase in the number of mechanical stimuli required to elicit a skin twitch response *in vivo*, was also observed following intradermal injection to guinea pig skin (0.05 – 0.5% solutions). Tapentadol inhibited guinea pig smooth muscle contraction *in vitro* (IC_{50} 1.49 µM). Effects of tapentadol treatment were abrogated by naloxone treatment, consistent with effects on the µOR.

Safety pharmacology

Numerous *in vivo* and *in vitro* studies investigated effects on the CNS (mice and rats), cardiovascular system (mice, rats, rabbits and dogs), renal and respiratory systems (rats), GI tract (mice) and cholinergic system (guinea pigs). The majority of studies were not GLP-compliant; the sponsor stated that this was because the studies were conducted prior to this requirement, but this did not appear to be the case for approximately half of the non-GLP studies. Nevertheless, the studies appeared to be adequately designed and documented.

CNS effects

In general, CNS effects following single IV or IP doses were consistent with effects on opioid pathways, for example, decreased exploration activity and motor coordination in mice and clinical signs (piloerection, pupil dilatation, loss of reflexes, reduced fear and grip strength, Straub response, *etc*.) in rats. Exposure in these studies was at least twice the estimated clinical C_{max} at the maximum recommended daily tapentadol dose, extrapolated from C_{1st}

values following a single IV dose in pharmacokinetic studies[5]. Animal plasma exposure at the No Observed Adverse Effect Level (NOAEL) for CNS effects was similar to estimated maximum clinical C_{max} values.

Convulsions were observed in rats at doses ≥ 18 mg/kg IV (circa 11x the clinical C_{max}) and an increased incidence of pentylenetetrazole (PTZ)-induced convulsions occurred at tapentadol doses ≥ 2 mg/kg IV. Pre-treatment with diazepam or phenobarbitone prevented tapentadol-induced convulsions and naloxone had a variable effect; no effect was observed in one study with 10 mg/kg IP naloxone, whereas a dose-related effect was observed in another study with 0.03 – 3 mg/kg IV or 10 mg/kg IP naloxone. The sponsor attributed the failure in the earlier study to the inconsistency of reversibility of opioid-induced convulsions by opioid antagonists. This was considered plausible, as other known opioid-related effects (for example the Straub response) were also unaffected by naloxone in that study. The effect of naloxone indicates that the convulsions are related to the opioidergic activity of tapentadol. Convulsions were also observed in multiple species in repeat dose toxicity studies, as discussed under the relevant subheading below.

Cardiovascular effects

In vitro studies indicated a potential for tapentadol-induced cardiac repolarisation disturbances, with concentration-related inhibition of hERG potassium (K^+) channel current amplitudes (IC_{50} 36.1 µM), effects on action potential duration in papillary muscle (increased in rabbits at ≥ 30 µM and decreased in guinea pigs at ≥ 10 µM) and decreased beating rate/heart rate in guinea pig cardiac tissue (≥ 3 µM). These concentrations are considerably greater than the clinical plasma C_{max} at the MRHD of 0.56 µM (145 ng/mL) or 0.77 µM (200 ng/mL)[6].

Heart rate and blood pressure were increased in conscious rats (for 60 min post-dose at ≥ 10 mg/kg IV) and dogs (≤ 15 min post-dose at ≥ 3 mg/kg IV; C_{1st} values were at least twice the estimated maximum clinical C_{max}) in a dose-related manner and tachycardia and atrioventricular block were observed at all doses in dogs. In contrast, blood pressure was decreased in anaesthetised rabbits (≥ 1 mg/kg IV) and dogs (≥ 0.5 mg/kg IV; C_{1st} values were 0.7 – 13x the estimated maximum clinical C_{max}), consistent with opioid-related cardiovascular depressant activity. There were no effects on QT interval[7] in anaesthetised dogs at extrapolated exposures at least twice the estimated maximum clinical C_{max}, although a dose-related (but not significant) prolongation of QT_c[8] was observed in conscious dogs at ≥ 3 mg/kg IV (3x the clinical C_{max}). Similarly, prolonged QT intervals (and generally QT_c when available) were frequently observed throughout treatment periods in repeat dose toxicity studies in dogs at PO doses ≥ 30 mg/kg/day (0.2x the clinical C_{max}). This was consistent with other opioid compounds and was considered to be potentially clinically relevant.

[5] Refer to '**Relative exposure**' below for a discussion of exposure comparisons.
[6] See '**Relative exposure**' below for a discussion of C_{max}.
[7] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

[8] QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Tapentadol-glucuronide, N-methyl tapentadol and tapentadol-sulfate demonstrated slight inhibition of hERG K^+ channel current amplitudes (respective IC_{50} values of >300 µM, 264 µM and >300 µM) *in vitro* and tapentadol-glucuronide showed no effect on action potentials in guinea pig papillary muscle at≤ 300 µM).

Effect on renal function

A transient reduction in electrolyte excretion was observed following tapentadol administration (10 mg/kg IV) to rats. In contrast, increased urinary volume with accompanying decreases in osmolality and specific gravity was observed in repeat dose toxicity studies in rats. There were no treatment-related effects on urinary volume in dogs. This is unlikely to be of clinical concern, as the changes were minor and transient and did not occur across species.

Respiratory effects

Tapentadol induced effects consistent with respiratory depression in conscious rats (for example, decreased respiratory rate, increased partial pressure of carbon dioxide (pCO2) and decreased partial pressure of oxygen (pO2)) at doses ≥ 4.64 mg/kg IV and 21.5 mg/kg IP, resulting in mortality with repeated doses at 15 mg/kg/day IV. Respiratory effects were observed following IV dosing at extrapolated C1st values≥ 2 times the estimated maximum clinical Cmax and mortality occurred at 9x the estimated maximum clinical C_{max}. The effect on blood gases occurred at higher doses than with morphine in one study (twenty-five percent effective dose (ED_{25}) values of 10.4 mg/kg IV for tapentadol and 7.9 mg/kg IV for morphine). Tolerance to respiratory depression developed at a similar rate as morphine (after 22 days of repeated dosing once every 3-4 days). These findings were consistent with clinical signs observed in rats, rabbits and dogs in repeat dose toxicity studies, with laboured or irregular breathing, panting and reduced respiratory volume reported at doses≥ 150 mg/kg/day PO (rats), 15 mg/kg/day IV (rabbits) and≥ 80 mg/kg/day PO (dogs). C_{max} values at these doses were in the range 2-3 (rats) and 0.7-2 (dogs) times the estimated maximum clinical C_{max}.

Gastrointestinal effects

Tapentadol (2.15 – 68.1 mg/kg IP; equivalent to 0.01 – 0.4x the maximum recommended clinical exposure, based on mg/m^2) demonstrated inhibition of gastrointestinal (GI) transit (≤ 50%) and inhibition of prostaglandin-induced diarrhoea in mice (≤ 100%). The quantitative effect on GI tract activity was between that of morphine and tramadol.

Cholinergic effects

Tapentadol (0.1-2.15 µM) induced a concentration-dependent inhibition of acetylcholine-induced isotonic contractions of guinea pig ileum *in vitro*. The effect was quantitatively similar to that of atropine. No effect was observed for morphine (≤ 100 µM), indicative of a non-opioid effect of tapentadol.

Pharmacodynamic drug interactions

Tapentadol increased the duration of barbiturate-induced anaesthesia in mice in a dose-related manner (two hundered percent effective dose (ED_{200}) value of 71.2 mg/kg IP), although it was less potent than tramadol (ED_{200} value 43.4 mg/kg IP).

Combination treatment of tapentadol (4.64 – 31.6 mg/kg IV) with diazepam or tetrazepam attenuated the muscle-relaxing activity of the latter compounds in mice, measured as a reduction in the incidence of the effect, the duration of relaxation and the relaxation score. The sponsor did not consider this to represent a pharmacodynamic interaction, as the changes

were not statistically significant. However, extrapolated AUC-based exposure margins were low (≤ 0.8), thus such interactions are potentially clinically relevant.

Pharmacokinetics

The pharmacokinetics of tapentadol following a single dose were investigated in mice (IV or PO dosing), rats (IV dosing) and dogs (PO dosing) and following repeated administration in mice (IP or SC dosing), rats (IV, IP, SC or PO dosing) and dogs (IV or PO dosing). Toxicokinetic data were obtained in most toxicity studies with tapentadol. Studies using the intended clinical (PO) route were investigated in mice, rats and dogs, as well as studies in the same species (and monkeys) with IV, SC and/or dietary administration. Validated methods were used in all studies. The studies were generally adequate.

Tapentadol was rapidly absorbed following PO administration in all nonclinical species, with C_{max} values reached within 1 h of dosing. This differed from the two formulations administered in clinical trials, with the time when the maximum plasma concentration was reached (t_{max}) estimated at 1.5-2 h (tapentadol IR). Tapentadol was generally detected at all measured time points post-dose in rats (≤ 12 h) and dogs (≤ 24 h) and for 2-5 h post-dose in mice. Tapentadol was rapidly metabolised, based on tapentadol half-lives and t_{max} values for the primary metabolite (tapentadol-glucuronide) and exposure (AUC-based) to tapentadol-glucuronide was markedly greater (as much as 300x) than that of the parent compound in all species. AUC-based exposure was approximately dose-proportional in mice, but greater than dose-proportional in rats and dogs. Similar to humans, exposure to tapentadol and tapentadol-glucuronide appeared to be greater in female rats than males; there were no sex differences in mice and dogs. There was generally no evidence for accumulation with repeated dosing in animals, except in rats with twice-daily administration. The half-life of tapentadol was longer in mice and rats following PO dosing compared to IV dosing, which is suggestive of enterohepatic circulation. The bioavailability of tapentadol in mice following PO dosing was 40-47%.

The toxicokinetics of tapentadol were investigated following PO administration to juvenile rats between post-natal day (PND) 13-26 during a pre/post-natal development study. AUC- and C_{max}-based exposure to tapentadol and its glucuronide on PND13 was generally an order of magnitude greater than that of adult rats at comparable doses, possibly consistent with the younger age of the juvenile rats. Exposure margins (AUC and C_{max}) on PND26 were generally similar to that of adult rats at similar doses.

Distribution

Tapentadol was rapidly and widely distributed in rats following a single IV dose in a tissue distribution study. Radioactivity was detected in all tissues tested and all tissues except for white fat had radioactivity concentrations higher than blood at the C_{max}. Highest levels of radioactivity were detected in the kidneys, preputial gland, secretory glands (for example, lachrymal glands, salivary glands) and liver, with concentrations 5-10 times greater than blood. Radioactivity in target tissues (brain and spinal cord) was 2x and 1.4x greater than blood, respectively, indicative of good uptake by the CNS. Radioactivity was not detected, or was approaching the lower limit of quantification, in most tissues 72 h after the final dose. Tapentadol-glucuronide was detected at low levels (0.06 – 0.2x plasma levels) in extracellular fluid in the brain of rats following PO dosing, indicative of transfer of the metabolite across the blood-brain barrier and exposure in target tissues. Consistent with extensive tissue distribution, the volume of distribution following IV dosing was generally high (circa 4 L/kg in mice and 9-20 L/kg in rats).

Plasma/serum protein binding ranged from 11-20% in rabbits, mice, dogs, rats and humans (in ascending order) and results were similar over a tapentadol concentration range of 50 - 800 ng/mL. The ratio of tapentadol concentrations in blood versus serum or plasma was indicative of no accumulation of tapentadol in erythrocytes in dogs and some accumulation in human erythrocytes (23-53%). Tapentadol bound to melanin *in vitro* in a manner inversely proportional to concentration, with 48 – 27% binding in the above concentration range.

Metabolism

In vitro studies of tapentadol metabolism were conducted in liver microsomes from mice, rats, hamsters, guinea pigs, rabbits, mini-pigs, dogs, cynomolgus monkeys and humans and in hepatocytes from humans. When incubated under conditions for Phase II metabolism[9], glucuronidation of tapentadol was observed, although the rate of glucuronidation in human liver microsomes was≥5x less than that of other species. Tapentadol glucuronidation was catalysed by several human isoforms *in vitro* and predominantly by uridine diphosphate-glucuronosyl transferases UGT1A6, UGT1A9 and UGT2B7. Under conditions favourable for activity by cytochrome P450 (CYP450) enzymes, metabolism of tapentadol produced a complex mix of oxidation, demethylation and cyclisation. As for glucuronidation pathways, the activity of CYP450 enzymes was lower (≥ 16-fold) in humans than other species. Human CYP450 enzymes involved in the formation of the major oxidative metabolites of tapentadol *in vitro* include CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6.

One *in vivo* study investigated the metabolism of tapentadol following repeated PO administration to mice, rats, dogs and humans. The overall pattern of metabolism was similar in all three species, with tapentadol-glucuronide being the primary metabolite in plasma/serum (accounting for 79-84% of total plasma/serum exposure (AUC)), followed by tapentadol catechol-glucuronide (4-10%) and N-desmethyl-tapentadol-glucuronide (4-9%). Tapentadol-sulphate was also detected in plasma from dogs (3%) and humans (4%), but not rats and tapentadol itself accounted for 3% of plasma exposure in humans and <1% in rats and dogs.

The potential for full chiral interconversion (switch of two chiral centers) of tapentadol *in vivo* was investigated in several species. Levels of the diastereomer (switch of one chiral center) in serum from rats, rabbits, dogs and humans following PO or SC dosing were 0.4-0.7% of tapentadol levels, compared to its specification limit (<1%) in the final product. Levels of the diastereomer in mouse serum were 1.1%. Extrapolated exposure levels (AUC) in animals at the doses administered were generally less than clinical exposure at the maximum recommended daily dose of tapentadol.

Excretion

The major route of elimination of tapentadol following PO dosing in mice, rats and dogs was in urine, accounting for 59-78% of the administered dose. Excretion was rapid in all species, with the majority excreted within 4-24 h. In rats, urinary excretion occurred to a greater extent in females (76%) than males (59%), with greater faecal excretion in male rats. A complex pattern of metabolites was detected in urine from mice, rats, dogs and humans,

[9] *Phase II reactions* — usually known as conjugation reactions (for example, with glucuronic acid, sulfonates (commonly known as sulfation) , glutathione or amino acids) — are usually detoxication in nature and involve the interactions of the polar functional groups of Phase I metabolites. Sites on drugs where conjugation reactions occur include carboxyl (-COOH), hydroxyl (-OH), amino (NH_2) and sulfhydryl (-SH) groups. Products of conjugation reactions have increased molecular weight and are usually inactive unlike Phase I reactions which often produce active metabolites. Quantitatively, the smooth endoplasmic reticulum of the liver cell is the principal organ of drug metabolism, although every biological tissue has some ability to metabolize drugs.

which was generally similar to the metabolite profile in plasma/serum. Tapentadol-glucuronide was the primary metabolite in urine from all species, accounting for 25-55% of the administered dose. Other major metabolites included tapentadol-catechol-glucuronide (2-39%), N-desmethyl-tapentadol-glucuronide (3-14%) and tapentadol itself (1-5%).

Pharmacokinetic drug interactions

Tapentadol was shown to be a slight inhibitor of CYP2D6 activity in human liver microsomes *in vitro*, with enzyme activity reduced by 19-61% in the concentration range 3.08-616 µM (compared to estimated clinical C_{max} of 0.8 µM at the MRHD). Induction of human CYP3A4 activity by tapentadol (≥ 0.7 µM) was observed in one *in vitro* study, although this finding was not observed in another *in vitro* study and following administration to rats (≤ 300 mg/kg PO). In the same *in vivo* study in rats, induction of CYP1A, CYP2B and slight induction of CYP2E activity was observed at doses ≥ 75 mg/kg PO (circa 0.1x AUC-based exposure at the MRHD); the results were generally dose-related and were more pronounced in males.

Tapentadol did not appear to be either an inhibitor or substrate of P-glycoprotein in human Caucasian colon adenocarcinoma cells (CACO-2) in vitro.

The potential for interactions with other medicines was investigated in an *in vitro* study. Glucuronidation of tapentadol was inhibited by several medicines, including diclofenac (≤ 90%), meclofenamate (≤ 90%), miconazole (≤ 70%), probenicid (≤ 67%) and naproxen (≤ 65%). Paracetamol enhanced tapentadol glucuronidation, although quantitative data were not provided. The sponsor did not consider the interaction with diclofenac to be clinically relevant, as inhibition of tapentadol glucuronidation was predicted to be low (circa 6%) at clinical diclofenac concentrations). The most relevant interactions were considered to be with probenicid, meclofenamate and naproxen, with 45%, 36% and 27% inhibition of tapentadol glucuronidation predicted at clinical exposure levels, respectively.

Relative exposure

Exposure levels (plasma AUC-based) of tapentadol from the toxicity studies were compared with exposure data from human patients at the maximum recommended clinical dose. The maximum recommended starting daily dose of Palexia IR is 700 mg, which may be given as 100 mg every 4 h, with possibly an additional dose 1 h after the first dose. Thereafter, the maximum recommended maintenance daily dose is 100 mg every 4 h. Pharmacokinetic data were obtained in several clinical trials although data were not obtained following repeated administration of the maximum recommended clinical dose.

The sponsor provided mean clinical pharmacokinetic parameters for tapentadol calculated from data normalised to a 100 mg (tapentadol IR) from all relevant clinical studies. For calculation of AUC-based exposure margins, examination of data from individual trials indicated that the mean values were generally representative of clinical tapentadol exposure and were considered suitable for extrapolation to different dosage levels (taking linear pharmacokinetics into account)[10]. When extrapolated to the maximum recommended daily dose, a mean clinical AUC value of 2502 ng.h/mL (tapentadol IR) was obtained[11]. The extrapolated clinical AUC value obtained with this dosage form (2502 ng.h/mL) was

[10] When examining the consistency of exposure data, greater reliance was placed on data obtained in clinical trials using the clinical formulation (or more closely related formulations).

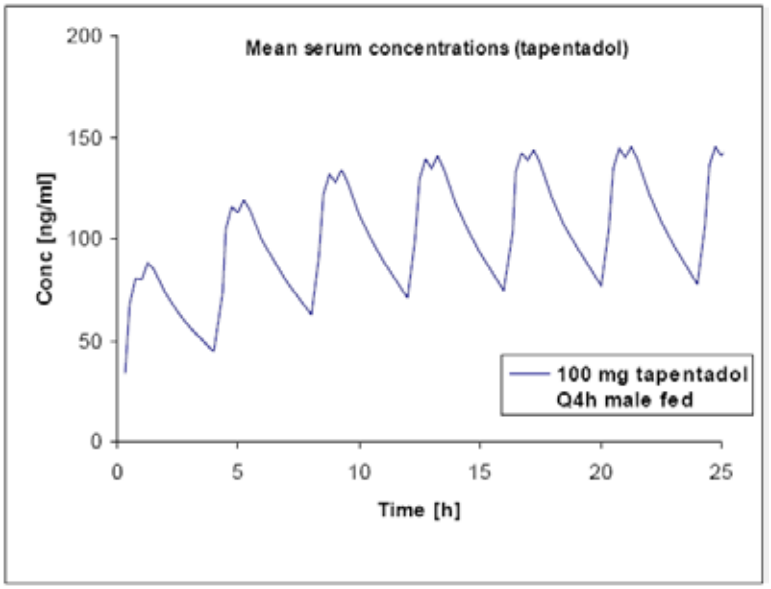
[11] IR: 417 x 6 = 2502 ng.h/mL. On the first day of dosing with IR, clinical exposure could be as much as 2919 ng.h/mL (417 x 7); however, for a comparison with repeated nonclinical dosing, the 6 doses/day clinical regimen is more appropriate.

therefore used for calculation of relative exposure (AUC) in nonclinical studies, as shown in Table 2 below.

AUC-based exposure comparisons were made based on values calculated from time zero to infinity (0-∞) or from time zero to a pre-define time t (0-t), with a preference for the former, wherever possible; the values for t in each study are specified in Table 2. Some accumulation was noted with repeated dosing in humans (but not animals); accumulation factors were 1.4-1.7 in one study with Palexia IR. Exposure margins in nonclinical studies would be reduced by circa 30% if this was taken into account.

Some of the observed toxicities observed in nonclinical studies (for example, cardiovascular and CNS effects) are likely to be related to the peak plasma concentrations achieved in the animals, rather than the time-weighted exposure. Thus, risk assessment involves a comparison of these peak plasma levels with clinical plasma C_{max} values, particularly for safety pharmacology studies. The available clinical data indicate a mean plasma C_{max} value of 90.1 ng/mL after a single dose of tapentadol IR; clinical plasma C_{max} concentrations with repeated dosing of tapentadol IR at the maximum recommended daily dose are unknown but likely to be higher. In response to a question, the sponsor provided an estimate of the clinical plasma C_{max} of 145 ± 52 ng/mL under steady state conditions following the maximum recommended daily dose of tapentadol IR. This value was obtained by computer modelling; a diagram of a graphical representation of the simulation is shown in Figure 2 below (taken directly from the sponsor's response).

Figure 2: Simulation of clinical serum concentrations following repeat dosing with tapentadol IR.



This graph indicates that the dosage regimen simulated was 100 mg tapentadol IR, every 4 h (that is, 600 mg/day) and not the maximum recommended starting dose of 700 mg/day (100 mg every 4 h, plus an extra 100 mg 1 h after the first dose). The sponsor provided relative exposure calculations by comparing plasma C_{max} values from nonclinical toxicity studies compared to the estimated clinical C_{max} of 145 ng/mL (from Figure 2 above); these are summarised in Table 3 below (column C_{max} A). There is no indication in the data of the steady state plasma C_{max} value at the maximum recommended starting dose of 700 mg/day tapentadol IR; it was estimated at circa 200 ng/mL, since each 100 mg dose in the graph above increases the peak concentration by circa 70 ng/mL. The sponsor stated that a C_{max} value of 197 ng/mL has been measured in a clinical trial (Study no. HP5503/25) with repeated dosing of 150 mg every 6 h (600 mg/day) which showed no effect on the

cardiovascular system. Thus, C_{max}- or C_{1st}-based exposure comparisons in nonclinical studies with a higher estimated clinical C_{max} of 200 ng/mL are also included in Table 3 below (column C_{max} B). Data from pharmacokinetic and safety pharmacology studies are also included in this table, to enable calculation of relevant exposure margins in safety pharmacology studies.

Doses highlighted in bold in both tables represent NOAELs for respective studies. AUC-based exposure margins were relatively low in most studies; the sponsor stated that the pharmacodynamic properties of tapentadol limited the dose in nonclinical studies. C_{max}-based exposure margins were generally adequate.

Table 2: Tapentadol exposure (AUC) calculations compared to. tapentadol IR in toxicity studies.

Study no.	Species	Treatment period	Dose (mg/kg/day)	Sex	AUC_{0-t} (ng.h/mL)	t (h)	Exposure multiples (AUC)
Repeat dose studies (PO administration)							
TP2470	Mouse	2 weeks	50, 100, 200	M/F	135, 257, 526	4[a]	0.05, 0.1, 0.2
TP2496		13 weeks	10, **30**, 100, 200	M/F	41, **178**, 548, 912	∞	0.02, **0.07**, 0.2, 0.4
TP2518		26 weeks[b]	**50**, 100, 200	M	**145**, 315, 763	V[c]	**0.06**, 0.1, 0.3
				F	**164**, 254, 633		**0.07**, 0.1, 0.3
TP2593	Rat	4 weeks	75, 150, 300	M	239, 718, 947	8[a]	0.1, 0.3, 0.4
				F	460, 1045, 2637		0.2, 0.4, 1.1
TP2645		13 weeks	**60**, 200, 400[d]	M	**1034**, 2254, 4828	24	**0.4**, 0.9, 1.9
				F	**979**, 4222, 11829		**0.4**, 1.7, 4.7
TP2397		26 weeks	**75**, 150, 300	M	**466**, 1115, 2165	∞	**0.2**, 0.4, 0.9
				F	**956**, 1505, 3114		**0.4**, 0.6, 1.2
TP2415	Dog	13 weeks	**10**, 35, 80	M/F	**18**, 106, 501	12[e]	**0.007**, 0.04, 0.2
TP2441		52 weeks	**10**, 30, 80	M	**23**, 142, 303	24	**0.009**, 0.06, 0.1
				F	**17**, 61, 407		**0.006**, 0.02, 0.2
Repeat dose studies (IV administration)							
TP2471	Rat	2 weeks	15, 30, 120	M/F	973, 2482, 10960	24	0.4, 1.0, 4.4
PH397/A	Monkey	SD	0.1, 0.32, 1, 3.2	M/F	191, 1212, 1380, 3568	∞	0.08, 0.5, 0.6, 1.4
TP2316		2 weeks	5[f]	M	1035	∞	0.4
Repeat dose studies (Dietary administration)							
TP2470	Mouse	2 weeks	50, 125, 250	M/F	75, 161, 210	24	0.03, 0.06, 0.08
TP2379	Mouse	13 weeks	50, 150, 250, 500, 1000	M	23, 78, 218, 417, 876	24	0.009, 0.03, 0.09, 0.2, 0.4
				F	33, 545*, 144, 261, 387		0.01, 0.2*, 0.06, 0.1, 0.2
TP2367	Rat	1 week	250, 1000	M	313, 1054	24	0.1, 0.4
				F	760, 2902		0.3, 1.2
TP2380		13 weeks	250, 500, 1000	M	470, 700, 1841	24	0.2, 0.3, 0.7
				F	1323, 2462, 1404		0.5, 1.0, 0.6
TP2418		26 weeks[b]	**10**, 50, 125, 250	M	**19**, 94, 274, 328	24	**0.007**, 0.04, 0.1, 0.1
				F	**17**, 156, 620, 1349		**0.006**, 0.06, 0.2, 0.5
Repeat dose studies (SC administration)							
TP2471	Rat	2 weeks	30, 45	M/F	1652, 4361	24	0.7, 1.7
TP2465	Rat	2 weeks	10, 30, 50[d]	F	838, 2288, 5130	∞	0.3, 0.9, 2.1
TP2464	Rabbit	2 weeks	10, 30, 50[d]	F	2712, 9512, 14046	∞	1.1, 3.8, 5.6
TP2559	Dog	13 weeks	8, 16, 32[d]	M/F	468, 528, 1956	∞	0.2, 0.4, 0.8
TP2455		13 weeks	40[d]	M	9270	∞	3.7
Studies in pregnant animals (PO administration)							
TP2834	Rat	GD6-17	**20**, **50**, 150, 300[d]	F	**155**, **760**, 3875, 5224	24	**0.06**, **0.3**, 1.5, 2.1
TP2772		GD6-17	50, 150, **300**[d]	F	542, 1668, **2546**	24	0.2, 0.7, **1.0**

Table continued on the next page.

Studies in pregnant animals (SC administration)							
TP2510	Rat	GD6-17	**10**, 20, 40[d]	F	**814**, 1764, 3126	∞	**0.3**, 0.7, 1.3
TP2511	Rabbit	GD6-20	**4**, 10, 24[d]	F	**614**, 1920, 5742	∞	**0.2**, 0.8, 2.3
Studies in juvenile animals (PO administration)							
TP2772	Rat	PND13	**25**, 75, 150	M	**478**, 3266, 4760	4.5	**0.2**, 1.3, 1.9
				F	**628**, 6081, 6764		**0.3**, 2.4, 2.7
Pharmacokinetics in humans							
NA	Human	NA	700 mg/day	M/F	2502[g]	∞	NA

[a]$AUC_{0\text{-}24\,h}$ values could not be extrapolated; not all exposure to analyte occurred within the measured time period (that is, actual exposure was greater than documented). [b]The study duration was 104 weeks (carcinogenicity study), but toxicokinetic data were only available after ≤26 weeks. [c]AUC values for tapentadol were 0-5, 8 or 24 h, depending on dose level & time point; tapentadol levels were usually very low or not detectable by 5 h post-dose. [d]Twice daily dosing; AUC values are for 24 h exposure.

[e]AUC values were estimated to be approximately similar to 0-24 h values, based on concentration profiles.

[f]Monkeys were administered 15 mg/day; dose was adjusted for 3 kg body weight. [g]Clinical exposure in cross-study comparison, normalised to 100 mg and multiplied by 6 to obtain exposure at maximum recommended daily dose (see text).

[*]Considered an outlier based on high values in one mouse. NA = not applicable; SD = single dose; V = variable; NOAELs are highlighted in bold

Table 3: Tapentadol exposure (C_{max}) calculations compared to. tapentadol IR in toxicity studies.

Study no.	Species	Treatment period	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	Exposure multiples (C_{max} A)	Exposure multiples (C_{max} B)
Repeat dose studies (PO administration)							
TP2470	Mouse	2 weeks	50, 100, 200	M/F	143, 292, 350	1.0, 2.0, 2.4	0.7, 1.5, 1.8
TP2496		13 weeks	10, **30**, 100, 200	M/F	33, **85**, 349, 1056	0.2, **0.6**, 2.4, 7.3	0.2, **0.4**, 1.7, 5.3
TP2518		26 weeks[a]	**50**, 100, 200	M	**114**, 467, 828	**0.8,** 3.2, 5.7	**0.6**, 2.3, 4.1
				F	**205**, 238, 610	**1.4,** 1.6, 4.2	**1.0**, 1.2, 3.1
TP2593	Rat	4 weeks	75, 150, 300	M	64, 312, 531	0.4, 2.2, 3.7	0.3, 1.6, 2.7
				F	308, 597, 2476	2.1, 4.1, 17	1.5, 3.0, 12
TP2645		13 weeks	**60**, 200, 400[b]	M	**414**, 758, 1244	**2.9**, 5.2, 8.6	**2.1**, 3.8, 6.2
				F	**425**, 1409, 3733	**2.9**, 9.7, 26	**2.1**, 7.0, 19
TP2397		26 weeks	**75**, 150, 300	M	**252**, 507, 1451	**1.7**, 3.5, 10	**1.3**, 2.5, 7.3
				F	**520**, 451, 912	**3.6**, 3.1, 6.3	**2.6**, 2.3, 4.6
TP2415	Dog	13 weeks	**10**, 35, 80	M/F	**4.3**, 39, 327	**0.03**, 0.3, 2.3	**0.02**, 0.2, 1.6
TP2441		52 weeks	**10**, 30, 80	M	**6.8**, 49, 145	**0.05**, 0.3, 1.0	**0.03**, 0.2, 0.7
				F	**6.3**, 32, 221	**0.04**, 0.2, 1.5	**0.03**, 0.2, 1.1
Repeat dose studies (IV administration)							
TP2471	Rat	2 weeks	15, 30, 120	M/F	44, 108, 473	0.3, 0.7, 3.3	0.2, 0.5, 2.4
PH397/A	Monkey	SD	0.1, 0.32, 1, 3.2	M/F	142, 1047, 1518, 3589	1.0, 7.2, 10, 25	0.7, 5.2, 7.6, 18
TP2316		2 weeks	5[c]	M	852	5.9	4.3
Repeat dose studies (Dietary administration)							
TP2470	Mouse	2 weeks	50, 125, 250	M/F	8.8, 19, 32	0.06, 0.1, 0.2	0.04, 0.1, 0.2
Repeat dose studies (SC administration)							
TP2471	Rat	2 weeks	30, 45	M/F	70, 182	0.5, 1.3	0.4, 0.9
TP2465		2 weeks	10, 30, 50[b]	F	352, 907, 2441	2.4, 6.3, 17	1.8, 4.5, 12
TP2464	Rabbit	2 weeks	10, 30, 50[b]	F	593, 2099, 2845	4.1, 14, 20	3.0, 10, 14
TP2559	Dog	13 weeks	8, 16, 32[b]	M/F	130, 337, 623	0.9, 2.3, 4.3	0.7, 1.7, 3.1
TP2455		13 weeks	40[b]	M	1965	14	9.8
Studies in pregnant animals (PO administration)							
TP2834	Rat	GD6-17	**20**, **50**, 150, 300[b]	F	**48**, **355**, 1186, 1441	**0.3**, **2.4**, 8.2, 10	**0.2**, **1.8**, 5.9, 7.2
TP2772		GD6-17	50, 150, **300**[b]	F	254, 601, **810**	1.8, 4.1, **5.6**	1.3, 3.0, **4.1**
Studies in pregnant animals (SC administration)							
TP2510	Rat	GD6-17	**10**, 20, 40[b]	F	**298**, 764, 1169	**2.1**, 5.3, 8.1	**1.5**, 3.8, 5.8
TP2511	Rabbit	GD6-20	**4**, 10, 24[b]	F	**149**, 582, 1513	**1.0**, 4.0, 10	**0.7**, 2.9, 7.6
Studies in juvenile animals (PO administration)							
TP2772	Rat	PND13	**25**, 75, 150	M	**129**, 1055, 2459	**0.9**, 7.3, 17	**0.6**, 5.3, 12
				F	**159**, 4070, 2347	**1.1**, 28, 16	**0.8**, 20, 12
Single dose pharmacokinetic studies (IV administration)							

PK653	Rat	SD	3.5, 7, 14	M/F	344, 854, 1692	2.4, 5.9, 12	1.7, 4.3, 8.5

Table continued on the next page.

Safety pharmacology studies (IV administration)							
SP103/A	Dog	SD	0.5, 1.5, 4.5	M/F	135, 257, 526	0.9, 3.3, 10	0.7, 2.4, 7.2
SP35/A		SD	3, 6, 9	M	665, 1105, 2531	4.6, 7.6, 17	3.3, 5.5, 13
Pharmacokinetics in humans							
NA	Human	NA	700 mg/day	M/F	145 (A) or 200 (B)[d]	NA	NA

[a]The study duration was 104 weeks (carcinogenicity study), but toxicokinetic data were only available after ≤26 weeks

[b]Twice daily dosing. [c]Monkeys were administered 15 mg/day; dose was adjusted for 3 kg body weight. [d]Estimated C_{max} at the maximum recommended clinical dose of 100 mg every 4 h (A) or with an additional 100 mg 1 h after the first dose (B). NA = not applicable; SD = single dose; NOAELs are highlighted in bold

Toxicology

General toxicity

The acute toxicity of tapentadol was investigated following a single IV or PO dose to mice and rats. Long-term repeat dose studies by the PO route were conducted in mice (13 weeks), rats (26 weeks) and dogs (52 weeks). More than 20 other repeat dose studies of shorter duration by various routes (PO, dietary, IV, SC) were also conducted in mice, rats and dogs, with limited analyses in rabbits and monkeys. The studies were generally adequate, although different dosage levels were tested at different time points in the 6-month study in rats and no control groups were included in the acute toxicity study. NOAELs were established in long term studies, although exposure margins (AUC) were generally low. Histopathology analysis was frequently not conducted in non-pivotal repeat dose studies.

Dosage levels were limited due to excessive toxicity at higher doses; dose-limiting toxicities were congestive/haemorrhagic changes and convulsions in mice, rats and dogs. Toxicity findings were generally dose-related, with incidence and severity increasing with dose. The primary toxicity observed in mice and rats was liver toxicity, as discussed further below. Other toxicities were generally consistent with the primary pharmacology of tapentadol and included CNS effects as discussed below. QT interval prolongation was observed in dogs; refer to '**Safety pharmacology**' above for details. Increased white blood cell (WBC) counts, primarily due to increased lymphocytes, was consistently observed in rats at PO doses ≥150 mg/kg/day. One study indicated that the relative proportion of lymphocyte subtypes remained consistent with control groups. Consistent with opioid administration, respiratory effects were observed in rats, rabbits and dogs; refer to '**Safety pharmacology**' above for details. Reduced body weight gain was observed in rats and dogs, generally consistent with reduced food intake.

Hepatic toxicity

Treatment related effects on the liver were frequently observed following repeated dosing in mice and rats. In mice, this was characterised by liver enlargement, with accentuated lobular pattern, congestion/haemorrhage and hepatocyte vacuolation, at doses ≥ 100 mg/kg/day PO (circa 0.1x clinical exposure, based on AUC). Typical changes in rats included enlarged liver and centrilobular hypertrophy at≥ 150 mg/kg/day PO or ≥ 30 mg/kg twice a day (bid) PO and an increased incidence of fatty change at≥ 75 mg/kg/day PO (exposures ≥ 0.3x clinical exposure). Increased serum hepatic enzymes (ALP, LDH, AST and ALT[12]) were frequently

[12]ALP= alkaline phosphatase, LDH= lactate dehydrogenase, AST=aspartate aminotransferase; ALT=alanine aminotransferase;

observed in both species at high doses. The sponsor attributed these findings to adaptive changes as a result of hepatic enzyme induction and provided a detailed discussion of this issue, particularly pertaining to the high variability and reversibility of any liver findings. This was considered plausible. No evidence of liver toxicity was observed in dogs. The relevance to humans appears to be low.

CNS effects

Severe convulsions, often leading to euthanasia were observed in mice, rats and dogs by various routes (respective AUC-based exposure margins following PO dosing were 0.5, 2.2-5.4 and 0.1-0.2). Convulsive effects were considered to be typical for opioids[13]. Other clinical signs consistent with effects on the CNS were observed in rats and dogs at exposures lower than human exposure at the maximum recommended clinical dose; these findings were considered to be exaggerated primary pharmacology. In rats, clinical signs included excited and abnormal behaviour (for example, bedding in mouth) and sedation in rats and exophthalmos, subdued behaviour, recumbency, hunched posture at high doses. Findings in dogs included hypoactivity, salivation, vomiting, recumbency, whimpering, tremor and fearful behaviour.

Toxicity of tapentadol-glucuronide

Intracerebroventricular (ICV) administration of high doses of several tapentadol metabolites (tapentadol-glucuronide, N-desmethyl-tapentadol-glucuronide and tapentadol catechol-glucuronide; ≥ 3.16 µg/animal) in primary pharmacodynamic studies induced severe convulsions in mice. Tapentadol-glucuronide is known to distribute to the brain following PO dosing in rats (refer to '***Distribution***' below), although at levels appreciably lower than plasma levels. The relationship between the brain concentrations achieved via ICV administration and those in the brain of patients on therapeutic doses is unknown. The risk of convulsions due to tapentadol-glucuronide exposure is considered to be low and unlikely to be of greater concern than the risk of convulsions from tapentadol itself. No data were available regarding the potential for CNS distribution for other relevant metabolites., although the same risk profile is expected to apply.

Genotoxicity

The genotoxicity of tapentadol was investigated *in vitro* with a bacterial reverse mutation assay and mammalian chromosomal aberration assays and *in vivo* with one chromosomal aberration assay and an unscheduled DNA synthesis assay in rats. The studies were GLP compliant, the concentrations used were adequate and the assays were validated with appropriate controls.

Negative results were observed in all studies, except for one mammalian chromosomal aberration assay. In this assay, an increased number of cells with chromosomal aberrations, primarily chromosome breaks or fragments and chromatid exchanges, were observed at tapentadol concentrations associated with cytotoxicity. The second chromosome aberration assay did not replicate the experimental conditions associated with positive findings. Toxicokinetic data were not obtained in the *in vivo* assays, although distribution to bone marrow was observed following administration of 10 mg/kg IV to rats in a pharmacokinetic study. Exposure at the maximum dose in the chromosomal aberration assay (40 mg/kg IV)

[13] Frenk H (1983) Pro- and anticonvulsant actions of morphine and the endogenous opioids: involvement and interactions of multiple opiate and non-opiate systems. *Brain Res Rev* **6**, 197-210.

was equivalent to 1.4x clinical exposure, based on extrapolated AUC and at the maximum dose in the unscheduled DNA synthesis assay (350 mg/kg PO) exposure was 1.5x MRHD.

The battery of genetic toxicology assays used to investigate tapentadol was consistent with the relevant EU ICH[14] Guideline[15]s and the weight of evidence from these assays suggested that tapentadol presented no significant genotoxic potential at the proposed clinical dose range.

Carcinogenicity

Two-year carcinogenicity studies were conducted by PO administration of tapentadol to mice and dietary administration to rats. The studies were GLP compliant and generally adequate. Toxicokinetic data were obtained only up to Week 26 in both studies, but extrapolation up to two years should be valid, given the lack of accumulation of tapentadol in these species. Actual dietary intake approximated the proposed doses in rats. AUC-based exposure margins were low in both species (less than human exposure at the maximum recommended daily clinical dose), although they were similar to exposure levels attained in repeat dose toxicity studies, during which pharmacological and toxicological effects were observed.

It is questionable whether the dosage levels in the mouse study were adequate, as there was limited evidence of toxicity (including negligible effects on body weight gain) and AUC-based exposure margins were low (≤ 0.3). There was no clear treatment-related effect on mortality; although a dose-related increase in mortality with undetermined cause was reported (≥ 100 mg/kg/day), it was difficult to determine whether this represented a true treatment-related effect due to the method of tabulation of mortality data and as there were limited data regarding in-life clinical signs. High mortality in this study and the pivotal 13-week repeat dose study (due to convulsions) at 300 mg/kg/day PO identified this as exceeding the maximum tolerated dosage (MTD) level by this route. The highest dosage level tested in PO studies in mice was 200 mg/kg/day. Exposure margins (AUC) of 0.4 were not exceeded in any study in mice; thus, it was unknown whether dosing at a higher level (between 200 and 300 mg/kg/day PO) may have been informative, but it seems feasible that a dosage level >200 mg/kg/day may have been tolerated, although the resultant exposure margin may not have escalated much further. The dosage levels in the study in rats were considered adequate, as body weight gain at the HD was reduced by sufficient magnitude and the toxicity profile was consistent with repeat dose toxicity studies.

Tapentadol was generally well-tolerated with long-term dosing in both species. A significant trend towards a dose-response relationship for hepatocellular tumours (adenoma and carcinoma) was observed in mice, when the highest dose group was excluded (due to a shortened treatment period). There were no accompanying pre-neoplastic lesions in mice and the total incidence was low. A high, dose-related incidence of hepatocellular hypertrophy was observed in rats at dietary doses ≥ 125 mg/kg/day, but there were no associated hepatocellular adenomas or carcinomas. Liver findings in both species occurred at AUC-based exposures circa 0.1x the MRHD. These findings may be consistent with adaptive changes to the liver reported in repeat dose toxicity studies. The potential clinical relevance of these liver findings is unknown.

Based on assumed treatment-related mortality (mice) and recorded effect on body weight gain (rats), dosing levels were probably approaching/at the MTD in these species; however,

[14] International Conference on Harmonisation

[15] ICH Topic S2B Genotoxicity: A standard battery of genotoxicity testing of pharmaceuticals. http://www.tga.gov.au/docs/pdf/euguide/ich/017495en.pdf

the low systemic exposure margins attained (due to toxicity) have limited the adequacy of the testing for carcinogenic potential.

A statistically significant trend towards increased incidence of thyroid follicular cell hypertrophy and hyperplasia was observed in treated female rats. These findings were attributed by the sponsor to enhanced liver enzyme activity as a consequence of centrilobular hepatocellular hypertrophy although an increased incidence of follicular cell hypertrophy was observed in the absence of hepatocellular hypertrophy at 50 mg/kg/day. Although a statistical trend was identified, the incidence of these findings was comparable to control groups, was similar in males and females and was consistent with known effects of CNS-acting drugs on thyroid function in rats[16]. Thus, the proliferative effects on the thyroid were not considered to be clinically relevant.

Reproductive toxicity

The submitted studies included a fertility and early embryonic development study in rats, embryofetal development studies in rats and rabbits and pre/post-natal development studies in rats. The studies were GLP-compliant and generally adequate.

Placental transfer of tapentadol was confirmed in a pre-postnatal study in rats, with relatively high levels of tapentadol and its glucuronide (≥ 23% of maternal plasma levels of tapentadol and ≥ 8% of maternal tapentadol-glucuronide levels) detected in F_1 fetuses on gestation day (GD) 20. Low levels of tapentadol and tapentadol-glucuronide were also detected in milk from lactating rats on PND7.

In a rat fertility study, there were no apparent effects in males at doses≤ 12 mg/kg/day IV (estimated AUC exposure 0.3-fold the clinical exposure[17]), although histopathology analyses were not conducted. In females, a dose-related reduction in the numbers of corpora lutea, implantations and live fetuses were observed, although these findings were associated with maternal toxicity and were within historical control ranges. Pre- and post-implantation losses were increased. These findings are most likely attributable to maternal toxicity (clinical signs and usually reduced body weight gain observed at doses ≥ 6 mg/kg/day). In rabbits, tapentadol administration at maternotoxic doses during organogenesis (15 mg/kg/day IV and ≥ 5 mg/kg bid SC) was associated with increased post-implantation loss, late resorptions and dead fetuses.

An increased incidence of incomplete fetal ossification at various sites was observed following SC dosing during organogenesis (5-20 mg/kg BID; AUC exposure 0.2-0.6x the MRHD) in rats. Although the incidence was generally dose-related and statistically significant at the highest dose, the toxicological significance of the finding was unclear as most values were within historical control ranges and no variations or malformations were reported in another rat embryofetal development study with IV dosing eliciting maternal toxicity (≤ 15 mg/kg/day). Fetal cerebral ventricular dilation was observed at SC doses ≥ 10 mg/kg BID. A possible treatment-related effect of tapentadol cannot be excluded for this finding, due to the observed dose-response and CNS activity of tapentadol; this finding occurred at maternotoxic doses.

Multiple dose-related fetal malformations (ablepharia, cleft palate, fused or misaligned sternebrae, spina bifida, amelia/phocomelia and gastroschisis or thoracogastroschisis) were observed in a rabbit embryofetal development study with SC dosing. The findings were generally associated with maternal toxicity (≥ 5 mg/kg BID), specifically their compromised

[16] Capen, CC (1999) Thyroid and parathyroid toxicology. In *Endocrine and hormonal toxicology*. Harvey PW, Rush K, Cockburn A (eds). John Wiley & Sons, New York.
[17] Extrapolated from Study TP2471.

nutritional status and exposures (AUC) were generally 0.8 – 2.3x exposure at the MRHD (0.2 at the NOEL). With IV administration to rabbits up to 9 mg/kg/day, post-implantation losses, late resorptions and dead fetuses were increased but no malformations reported (although maternotoxicity was also less severe); unfortunately, toxicokinetics was not included in the study design as only serum concentrations were measured. Serum concentrations in rabbits at the highest IV dose were similar to those at the highest dose in the rabbit study with SC dosing. Thus, exposure at the highest dose by both routes was apparently comparable. This apparent inconsistency between SC and IV results in rabbits is puzzling and could have been investigated further. The toxicological significance of these findings is uncertain. Tapentadol administration (≥ 25 mg/kg bid PO; AUC-based exposure 0.2x the MRHD) during lactation was associated with increased pup mortality, particularly between PND1-4, in rats. Pup mortality occurred at doses lower than maternotoxic doses. Several treated females experienced difficulties delivering (and were euthanised); the relationship to treatment was unclear given the low incidence and lack of dose-response.

Pregnancy classification

The sponsor proposes a Pregnancy Category C for tapentadol. This was considered acceptable, as the majority of fetal/pup findings reported in reproductive toxicity studies were associated with maternal toxicity and compromised nutritional status and the malformations in rabbits were not seen consistently in all studies. The majority of other registered opioid analgesics are Pregnancy Category C.

Use in children

Tapentadol is contra-indicated for use in children.

Limited toxicity data were obtained following PO dosing of juvenile rats in a pre/post-natal development study. The findings were generally similar to those seen with adult rats, namely mortality (one death was associated with convulsions), clinical signs consistent with opioid administration (sedation, tremors, hypoactivity, hypersensitivity to noise) and reduced body weight gain at doses ≥ 75 mg/kg/day (circa twice the AUC-based clinical exposure at the MRHD). Exposure at the NOAEL was 0.2-0.3x the clinical AUC.

Local tolerance

The absence of local tolerance studies was acceptable for an orally administered drug.

Dependence

Several studies investigated the dependence and tolerance potential of tapentadol in mice, rats and monkeys. The studies were generally adequate and validated with appropriate positive and negative controls.

A dose related increased incidence of naloxone-precipitated (1 and 1.5, but not 2 h post-dose) withdrawal jumping was observed in mice at doses≥ 10 mg/kg IP (estimated exposure <0.1x AUC-based exposure at the MRHD). Likewise, behavioural changes (teeth chattering, sniffing, licking, grooming, hyperactivity and Straub tail) were observed following naloxone induced- or spontaneous withdrawal in rats, at tapentadol doses ≥ 4.64 mg/kg/day SC (estimated exposure 0.1x AUC-based exposure at the MRHD). The behavioural effects of tapentadol withdrawal were generally less pronounced than that of morphine or tramadol. Thus, consistent with its μOR agonist activity, tapentadol was considered to confer potential for dependence in mice and rats.

Positive reinforcing and rewarding effects were observed in rats (increased time spent in a tapentadol-associated environment) and monkeys (increased self-administration) at exposures markedly lower (<0.1x, based on AUC) than that at the MRHD. The effects in rats were

prevented by co-administration of naloxone. In a drug discrimination study in rats, tapentadol demonstrated morphine-like discriminative stimulus effects and no response to D-amphetamine (suggestive of no psychostimulant-like behavioural effects). The reinforcing and rewarding effects of tapentadol were comparable with morphine and tramadol.

Tolerance to the analgesic effect of tapentadol was observed in rats following repeated administration in tail flick assays and in chronic constriction injury models of peripheral mono-neuropathy. This effect was observed as early as three days of treatment, with full tolerance development after several weeks, at estimated exposures less than the MRHD. Development of tolerance to tapentadol was delayed compared to that of morphine or tramadol, generally by circa 10 days. Cross-tolerance to morphine was observed with tapentadol: tapentadol-tolerant rats were also tolerant to morphine, however morphine-tolerant rats remained sensitive to tapentadol.

Factors to consider in a benefit risk assessment

Tapentadol is a new chemical entity for the treatment of moderate to severe pain. A wide variety of different patient groups could be envisaged to receive tapentadol treatment, including both short-term and chronic treatment. Thus, the risk-benefit analysis of tapentadol may vary, depending on the specific patient group, the etiology/pathology of the pain/pain syndrome being treated and intended duration of treatment. Tapentadol-induced analgesia is mediated primarily through μOR activation and also via inhibition of noradrenaline re-uptake pathways; possible functional contribution(s) through other receptor pathways was not fully explored. Antinociception was clearly and quantitatively demonstrated in several nonclinical species, with an efficacy profile generally between that of morphine and tramadol. The nonclinical activity profile is supportive of the proposed clinical indication.

The toxicity profile of tapentadol is not dissimilar from other analgesics, particularly tramadol. The primary toxicities observed were CNS effects, including convulsions and hepatotoxicity in rodents (including proliferative/neoplastic changes), possibly consistent with adaptive changes. A multi-species effect on the cardiovascular system was observed, including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/teratogenicity and postnatal survival were observed in test species, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. Achieved animal/human exposure margins in the nonclinical studies were quite low due to dose-limiting toxicity, particularly CNS, thereby limiting the ability of the nonclinical studies to assess the safety of tapentadol despite the nonclinical toxicity profile *per se* not necessarily representing a greater concern than that of other μ-opioid agonists.

There are a number of concerns with the use of tapentadol, which should be considered in a risk-benefit analysis for the proposed indication:

- As relative exposure in nonclinical studies was generally quite low, the safety assessment of tapentadol will rely primarily on clinical data.
- The adequacy of testing for carcinogenic potential was constrained by dose-limiting toxicity in the rodent species at exposures below clinical exposure.
- Tapentadol should not be used during pregnancy, unless the possible benefits of tapentadol treatment outweigh the risks to the fetus or infant. Tapentadol should not be used during lactation.

The above toxicity concerns have been identified and described in the safety specification in the Risk Management Plan.

A risk-benefit assessment therefore needs to consider: (i) the adequacy of evidence for clinical safety, (ii) the relative safety and efficacy of tapentadol compared to other registered analgesics and (iii) the potential toxicities versus the clinical need, severity of the proposed indications and duration of treatment.

Nonclinical Summary and Conclusions

- The submitted non clinical data were extensive and generally adequate. The relevant studies were mainly GLP-compliant, apart from some safety pharmacology studies. Relative animal/human exposure to tapentadol in most toxicity studies was quite low, due to dose-limiting toxicity. Most pharmacological effects occurred at dose levels between that of morphine and tramadol, on a dose per body weight basis.

- Tapentadol exerts its pharmacological effects primarily through activation of the μ-opioid receptor (μOR), which was demonstrated *in vitro* (K_i 0.096-0.164 μM, compared to C_{max} of 145 ng/mL or 0.56 μM at the maximum recommended clinical dose) and *in vivo*, based on antagonism of its pharmacological effects by naloxone in mice and rats. Tapentadol binding affinity to the μOR was circa 10x greater than to other ORs, 18x less than morphine and 7x less than morphine-6-O-glucuronide. High affinity binding to several other receptors was observed, including σ_2 receptor (K_i 0.43 μM), noradrenaline uptake transporter (K_i 0.48 μM), β_1-adrenergic receptor, 5-HT_{2A} receptor (IC_{50} values <1 μM), κ- and δ-ORs and M_1 muscarinic receptor (K_i values <1 μM).

- The pharmacological effects of tapentadol are partially attributable to inhibition of noradrenaline re-uptake in the CNS. The functional role of 5-HT receptor pathways was unclear from the nonclinical data. The potential contribution of other candidate receptor pathways to tapentadol-induced analgesia was not investigated.

- Tapentadol induced dose-related analgesia in several mouse, rat, rabbit and dog models of acute, neuropathic and inflammatory pain, generally at extrapolated exposures (AUC) lower than that at the minimum recommended clinical dose. The efficacious dose range of tapentadol was generally between that of tramadol and morphine; efficacious tapentadol doses were generally 2-3x greater than morphine, on a dose (mg) per body weight basis.

- In ferrets, tapentadol (IV) reduced the incidence and frequency of morphine-induced emesis, but induced an emetic effect with IP dosing. Tapentadol exhibited antitussive properties in rats and a local anaesthetic effect on guinea pig skin.

- Tapentadol inhibited smooth muscle contraction *in vitro*. Consistent with this, inhibition of GI transit and prostaglandin-induced diarrhoea was observed in mice (exposure margins 0.01-0.5). Additionally, combination treatment with diazepam or tetrazepam attenuated their muscle-relaxing activity at clinically relevant doses in mice.

- Safety pharmacology studies identified a multi-species effect on the cardiovascular system. Decreased blood pressure was observed in anaesthetised rabbits and dogs (IV dosing), consistent with opioid-related cardiovascular depressant activity. In contrast, increased heart rate and blood pressure occurred in conscious rats and dogs, in addition to tachycardia and atrioventricular block in dogs following IV administration. This was associated with QT interval prolongation in dogs at exposures similar to or lower (0.2-3x) than clinical exposure. Respiratory depression (bradypnea, changes in blood gas levels,

irregular breathing, reduced respiratory volume) were observed in safety pharmacology and toxicity studies in rats, rabbits and dogs, at 0.7-3x maximum clinical exposure (C_{max}).

- The pharmacokinetics of tapentadol were generally similar in mice, rats, dogs and humans, although oral absorption profiles differed in animals and humans, primarily due to the different dosage forms involved (administration of an oral solution to animals compared to immediate- or slow-release tablets to humans). There was generally no accumulation in animals with repeated dosing, although exposure was greater in female rats and humans than males but similar in both sexes in mice and dogs. Tapentadol was rapidly and widely distributed following IV administration to rats, almost all tissues had radioactivity levels higher than blood (brain 2x, spinal cord 1.4x). Highest levels were detected in the kidneys, preputial gland, secretory glands and liver (5-10x blood). Plasma protein binding was low (11-20%) in rabbits, mice, dogs, rats and humans.

- Tapentadol is rapidly metabolised in all species to form a complex mix of glucuronidation and oxidation products. Exposure to the pharmacologically inactive primary metabolite of tapentadol (tapentadol-glucuronide; circa 80% of total plasma/serum exposure) was up to 300x parent compound. Tapentadol glucuronidation was catalysed primarily by human UGT1A6, UGT1A9 and UGT2B7 *in vitro* and human CYP450 enzymes involved in tapentadol metabolism *in vitro* include CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. Tapentadol and its metabolites were rapidly excreted in all species, primarily in urine (59-78% of dose). Tapentadol glucuronidation was inhibited *in vitro* by probenicid, meclofenamate and naproxen (45%, 36% and 27% inhibition at clinical exposures, respectively). Tapentadol inhibited human CYP2D6 activity *in vitro* by 19-61% at high concentrations (3.1-616 µM, compared to clinical C_{max} of 0.56 µM) and induced CYP1A, CYP2B and CYP2E in rats at PO exposures one-tenth the maximum anticipated clinical exposure.

- Toxicity studies consisted of single dose IV and PO (mice, rats), long-term PO repeat dose (mice, 13 weeks; rats, 26 weeks; dogs, 52 weeks) and >20 other repeat dose studies of shorter duration (PO, dietary, IV, SC) in these species. Excessive toxicity(congestive changes and convulsions/CNS effects in mice, rats and dogs) constrained dose levels and exposure margins were low (generally <1). Severe convulsions, considered an opioid effect, were observed by various routes (exposure margins: mice 0.5, rats 2.2-5.4, dogs 0.1-0.2); other CNS effects represented exaggerated pharmacology. The primary finding in rodents was hepatic effects, consistent with adaptive changes following hepatic enzyme induction (enlarged liver, accentuated lobular pattern, hepatocyte vacuolation, centrilobular hypertrophy), at exposures ≥ 0.1-0.3x the maximum clinical exposure.

- An adequate battery of genotoxicity studies comprised an *in vitro* bacterial reverse mutation assay, *in vitro* mammalian chromosome aberration assays and an *in vivo* mammalian chromosome aberration assay and unscheduled DNA synthesis assay. Tapentadol gave a positive result in 1 of 2 *in vitro* chromosome aberration assays at cytotoxic concentrations, but the weight of evidence suggested that tapentadol presented no significant genotoxic potential at the proposed clinical dose range.

- Two-year carcinogenicity studies were conducted in mice (PO) and rats (dietary). A trend towards hepatocellular adenoma and carcinoma was observed in mice and dose-related hepatocellular hypertrophy was observed in rats (exposure margins of circa 0.1 in both species). These lesions were possibly related to adaptive changes seen in toxicity studies.

- In a rat fertility study, there were reductions in the number of corpora lutea, implantations and live fetuses at tapentadol doses associated with maternal toxicity. Tapentadol administration to pregnant rats and rabbits was also associated with increased pre- and post-implantation loss, increased resorptions and reductions in the number of implantations at maternotoxic doses.

- Placental transfer of tapentadol was confirmed in rats. Administration during organogenesis elicited delays in skeletal maturation (incomplete ossification) and cerebral ventricular dilation in rats at SC doses≥ 10 mg/kg/day (exposure 0.2-0.6x maximum clinical exposure), but limited effects followed IV treatment (≤ 15 mg/kg/day). In rabbits, reduced fetal viability, skeletal delays and other variations were observed with SC dosing (≥ clinical exposure), along with multiple malformations including gastroschisis/ thoracogastroschisis, amelia/phocomelia and cleft palate (≥ 10 mg/kg/day) and ablepharia, encephalopathy and spina bifida (24 mg/kg/day). Rabbits treated IV (9 mg/kg/day) showed fewer effects and no malformations. Embryofetal toxicity, including malformations, may be secondary to compromised maternal nutrition.

- Low levels of tapentadol and tapentadol-glucuronide were detected in milk from lactating rats following PO dosing. Tapentadol administration (PO) during lactation resulted in increased pup mortality between PND1-4 in rats at doses lower than maternotoxic doses (exposure margins of 0.3).

- Tapentadol demonstrated potential for dependence in rodents, at very low exposure margins (≤0.1). Behavioural signs of tapentadol withdrawal were generally less pronounced than those of morphine or tramadol. Positive reinforcing effects were observed in rats and monkeys (exposure margins <0.1) and were generally comparable with morphine and tramadol. Tolerance to tapentadol analgesia commenced in rats within days, with full development after 3 weeks (slower than morphine or tramadol tolerance). Tapentadol-tolerant rats were also tolerant to morphine, however morphine tolerant rats remained sensitive to tapentadol.

Recommendations

Tapentadol-induced analgesia is mediated primarily through μOR activation and also via inhibition of noradrenaline re-uptake pathways. Antinociception in several non clinical models was clearly demonstrated, with an efficacy profile between that of morphine and tramadol. The nonclinical activity profile is supportive of the proposed clinical indication.

The primary toxicities observed were CNS effects, including convulsions and hepatic effects in rodents (including proliferative/neoplastic changes), possibly consistent with adaptive changes. A multi-species effect on the cardiovascular system was observed, including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/ teratogenicity and postnatal survival were observed, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. The risk of reproductive toxicity is not addressable by clinical data and appropriate statements in the Product Information are recommended. Tapentadol dose levels were limited in all nonclinical species due to excessive toxicity(particularly CNS) and resulting animal/human systemic exposure margins were quite low, thereby limiting the ability of the nonclinical studies to assess the safety of tapentadol.

The above toxicity concerns have been identified and described in the safety specification in the Risk Management Plan.

Provided the clinical data adequately address the relevant concerns above, there are no nonclinical objections to the registration of tapentadol.

IV. Clinical Findings

Introduction

Clinical Development Programme

The clinical development programme for tapentadol IR was designed to study moderate to severe acute pain to fulfil the different needs for global markets. Where comparators were used in the Phase III clinical trials, morphine or oxycodone was chosen in order to satisfy the needs of a global clinical development program.

This submission included data from 34 completed clinical studies of tapentadol IR tablets and capsules (21 Phase I and 13 Phase II/III studies), including a Phase III study which used tapentadol IR and a tapentadol sustained release (SR) formulation. In addition, data from a study examining the effect of tapentadol SR on the QT interval was presented (HP5503/10).

The submission also included full reports of studies with intravenous and oral formulations which were used during early development: an intravenous formulation and an oral solution were used to obtain pharmacokinetic data (4 Phase I studies) and to obtain initial efficacy data (1 Phase II study).

Reports of serious adverse events and pregnancies were provided for 3 Phase III ongoing studies of the IR formulation as of the cut-off date of 31 October 2008.

The Phase I studies of tapentadol IR formulations included in this submission mainly provide biopharmaceutical, pharmacokinetic, pharmacodynamic, safety and tolerability information. The efficacy and tolerability of tapentadol IR was investigated in 5 Phase II double-blind, placebo and active-controlled studies. Six Phase III studies were also submitted.

Efficacy and safety studies

Overview of pivotal studies

The treatment of moderate to severe pain was investigated in four pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in in-patients following bunionectomy (clinical trials KF5503/32 and KF5503/37), one in in-patients following abdominal hysterectomy (clinical trial KF5503/35) and one in out-patients with end stage degenerative joint disease of the hip or knee (clinical trial KF5503/33) (summarised in Table 4 below). These pain models were chosen because of the severity of pain experienced in these patient groups and because treatment of pain following surgery frequently involves oral opioids in clinical practice.

Table 4: Key studies supporting the efficacy of tapentadol IR

Phase	Study number	Short description	Treatment (tapentadol)
Phase 2a	KF5503/01	Abdominal surgery	Single dose as a 15 minute intravenous infusion of 8.6 mg, 17 mg, 34 mg, 69 mg
	KF5503/02	Third molar tooth surgery	Single immediate-release dose of 43 mg, 64 mg, 86 mg, 129 mg, or 172 mg
	KF5503/04	Third molar tooth surgery	Single immediate-release dose of 21.5 mg, 43 mg, 64 mg, 86 mg, or 172 mg
	KF5503/05	Bunionectomy	Single immediate-release dose of 21.5 mg, 43 mg, 64 mg, 86 mg, or 172 mg
Phase 2b	KF5503/21	Bunionectomy	Multiple immediate-release dose [a] for 72 hours of 50 mg or 100 mg
	KF5503/22	Bunionectomy	Multiple immediate-release dose for 12 hours of 3 doses 4 hourly: 80/80/80 mg, 120/120/120 mg, 120/60/60 mg, or 160/80/80 mg
Phase 3	KF5503/31	Hip replacement [b]	Multiple immediate-release dose [a] for 72 hours of 50 mg, 75 mg or 100 mg
	KF5503/32	Bunionectomy	Multiple immediate-release dose [a] for 72 hours of 50 mg, 75 mg or 100 mg
	KF5503/33	End-stage degenerative joint disease	Multiple immediate-release dose [a] for 10 days of 50 mg or 75 mg
	KF5503/35	Abdominal hysterectomy	Multiple immediate-release dose [a] for 72 hours of 50 mg, 75 mg or 100 mg
	KF5503/37	Bunionectomy	Multiple immediate-release dose [a] for 72 hours of 75 mg

a) 4 hourly to 6 hourly administration.

b) KF5503/31 was terminated early because of slow recruitment and high discontinuation rates most likely reflecting the fact that the design of the study was not in line with current clinical practice (eg, duration of hospital stay required by the protocol). Due to the slow recruitment and high discontinuation rates, it was highly unlikely that by continuing the study, clinically meaningful data would be generated.

Study KF5503/31 was terminated early and will not be discussed in this evaluation report. All above Phase III studies of the IR formulation used a fixed dose with an administration regimen of every 4 hours to 6 hours to optimize each subject's level of efficacy and tolerability. In Australia, oxycodone is very commonly used in clinical practice for the treatment of moderate to severe nociceptive pain so the choice of comparators is considered appropriate for Australian needs.

Data intended to support the indication proposed for Australia is provided from Study KF5503/33 which investigated the efficacy of tapentadol IR in a chronic pain indication (end stage degenerative joint disease) and a 90-day safety study performed in chronic patients.

Further efficacy data were derived from the latter Phase III Study (KF5503/34) designed to examine the safety of tapentadol IR tablets administered as flexible doses of 50 mg or 100 mg

every 4 hours to 6 hours, as needed, over a 90-day period in subjects with low back pain or pain from osteoarthritis of the hip or knee. Efficacy over this time period was a secondary objective of this study.

In the pivotal Phase III trials the efficacy and safety of tapentadol IR was examined across pain intensities from moderate to severe. Patients included in the trials had a baseline score of ≥5 on an 11-point numerical rating scale (NRS). In 3 of the 4 pivotal Phase III studies, approximately 75% of the subjects were rated as having severe pain at baseline. In the fourth pivotal Phase III study, approximately 70% of subjects had moderate pain at baseline.

GCP aspects

All clinical studies were performed according to Good Clinical Practice (GCP) guidelines.

Pharmacokinetics

Introduction

The pharmacokinetics and pharmacodynamics of tapentadol were examined in 17 clinical pharmacology studies. The pharmacokinetics of tapentadol were also assessed in subjects with moderate to severe pain in 4 Phase II studies and in 4 Phase III studies.

Tapentadol IR will be administered as a single or multiple doses to control acute pain; therefore, single- and multiple-dose clinical pharmacology studies were performed to assess the pharmacokinetic parameters of tapentadol. Studies were also performed with selected populations (elderly, hepatic impairment, renal impairment) to investigate possible effects on pharmacokinetics.

A film-coated tablet, referred to as tapentadol IR tablet, was chosen as the preferred to be marketed (TBM) dosage form prior to the initiation of Phase III clinical studies. The tablet strengths are 50 mg, 75 mg and 100 mg doses. The IR tablet cores used during Phase III clinical studies and for the manufacture of the registration stability batches, are identical regarding formulation and dose-dependent tablet weights. Population pharmacokinetic and pharmacokinetic-pharmacodynamic analyses were also conducted.

Methods

Different bioanalytical methods were used during the course of the clinical pharmacokinetics programme of tapentadol. Concentrations of the unchanged drug and its O-glucuronide and its O-sulfate metabolites were mainly determined in serum and for some studies, in urine. All assays were validated according to the FDA guidelines and all acceptance criteria as specified in that guidance were met (FDA Guidance for Industry - Bioanalytical Method validation. May 2001)[18].

Absorption

Bioavailability

Absolute oral bioavailability and effect of food on IR capsules (HP5503/04)

Study HP5503/04 was a single-centre, single-dose, open-label, randomised, 6-sequence, 3-way crossover study in 24 healthy male subjects. All subjects completed the trial. Pharmacokinetic objectives were to determine the absolute oral bioavailability and the effect of food on the bioavailability of tapentadol. Subjects received tapentadol (86 mg IR dose composed of 4 oral IR capsules of 21.5 mg) either after an overnight fast (oral fasted) or after a standardised continental breakfast (oral fed) and as a 34 mg 15 minute intravenous infusion

18 http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

(69 mg/50 mL). The breakfast contained 2686 kiloJoule (kJ) [642 kilocalories (kcal)] (23.4 g fat, 19.4 g protein, 86.5 g carbohydrates).

Results: The mean pharmacokinetic parameter estimates of tapentadol are presented in Table 5 below. The absolute oral bioavailability of tapentadol from the IR capsules was 32% under fasted conditions. The C_{max} and AUC of tapentadol administered as IR capsules within 30 minutes of a standardised continental breakfast (fed state) increased 25% and 32%, respectively, compared to the fasted state. The t_{max} was similar under fasted and fed conditions.

Table 5: Tapentadol pharmacokinetic parameters after single dose administration of IV infusion and oral capsule with or without food (HP5503/04)

	34 mg i.v. (batch WMAK01) (n = 24)	4 × 21.5 mg p.o. fed (batch XDAM04) (n = 24)	4 × 21.5 mg p.o. fasted (batch XDAM04) (n = 24)	Oral fed/fasted Ratio,% (90% CI) [a]
C_{max} (ng/mL)	243 ± 93.4 [38.4]	101 ± 43.2 [42.8]	78.0 ± 26.9 [34.4]	125.3% (106.9-146.9)
AUC_{last} (ng•h/mL)	374 ± 41.0 [11.0]	406 ± 105 [25.8]	310 ± 91.5 [29.5]	132.4% (123.3-142.2)
AUC_{∞} (ng•h/mL)	379 ± 42.2 [11.2]	411 ± 105 [25.7]	314 ± 91.6 [29.1]	131.9% (123.0-141.4)
t_{max} (h)	0.23 (0.17-0.58)	1.25 (0.50-3.00)	1.00 (0.75-3.00)	
$t_{1/2}$ (h)	4.1 ± 0.7 [17.0]	4.6 ± 0.7 [14.9]	4.9 ± 0.7 [14.8]	
CL (CL/F) (mL/min)	1530 ± 177 [11.6]	3763 ± 1233 [32.8]	5007 ± 1820 [36.3]	
V_{dz} (V_{dz}/F) (L)	540 ± 98 [18.2]	1489 ± 564 [37.9]	2127 ± 970 [45.6]	
F,% (95% CI) [a]		42.2 (38.8-45.8)	32.0 (29.4-34.8)	

Data expressed as mean ± SD [%CV], except for t_{max} where median (range) is provided

a) Based on the conversion of log-transformed data back to the original scale

CI = confidence interval; %CV = coefficient of variation in percent; i.v. = intravenous; n = number of subjects; p.o. = per os; SD = standard deviation

Effect of food on the IR tablet (key Study HP5503/34)

Study HP5503/34 (R331333-PAI-1014) was a single-centre, single-dose, open-label, randomized, 2-way crossover study in 36 healthy subjects (18 men, 18 women). Thirty-four (17 men/17 women) subjects completed the trial. The primary objective was to investigate the effect of food (high-fat, high-calorie breakfast) on the bioavailability of a single 100 mg dose of tapentadol IR tablets, the highest strength of the IR tablet formulation, used in Phase III studies. The high-fat, high-calorie breakfast had the composition as proposed in the FDA guidance document (FDA Guidance for Industry – Food Effect Bioavailability and Fed Bioequivalence Studies. December 2002[19]). It was provided 30 minutes before drug administration and had to be consumed within 30 minutes or less. The study fulfils the requirements specified in the FDA and Committee for Medicinal Products for Human Use (CHMP) guidelines[20].

[19] http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf

[20] FDA Guidance for Industry – Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. March 2003, CPMP –Note for Guidance on the Investigation of Bioavailability and Bioequivalence [CPMP/EWP/QWP/1401/98]. July 2001 (http://www.tga.gov.au/docs/pdf/euguide/ewp/140198entga.pdf) and FDA Guidance for Industry – Food Effect Bioavailability and Fed Bioequivalence Studies. December 2002.

Results: Mean pharmacokinetic parameter estimates of tapentadol are summarised in Table 6 below. The C_{max} and AUC of tapentadol administered as a 100 mg IR tablet within 30 minutes of a high-fat, high-calorie breakfast (=fed state) increased 16% and 25%, respectively, compared to fasted administration. For C_{max} the 90% CI for the treatment ratio for the fed state versus the fasted state was 107.65% to 124.99% (within the 80% to 125% range); for AUC_{last} it was 119.24% to 131.42% and for $AUC_{0-\infty}$ it was 119.26% to 131.40% (outside the upper limit of the 80% to 125% range). The median t_{max} of tapentadol and its O-glucuronide metabolite increased from 1.5 hours to 3 hours upon administration of food. The mean C_{max} of tapentadol-O-glucuronide decreased slightly upon administration of the drug in the fed state, whereas AUCs were not affected.

Table 6: Tapentadol pharmacokinetic parameters after single dose administration of tapentadol IR tablets when fed and fasted (HP5503/34)

	100 mg IR tablet fed (PD2213) (n = 35)	**100 mg IR tablet fasted (PD2213) (n = 34)**	**Fed/Fasted Ratio,% (90% CI) [a] (n = 34)**
C_{max} (ng/mL)	83.4 ± 28.1 [33.7]	72.8 ± 30.8 [42.4]	115.99 (107.65 - 124.99)
AUC_{last} (ng•h/mL)	525 ± 154 [29.2]	421 ± 151 [36.0]	125.18 (119.24 - 131.42)
AUC_{∞} (ng•h/mL)	536 ± 157 [29.3]	429 ± 154 [35.9]	125.18 (119.26 - 131.40)
t_{max} (h)	3.00 (1.02 – 6.00)	1.50 (1.00 – 4.00)	
$t_{1/2}$ (h)	3.9 ± 0.4 [10.6]	4.2 ± 0.4 [10.2]	

Data expressed as mean ± SD [%CV], except for t_{max} median (range)
a) Based on the conversion of log-transformed data back to the original scale
CI = confidence interval; %CV = coefficient of variation in percent; i.v. = intravenous; n = number of subjects; SD = standard deviation

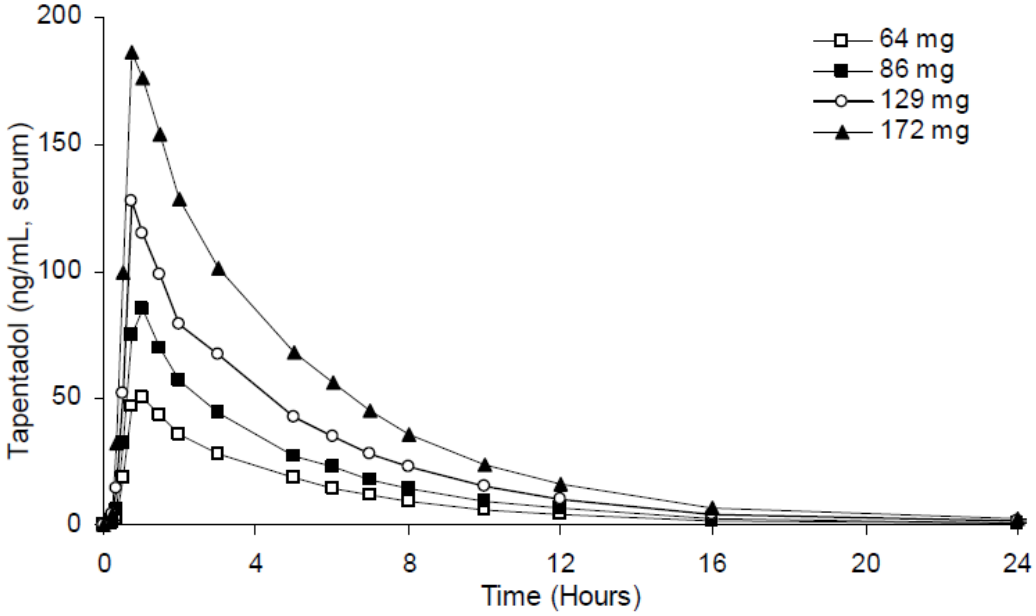
Dose-linearity of immediate-release capsules, dose range 64 mg to 172 mg (HP5503/03)

Study HP5503/03 was a single-centre, single-dose, double-blind, placebo-controlled, randomised, dose-escalation study in 33 healthy subjects (16 men and 17 women). Thirty-two subjects completed the trial. One objective was to evaluate the dose-linearity of tapentadol. Subjects received tapentadol 64, 86, 129 and 172 mg as a 21.5 mg IR capsule formulation or matching placebo. Each subject was to receive active drug on 3 occasions and placebo on 1 occasion during the trial. Pharmacokinetic data were therefore only available for 24 of the 32 participating subjects at each dose. Furthermore, since different subjects received placebo in each dosing session, less subjects (16) were available for comparison between each dose level.

Results: Mean serum concentration-time curves are presented in Figure 3. After oral administration of 64, 86, 129 and 172 mg tapentadol as IR capsules, there was a dose-linear increase in mean C_{max}- and AUC-values.

The inter-subject variability was comparable between the doses, indicating that the number of capsules taken did not substantially influence the variability of tapentadol pharmacokinetics. Furthermore, at the 2 higher doses for which 6 or 8 capsules were used, dose-proportionality was confirmed indicating that the number of units administered did not influence the absorption characteristics of tapentadol.

Figure 3: Mean serum tapentadol concentration-time profiles after single dose administration of tapentadol immediate-release capsules to male and female subjects (HP5503/03)



Dose-proportionality of immediate release capsules, doses 21.5 mg and 86 mg (HP5503/07)

Study HP5503/07 was a single-centre, single-dose, open-label, randomised, 4-way crossover study in 16 healthy male subjects. All subjects completed the trial. The objective was to determine the relative bioavailability of tapentadol 21.5 mg and 86 mg IR capsules and 86 mg and 172 mg extended release tablets. Results from the extended release tablets are not included in this section.

Results: Mean pharmacokinetic parameter estimates of tapentadol for the IR capsules are presented in Table 7. The lower limit of the 90% CI for 21.5 mg (dose-normalised to 86 mg) compared to the 86 mg dose on C_{max} was 79.2%, which is marginally below 80%. The 90% CI for the dose-normalised 21.5 mg compared to the 86 mg dose was 81.0% to 96.3% for AUC_{∞}, which is within the 80% to 125% bioequivalence limit. The dose of 21.5 mg is below the proposed clinical dose range of 50 mg to 100 mg.

Table 7: Tapentadol pharmacokinetic parameters after single dose administration of tapentadol 21.5 mg and 86 mg IR capsules (HP5503/07)

	21.5 mg (n = 16)	21.5 mg, DN to 86 mg (n = 16)	86 mg (n = 16)	DN 21.5 mg / 86 mg Ratio,% (90% CI) [a] (n = 16)
C_{max} (ng/mL)	14.0 ± 3.83	55.8 ± 15.3	64.2 ± 18.7	88.9 (79.2-99.8)
AUC_{last} (ng•h/mL)	66.3 ± 13.8	265 ± 55.1	316 ± 56.0	85.3 (78.2-93.0)
AUC_{∞} (ng•h/mL)	69.1 ± 14.0	277 ± 55.9	318 ± 55.9	88.3 (81.0-96.3)
t_{max} (h)	1.00 (0.75-2.00)	-	1.50 (0.75-4.00)	

Data expressed as mean ± SD, except t_{max}: median (range)

a) based on the conversion of log-transformed data back to the original scale

CI = confidence interval; DN = dose-normalized to 86 mg; IR = immediate release; n = number of subjects; SD = standard deviation

C_{max} and AUC_{∞} behaved in a dose-proportional manner for the 21.5 mg and 86 mg doses, although a minor deviation from dose-proportionality was found for C_{max} (90% CI for the treatment ratio 79.2% to 99.8%).

Dose-proportionality of IR capsules, doses 43 mg and 86 mg (HP5503/09)

Study HP5503/09 was a randomised, single-centre, single-dose, double-blind, placebo- and morphine-controlled, 4-way crossover study to determine the effect of tapentadol IR (43 mg and 86 mg doses) or a presumed equi-analgesic dose of morphine sulfate (40 mg corresponding to 30 mg morphine base) on orocaecal transit time (OCTT). This study also assessed the basic pharmacokinetic parameters of tapentadol in 24 healthy men aged between 26 years and 49 years.

Results: A summary of pharmacokinetic parameters is given in Table 8. Following the oral administration of tapentadol IR capsules 43 mg and 86 mg, the mean C_{max} and AUC appeared to increase dose-proportionally.

Table 8: Tapentadol pharmacokinetic parameters of tapentadol following single-dose administration of 43 mg or 86 mg tapentadol IR (HP5503/09)

Parameter	Tapentadol IR 43 mg (n = 24)	Tapentadol IR 86 mg (n = 23)
t_{max} (h)	1.00 (0.75-2.00)	1.42 (0.75-3.00)
C_{max} (ng/mL)	30.6 ± 15.9	61.0 ± 26.1
AUC_{∞} (ng•h/mL)	132 ± 43.0	265 ± 72.2
$t_{½}$ (h)	4.0 ± 0.7	4.0 ± 0.4

Data expressed as mean ± SD, except t_{max} which is depicted as median (minimum -maximum)
IR = immediate release; n = number of subjects; SD = standard deviation

Dose-proportionality of IR capsules, dose range 75 mg to 175 mg (HP5503/13)

Study HP5503/13 was a single-centre, multiple-dose, double-blind, placebo-controlled, parallel-group, dose-escalation study in healthy subjects. Sixteen male and 16 female subjects were included and 22 subjects were randomised when the study was terminated for operational reasons. One of the objectives was to assess the dose-proportionality of tapentadol. Subjects were divided into two panels. Panel 1 was to receive 75, 125, 175 and 225 mg tapentadol; Panel 2 was to receive 100, 150, 200 and 250 mg tapentadol. All subjects were to receive multiple doses (6 doses; 1 every 6 hours). Each subject was allocated to three dose levels of tapentadol and one administration of placebo. Tapentadol capsules of 25 mg, 50 mg and 100 mg and matching placebos were used.

Results: The mean pharmacokinetic parameter estimates of tapentadol are provided in Table 9. Following oral administration of tapentadol IR capsules, results suggest that C_{max} and AUC were approximately dose-proportional up to a dose of 175 mg, both on Day 1 (single-dose) and on Day 2 (multiple-dose). The ratios of dose-normalized geometric means of C_{max} and AUC for 100 mg, 125 mg and 150 mg tapentadol versus 75 mg, ranged from 98% to 105% on Day 1 and from 104% to 119% on Day 2. The dose-normalised geometric mean ratios of C_{max} and AUC for 175 mg versus 75 mg ranged from 77% to 103%.

Table 9: Tapentadol pharmacokinetic parameters after first and repeated dose administration of tapentadol IR capsules (HP5503/13)

	75 mg [a] (n = 10)	100 mg (n = 12)	125 mg [a] (n = 11)	150 mg [a] (n = 11)	175 mg [a] (n = 10)
First dose					
	(n = 10)	(n = 12)	(n = 11)	(n = 11)	(n = 10)
C_{max} (ng/mL)	72.7 ± 36.3	95.1 ± 21.3	124 ± 40.7	135 ± 45.0	125 ± 37.3
AUC_{0-6h} (ng•h/mL)	229 ± 90.3	299 ± 87.5	413 ± 132	439 ± 121	446 ± 126
t_{max} (h)	1.50 (0.52-3.00)	1.75 (1.00-4.00)	1.50 (0.50-5.95)	1.50 (1.00-3.00)	2.00 (0.50-3.00)
DN-C_{max} (ng/mL)	96.9 ± 48.4	95.1 ± 21.3	99.2 ± 32.6	90.0 ± 30.0	71.4 ± 21.3
DN-AUC_{0-6h} (ng•h/mL)	305 ± 120	299 ± 87.5	330 ± 106	293 ± 80.7	255 ± 72.0
DN-C_{max} ratio [b] (90% CI)	reference	105.01 (83.19-132.56)	98.63 (80.88-120.27)	98.37 (77.60-124.70)	76.83 (62.54-94.38)
DN-AUC_{0-6h} ratio [b] (90% CI)	reference	100.38 (81.30-123.94)	100.91 (88.01-115.70)	103.64 (83.73-128.29)	84.78 (73.50-97.78)
Repeated doses (steady-state)					
	(n = 10)	(n = 10)	(n = 10)	(n = 9)	(n = 9)
$C_{max,ss}$ (ng/mL)	76.2 ± 31.0	118 ± 33.1	138 ± 64.6	160 ± 61.0	162 ± 42.2
AUC_{τ} (ng•h/mL)	324 ± 143	494 ± 123	567 ± 199	675 ± 225	737 ± 166
t_{max} (h)	2.95 (1.93-3.98)	2.95 (0.88-5.98)	2.08 (0.92-3.97)	2.03 (0.98-6.00)	2.00 (1.42-3.13)
$t_{1/2}$ (h)	3.9 ± 0.4	4.4 ± 0.6	4.0 ± 0.3	4.2 ± 0.7	4.0 ± 0.4
DN-$C_{max,ss}$ (ng/mL)	102 ± 41.3	118 ± 33.1	110 ± 51.7	107 ± 40.7	92.6 ± 24.1
DN-AUC_{τ} (ng•h/mL)	432 ± 191	494 ± 123	454 ± 159	450 ± 150	421 ± 94.9
DN-$C_{max,ss}$ ratio [b] (90% CI)	reference	118.11 (91.68-152.14)	105.00 (87.14-126.52)	104.36 (80.61-135.09)	88.63 (72.90-107.75)
DN-AUC_{τ} ratio [b] (90% CI)	reference	118.94 (94.53-149.66)	108.05 (91.38-127.75)	111.28 (88.05-140.64)	103.01 (86.43-122.77)

Data expressed as mean ± SD, except for t_{max} median (range)

a) Administered as a combination of 25 mg, 50 mg and 100 mg capsules (batches PD1428, PD1471 and PD1470)

b) Based on the conversion of log-transformed data back to the original scale

CI = confidence interval; DN = dose-normalized to 100 mg (post-hoc analysis; in the study report dose-normalization to 75 mg was used); IR = immediate release; n = number of subjects; SD = standard deviation; τ = dosing interval (6 hours)

Dose-proportionality of IR capsules, dose range 50 mg to 200 mg (HP5503/14)

Study HP5503/14 was a single-centre, single-dose, double-blind, double-dummy, placebo-controlled, randomised, 7-way crossover study to evaluate the abuse potential of tapentadol, as compared to placebo and hydromorphone IR in opiate-experienced but non-dependent recreational drug users. The pharmacokinetics of 3 doses of tapentadol IR (50 mg, 100 mg, or 200 mg) and hydromorphone IR (4 mg, 8 mg, or 16 mg) were evaluated.

Results: Across tapentadol doses (from 50 mg to 200 mg), the mean C_{max} for tapentadol was reached at 1.29 hours to 1.50 hours after drug intake indicating rapid oral absorption of the drug. The pharmacokinetic parameters for tapentadol, after dose-normalisation to the 100 mg dose, were very similar across different dose levels. The statistical analysis (mixed-effect ANOVA) of dose-normalised pharmacokinetic parameters indicated dose-proportionality between 50 mg and 200 mg.

Pharmacokinetics of single- and multiple doses of tapentadol 21.5 mg and 43 mg in subjects with chronic non-malignant pain (KF5503/08)

Study KF5503/08 was a randomised, double-blind, parallel group, single- and multiple-dose Phase II study designed to assess the safety, tolerability and pharmacokinetics of tapentadol following single- and multiple doses in subjects with chronic non-malignant pain. During the single-dose treatment period, subjects received a single dose of 21.5 mg or 43 mg tapentadol IR. Thirty-six hours after the administration of the single-dose, subjects started taking the same dose of tapentadol IR every 6 hours for 5 days. Serum concentrations of tapentadol were determined from blood samples collected at regular time-points up to 36 hours in the single-dose period and up to 48 hours after the last dose in the multiple-dose period.

Results: After the single dose and the last of the multiple doses, tapentadol serum concentrations peaked on average within 1.5 hours to 2.5 hours in both dose groups (see Table 10), indicating an expected rapid absorption in this subject population. After the single dose of 21.5 mg or 43 mg tapentadol IR and the last of the multiple doses (every 6 hours for 5 days, a total of 19 doses), median t_{max} was 1.5 hours (21.5 mg) and 2.5 hours (43 mg). Maximum tapentadol serum concentrations and AUCs increased with increasing dose, both after single- and multiple-dose administration. In the multiple-dose phase, the accumulation ratio for AUC_{τ} [21] was 1.8, close to the theoretically expected value based on terminal half-life and dosing interval. The terminal elimination half-life determined after the last dose of 43 mg was 4.6 ± 1.0 hours in men and 5.2 ± 1.1 hours in women. The pharmacokinetics of tapentadol were close to dose-proportional, although the study was not designed (parallel groups) and powered for this evaluation.

Table 10: Tapentadol pharmacokinetic parameters after single- or multiple-dose administration of tapentadol IR (KF5503/08)

Parameter	Tapentadol IR 21.5 mg (n = 22)	Tapentadol IR 43 mg (n = 23)
Single dose		
t_{max}, (h)	2.3 (0.8–4.0)	2.0 (1.0–4.0)
C_{max} (ng/mL)	17.1 ± 6.7	30.1 ± 10.4
AUC_{∞}, (ng•h/mL)	90.5 ± 36.3	169 ± 58.9
$AUC_{0\text{-}6h}$, (ng•h/mL)	57.5 ± 23.3	106 ± 37.5
$t_{1/2}$ (h)	4.6 ± 1.3	4.4 ± 0.6
Multiple dose		
t_{max}, h	1.5 (1.0–4.0)	2.0 (1.0–5.0)
$C_{avg,ss}$ (ng/mL)	16.3 ± 7.3	30.6 ± 9.1
$C_{max,ss}$ (ng/mL)	26.5 ± 12.6	46.6 ± 13.8
$C_{min,ss}$ (ng/mL)	10.3 ± 4.6	20.4 ± 7.2
$AUC_{\tau,ss}$ (ng•h/mL)	97.8 ± 44.0	184 ± 54.7
$t_{1/2}$ (h)	4.9 ± 1.1	4.9 ± 1.1
Accumulation ratio	1.8 ± 0.7	1.9 ± 0.6

Data expressed as mean ± SD, except for t_{max} where median (range) is provided
IR = immediate release; n = number of subjects; SD = standard deviation

Other studies investigating dose-proportionality

Data supporting dose-proportionality were also obtained in HP5503/48 and HP5503/25. In HP5503/48, a Japanese population was administered doses of 10 mg, 20 mg and 40 mg of

[21] AUC over a dosing interval, t.

tapentadol IR. Data showed dose-proportionality for both C_{max} and AUC_{∞} in this population, over this dose range.

In a thorough QT trial, 5 doses of 100 mg or 150 mg were administered every 6 hours and the steady-state pharmacokinetic parameters for tapentadol are shown in Table 11 (for the 150 mg dose both the original data and dose-normalised [to 100 mg] data are presented). All the concentration-related parameters (maximal plasma concentration during multiple dosing, steady state ($C_{max,ss}$), trough plasma concentration (C_{trough}), mean or average steady-state concentration during multiple dosing, steady state ($C_{avg,ss}$) and AUC_{τ}) were consistent with dose-proportionality between 100 mg and 150 mg.

Table 11: Tapentadol pharmacokinetic parameters of tapentadol at steady-state (HP5503/25)

Parameter	n	Tapentadol IR 100 mg	Tapentadol IR 150 mg	DN Tapentadol IR 150 mg
$t_{max,ss}$ (h)	58	1.45 (0.87–6.00)	1.49 (0.40–6.02)	
$C_{max,ss}$ (ng/mL)	58	129 ± 42.0	197 ± 89.1	131 ± 59.4
C_{trough} (ng/mL	55	55.2 ± 25.2	93.3 ± 50.7	62.2 ± 33.8
$C_{avg,ss}$ (ng/mL	58	78.4 ± 24.3	122 ± 48.0	81.3 ± 32.0
AUC_{τ} (ng•h/mL	58	465 ± 146	729 ± 282	486 ± 188
$t_{1/2}$, (h)	53/52	3.7 ± 0.9	3.7 ± 0.9	
CL_{ss}/F (mL/min)	58	3969 ± 1351	3820 ± 1176	

Data expressed as mean ± SD, except for t_{max} where median (range) is provided
DN = dose-normalized (to 100 mg) concentration-related parameters from a post-hoc analysis; IR = immediate release; n = number of subjects; SD = standard deviation

Bioequivalence of tapentadol IR tablet and IR capsule (key Study HP5503/24)

Study HP5503/24 was a single-centre, single-dose, open-label, randomised, 2-period, crossover study in 32 healthy subjects (16 men and 16 women). Thirty-one subjects completed the study and 30 subjects were included in the pharmacokinetic analysis. The primary objective was to demonstrate bioequivalence between the tapentadol IR tablets (80 mg, batch PD1707, assay 97.6% of label claim) and tapentadol IR capsules (80 mg, batch PD1549, assay 100.9% of label claim).

Results: The tapentadol IR tablet formulation is bioequivalent to the IR capsule formulation administered as an 80 mg dose. Mean pharmacokinetic parameter estimates of tapentadol are shown in Table 12.

Table 12: Tapentadol pharmacokinetic parameters after single dose administration of tapentadol IR tablets and IR capsules (HP5503/24)

	80 mg IR tablet (PD1707) (n = 30)	80 mg IR capsule (PD1549) (n = 30)	Tablet/capsule Ratio,% (90% CI) (n = 30)
C_{max} (ng/mL)	76.6 ± 22.5	82.4 ± 25.6	93.77 (85.58 – 102.73)
AUC_{last} (ng•h/mL)	322 ± 84.1	345 ± 107	94.48 (89.78 – 99.43)
AUC_{∞} (ng•h/mL)	326 ± 85.0	349 ± 108	94.41 (89.73 – 99.34)
t_{max} (h)	1.00 (0.50 – 4.00)	1.00 (0.50 – 2.02)	

Data expressed as mean ± SD, except t_{max}: median (range)
CI = confidence interval; IR = immediate release; n = number of subjects; SD = standard deviation

Analyses of results across pharmacokinetic trials

For cross-study comparison, a pooled dataset ('dataset for cross-study comparison') was created containing the data from the single-dose Phase I clinical pharmacology and biopharmaceutic studies listed previously, except for 3 studies (Studies HP5503/25, HP5503/48 and HP5503/05).

Absorption and bioavailability

The absorption of tapentadol following an IR dose is both fast, given the median t_{max} of around 1.25 hours (see Table 13 below) and almost complete, based upon the radioactively labelled carbon (^{14}C)-tapentadol Study HP5503/05. The absolute oral bioavailability of tapentadol under fasting condition was 32.0% (95% confidence interval: 29.4% to 34.8%) Together, these results indicate that tapentadol undergoes extensive first-pass metabolism. Some 96% of an administered dose of tapentadol is eliminated via urine as tapentadol metabolites. Bioavailability was similar when tapentadol IR was administered as a capsule formulation or as tablet formulation.

A summary of cross-study pharmacokinetic parameters for tapentadol is shown in Table 13. For the C_{max} of tapentadol, dose-normalised to 100 mg, the inter-subject CV was estimated at 39% and the intra-subject coefficient of variation was estimated at 20% in a post-hoc analysis. For the AUC_∞ of tapentadol, dose-normalised to 100 mg, the inter-subject coefficients of variation (CV) was estimated at 34%, whereas the intra-subject CV was estimated at around 13% (n = 376, post-hoc evaluation, data on file).

Table 13: Cross-study, mean pharmacokinetic parameters after a single dose of tapentadol IR, dose–normalised to 100 mg tapentadol (dataset for cross-study comparison)

Parameter [a]	n	Mean ± SD	%CV
t_{max}, h	631	1.25 (0.50 - 6.27)[b]	
C_{max}, ng/mL	631	90.1 ± 36.2	39
AUC_∞, ng•h/mL	576	417 ± 143	34
$t_{1/2}$, h	576	4.3 ± 0.8	16
CL_R, mL/min	78	99.0 ± 37.3	38

a) Data expressed as mean ± SD, except for t_{max} where median (range) is provided

b) More than 90% of observations was below or equal to 3 hours;

%CV = coefficient of variation in percent; n = number of observations; SD = standard deviation.

Source: post-hoc analysis, data on file

No clinically relevant influence on the absorption of tapentadol was observed upon changes in the gastric pH after omeprazole co-medication or by alterations in the gastric motility due to metoclopramide co-administration.

Distribution

Protein binding can affect the pharmacokinetics of drugs and was therefore assessed for tapentadol in an *in vitro* study and found to be approximately 20%. This indicates that the majority of tapentadol remains unbound in serum and, therefore, is potentially available for tissue penetration and access to the receptor-binding site as well.

The estimated tapentadol apparent volume of distribution (V_z) (mean ± standard deviation (SD)) in healthy subjects following an intravenous dose of 34 mg tapentadol was estimated using non-compartmental analysis at 540 ± 98 L (HP5503/04). This large volume of distribution is typical for small basic and slightly lipophylic drugs, suggesting that intra-cellular distribution into tissues occurs to an appreciable extent.

The distribution of tapentadol into red blood cells was investigated *in vitro* with human blood (PK1166). A mean blood/plasma ratio of 1.23 was calculated at a concentration of 80 ng/mL for tapentadol. This means on average that the blood concentration of tapentadol is 23% higher than the plasma concentration. The blood cells/plasma ratio was 1.53.

The *in vivo* distribution of tapentadol and its metabolites into red blood cells was investigated in dogs and humans (PK581K/A) and was estimated from the concentration of radioactivity

in whole blood and the corresponding serum concentration after oral administration of ^{14}C-labelled tapentadol. The blood concentration did not exceed the serum concentration in either species (only 5% to 10 % of the total radioactivity in red blood cells compared to serum), which indicates that mainly tapentadol and not its metabolites is distributed into red blood cells.

Elimination

Tapentadol shows substantial pre-systemic metabolism. The main metabolic pathways for the elimination of tapentadol in all species are direct glucuronidation and sulfation and the main metabolites are tapentadol 0-glucuronide, tapentadol 0-sulfate, M1 0-glucuronide I and II and M2 0-glucuronide.

In-vitro tapentadol readily undergoes glucuronide-conjugation. Only a small amount of the parent drug was oxidized *in vitro*, indicating that oxidative metabolism via the cytochrome P450 (CYP) system is of minor importance. This was reflected in *in vivo* studies. The most prominent metabolite detected in serum was always tapentadol-O-glucuronide (80% to 85% of the conjugates). The O-glucuronides of M2 and M1 metabolites were the next most abundant systemic metabolites after tapentadol-O-glucuronide, but together they amounted only to approximately 10% (human) of the total exposure to conjugates.

The formation of hydroxy-tapentadol (M1) was catalysed by CYP2D6, CYP2B6 and CYP2C19, whereas the formation of N-demethyl tapentadol (M2) was catalysed by CYP2C9, CYP2C19 and CYP2C8. Of these enzymes, CYP2C9 and CYP2D6 are the most important ones.

The *in vitro* potential of tapentadol to inhibit the cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4 was assessed in human liver microsomes. No CYP inhibition was observed apart from inhibition of CY2D6 at very high concentrations of tapentadol, which is not likely to be clinically relevant.

The potential of tapentadol to induce CYP1A2, CYP2C9 and CYP3A4 was investigated *in vitro* with freshly isolated human hepatocytes. The results strongly suggested that tapentadol is not a potent CYP inducer at concentrations that may be achieved at the expected therapeutic doses of 50 mg to 100 mg.

The metabolic clearance of tapentadol in humans is primarily due to glucuronidation. The capacity of glucuronidation by uridine diphosphate-glucuronosyl transferase is accepted to be high and the concentration at which half maximum rate (K_m) of drug glucuronidation reactions occurs is much higher than the drug concentrations found in clinical practice. For tapentadol, the K_m is estimated at 390 μM or higher, which is approximately 400-fold the maximum clinical serum concentration of around 1 μM. Therefore, limitation of this metabolic elimination route by direct drug-drug interactions during treatment is considered to be unlikely. A number of *in vitro* studies in which a possible influence of concomitant medications on the glucuronidation of tapentadol was investigated revealed that a risk of clinically significant drug-drug interactions due to interference with glucuronidation would be low (see Nonclinical evaluation *Pharmacokinetic drug interactions*). Nonetheless, probenecid and naproxen were identified from the *in vitro* data as potential candidates for *in vivo* inhibition of glucuronidation and were subsequently included in the clinical pharmacology drug-drug interaction program.

Clearance after oral administration of tapentadol across studies

Tapentadol is rapidly eliminated from the systemic circulation in healthy subjects.

The elimination parameters of tapentadol from healthy subjects were pooled across trials, excluding subjects with organ dysfunction, elderly subjects and data from treatment periods in which another drug was co-administered or when administration of tapentadol occurred with food. The total clearance after oral tapentadol for healthy subjects aged 18 years to 54 years and elimination half-life are summarised in Table 14. The mean half-life ($t_{1/2}$) for individual studies ranged from 3.9 hours to 4.9 hours, with an overall mean (± SD) of 4.3 ± 0.8 hours, which is independent of the dose (21.5 mg to 200 mg). The clearance after oral tapentadol per individual study ranged from 3524 ± 1056 mL/min to 5843 ± 1571 mL/min. The mean cross-study CL/F was 4470 ± 1519 mL/min (n = 576), with an inter-subject CV of 34%, which is in good agreement with the population approach for estimating inter-individual variance. The intra-subject CV for the CL/F was estimated at around 13% in a post-hoc analysis (data from 137 subjects who had received more than one dose of tapentadol).

The half-life of tapentadol after intravenous administration is 4.1 ± 0.7 hours and is very similar to that observed after oral administration of tapentadol, 4.3 ± 0.8 hours. The inter-subject variability for tapentadol $t_{1/2}$ was estimated at 16% (n = 376) and the intra-subject variability was estimated at 9% in a post hoc analysis (n = 137).

CL_R was only determined in Studies HP5503/ 15, HP5503/16, HP5503/22 and HP5503/30. The mean CL_R of tapentadol in healthy subjects was calculated to be 99.0 ± 37.3 mL/min. The creatinine clearance, a measure for glomerular filtration rate, was estimated (from all 16 studies) using the Cockcroft and Gault (1976) method22 and was calculated to be 112 ± 23.3 mL/min. The similarity of renal clearance (CL_R) and creatinine clearance, taking into account the unbound tapentadol fraction (about 80%), suggests that the renal elimination of the parent drug is most likely predominantly via (passive) glomerular filtration.

[22] Cockroft DW, Gault MH. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron* 16:31-42. A commonly used surrogate marker for actual *creatinine clearance* is the Cockroft-Gault formula, which employs creatinine measurements and a patient's weight to predict the clearance. The formula is: <math>{x} = \frac{(140-{age}) \times {weight} \times {constant} } {creatinine}<math>. This formula uses metric units (weight in kilograms, creatinine in µmol/L). The *constant* is *1* for men and *0.85* for women.

Table 14: Elimination parameters (mean ± SD) for tapentadol following a single dose of tapentadol to healthy subjects (dataset for cross-study comparison)

Study number	N	$t_{1/2}$ h	%CV	CL/F mL/min	%CV	CL_R mL/min	%CV
HP5503/03	96	4.9 ± 0.9	18	4228 ± 1485	35	ND	ND
HP5503/04	24	4.9 ± 0.7	15	5007 ± 1820	36	ND	ND
HP5503/07	32	4.4 ± 1.0	23	5001 ± 1038	21	ND	ND
HP5503/09	47	4.0 ± 0.6	15	5843 ± 1571	27	ND	ND
HP5503/14	105	3.9 ± 0.4	10	4087 ± 1192	29	ND	ND
HP5503/15	9	4.7 ± 0.5	11	4579 ± 919	20	105 ± 32.5	31
HP5503/16	10	4.3 ± 0.6	14	5602 ± 1521	27	97.0 ± 39.8	41
HP5503/19	22	4.3 ± 0.7	17	4515 ± 1203	27	ND	ND
HP5503/20	30	4.5 ± 0.9	21	4500 ± 1759	39	ND	ND
HP5503/21	27	4.1 ± 0.5	11	4018 ± 1350	34	ND	ND
HP5503/22	34	4.2 ± 0.7	16	3524 ± 1056	30	105 ± 43.0	41
HP5503/23	21	4.1 ± 0.6	15	5006 ± 2312	46	ND	ND
HP5503/24	60	4.0 ± 0.5	12	4266 ± 1177	28	ND	ND
HP5503/30	25	4.0 ± 0.6	16	4243 ± 1301	31	88.9 ± 28.3	32
HP5503/34	34	4.2 ± 0.4	10	4405 ± 1670	38	ND	ND

Data expressed as mean ± SD [%CV]; parameters are calculated from individual data per trial; n = number of observations; ND = not measured/determined

For HP5503/13 no single-dose elimination data are available.

N = total number of subjects; %CV = coefficient of variation in percent; SD = standard deviation.

Pharmacokinetics of tapentadol following multiple-dose administration

Two Phase I multiple-dose studies were performed in healthy subjects, one was a dose escalating study (HP5503/13) and one was to evaluate electrocardiogram (ECG) parameters upon tapentadol IR dosing (HP5503/25). The calculated accumulation ratio (ratio of AUC_τ [multiple-dose] and $AUC_{0\text{-}6h}$ [single-dose], as shown in Table 15) was between 1.4 and 1.7 in Study HP5503/13. The accumulation ratio of tapentadol-O-glucuronide was in the range of 1.7 to 2.0 (HP5503/13). The accumulation ratio for tapentadol is close the theoretical ratio derived from equation: $R = 1/(1\text{-}e^{\lambda z \tau})$. With a dosing scheme of every 6 hours, the predicted accumulation ratio amounts to 1.6 ($t_{1/2}$: 4.3 hours and τ: 6 hours), suggesting that the accumulation of tapentadol is predictable from single-dose data. This provides evidence that the pharmacokinetics of tapentadol is time-independent.

In the thorough QT[23] study (HP5503/25), steady-state was achieved at Day 2 after 4 to 5 consecutive doses of tapentadol IR. In Study HP5503/25, the accumulation ratios for AUC could not be determined due to sparse sampling after the first dose. The observed Fluctuation Index was somewhat higher than that observed in HP5503/13 (see Table 15) but was in good agreement with the values calculated from the multiple-dose data in subjects with pain (KF5503/08) (see Table 16).

Table 15: Pharmacokinetic parameters for tapentadol at steady-state following dosing, every 6 hours, in healthy subjects (HP5503/13, HP5503/25)

[23] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

Dose (mg)	Pharmacokinetic parameters						
	$C_{min,ss}$ [a] ng/mL	$C_{max,ss}$ ng/mL	$C_{avg,ss}$ ng/mL	AUC_{0-6h} ng·h/mL	AUC_{τ} ng·h/mL	Accumulation ratio [b]	Fluctuation index
HP5503/13							
75	41.0 ± 24.1	76.2 ± 31.0	54.1 ± 23.8	229 ± 90.3	324 ± 143	1.44 ± 0.41	68.9 ± 19.4
(n = 10)	[59]	[41]	[44]	[39]	[44]	[28]	[28]
100	62.7 ± 19.7	118 ± 33.1	82.3 ± 20.5	299 ± 87.5	494 ± 123	1.73 ± 0.54	66.7 ± 29.8
(n = 10)	[32]	[28]	[25]	[29]	[25]	[31]	[48]
125	67.6 ± 28.2	138 ± 64.6	94.4 ± 33.2	413 ± 132	567 ± 199	1.50 ± 0.51	71.9 ± 23.0
(n = 10)	[42]	[47]	[35]	[32]	[35]	[34]	[32]
150	86.6 ± 41.1	160 ± 61.0	113 ± 37.5	439 ± 121	675 ± 225	1.70 ± 0.62	63.5 ± 20.7
(n = 9)	[47]	[38]	[33]	[28]	[33]	[36]	[33]
175	92.9 ± 33.3	162 ± 42.2	123 ± 27.6	446 ± 126	737 ± 166	1.70 ± 0.30	57.8 ± 21.4
(n = 9)	[36]	[26]	[23]	[28]	[23]	[18]	[37]
HP5503/25							
100	55.2 ± 25.2	129 ± 42.0	78.4 ± 24.3	ND	465 ± 146	ND	95.9 ± 46.9
(n = 55/58)	[46]	[33]	[31]		[31]		
150	93.3 ± 50.7	197 ± 89.1	122 ± 48.0	ND	729 ± 282	ND	85.5 ± 50.3
(n = 55/58)	[54]	[45]	[39]		[39]		

Data expressed as mean ± SD [%coefficient of variation]; ND = not determined; n = number of observations

a) For study HP5503/25 C_{trough} was used to calculate the Fluctuation Index

b) Calculated from ratio of AUC_{τ} and AUC_{0-6h}

%CV = coefficient of variation in percent; SD = standard deviation.

Table 16: Pharmacokinetic parameters for tapentadol at steady-state after multiple dosing in subjects with pain (KF5503/04 and Study KF5503/08)

Dose (mg)	Pharmacokinetic parameters						
	C_{min} ng/mL	C_{max} ng/mL	$C_{avg,ss}$ ng/mL	AUC_{0-6h} ng·h/mL	AUC_{τ} ng·h/mL	Accumulation ratio	Fluctuation index
Fasted							
43 n = 19	27.3 ± 10.1	60.3 ± 21.1	41.6 ± 13.6	122 ± 39.4	250 ± 81.4	2.13 ± 0.57	80.6 ± 34.3
	[37]	[35]	[33]	[32]	[33]	[27]	[43]
Fed							
21 (n = 22)	10.3 ± 4.6	26.5 ± 12.6	16.3 ± 7.3	57.5 ± 23.3	97.8 ± 44.0	1.8 ± 0.7	99.4 ± 32.3
	[44]	[48]	[45]	[41]	[45]	[39]	[33]
43 (n = 23)	20.4 ± 7.2	46.6 ± 13.8	30.6 ± 9.1	105.8 ± 37.5	184 ± 54.7	1.9 ± 0.6	87.3 ± 33.8
	[35]	[30]	[30]	[35]	[30]	[32]	[39]

Data expressed as mean ± SD (%coefficient of variation)

%CV = coefficient of variation in percent; n = number of observations; SD = standard deviation

Pharmacokinetics in the target population

Exposure of tapentadol in healthy subjects and subjects with pain after administration of the tablet formulation

Pharmacokinetic information was derived in the following studies after administration of the tapentadol IR tablet:

• The pivotal bioequivalence Study HP5503/24 in healthy subjects.

• The pivotal food effect Study HP5503/34 in healthy subjects.

• The thorough QT Study HP5503/25 with over encapsulated IR tablets in healthy subjects.

• The Phase III efficacy studies with over encapsulated IR tablets in subjects with moderate to severe acute pain: KF5503/31, KF5503/32, KF5503/35 and KF5503/37.

The pharmacokinetic parameters of tapentadol obtained after administration of the tapentadol IR tablet in the Phase I studies HP5503/24, HP5503/25 and HP5503/34 are listed in Table 17. The concentration-related parameters have been dose-normalised to a 100 mg dose for ease of comparison.

Table 17: Dose-normalised (to 100 mg) pharmacokinetic parameters of tapentadol after administration of tapentadol IR tablets in the fasted state to healthy male and female subjects (HP5503/24, HP5503/25 and HP5503/34)

Study	Dose	n	t_{max}, h	DN-C_{max}, ng/mL	DN-AUC_{∞}, ng.h/mL	$t_{1/2}$, h
Single dose						
HP5503/34	100 mg	34	1.50 (1.00 – 4.00)	72.8 ± 30.8 [42.4%]	429 ± 154 [35.9%]	4.2 ± 0.4
HP5503/24	80 mg	30	1.00 (0.50 – 4.00)	95.8 ± 28.1 [29.3%]	408 ± 106 [26.1%]	4.0 ± 0.5
Repeat dose (steady-state)						
HP5503/25	100 mg	58	1.45 (0.87 – 6.00)	129 ± 42.0 [32.6%]	465 ± 146[a] [31.4%]	3.7 ± 0.9[b]
	150 mg	58	1.49 (0.4 – 6.02)	131 ± 59.4 [45.3]	486 ± 188[a] [38.7]	3.7 ± 0.9[c]

Data expressed as mean ± SD [% CV]. except for t_{max}: median (range)

a) AUCτ; b) n=53; c) n=52

%CV = coefficient of variation in percent; DN = dose-normalized to 100 mg; h = hour; n = number of subjects

The dose-normalised AUC was similar for Studies HP5503/24 and HP5503/34, whereas C_{max} was lower in Study HP5503/34 than in Study HP5503/24. The %CV was higher in Study HP5503/34 than in Study HP5503/24. Differences of this magnitude occur frequently when comparing across trials, although the protocols of the studies were identical concerning, for example, the sampling scheme, fasting requirements and posture; the demographics of the study populations were also comparable. The $t_{1/2}$ and t_{max} estimates were comparable in both studies.

The data shown from Study HP5503/25 refer to steady-state values in each case. The similarity between AUC_{τ} observed at steady-state in HP5503/25 and AUC_{∞} after single-dose in HP5503/34 and HP5503/24 gives further support to the claim that the pharmacokinetics of tapentadol are time-independent.

Descriptive statistics of exposure after administration of the IR tablet in the Phase III studies is provided in Table 18. Once again, the concentrations have been dose normalised to a dose of 100 mg for ease of comparison. The sparse blood sampling schemes adopted in these Phase III studies were similar. Thus, pharmacokinetic samples were collected on Day 1 at approximately 1 hour and 3 hours after the first study drug administration and pre-dose and approximately 2 hours after the third study drug administration on Day 2 (in studies KF5503/35 and KF5503/37 one-half of the subjects had samples taken on Day 2 and the remaining half on Day 3). Study drug was administered as a single, oral dose once every 4 to 6 hours. In the event that the subject had pain which was not adequately managed with the first dose of study drug, the second dose could have been administered as early as 1 hour after but no later than 6 hours after the first study drug administration ("early second dose"). These data indicate that the IR tablet formulation of tapentadol performs consistently and predictably between studies and dose levels, both in healthy subjects and in subjects with moderate to severe acute pain.

Table 18: Dose-normalised (to 100 mg) serum tapentadol concentrations after administration of IR tablets (KF5503/31, KF5503/32, KF5503/35, KF5503/37)

	Day 1				Day 2			
	1 h post-dose		3 h post-dose		Predose		2 h post-dose	
Dose	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD	n	Mean ± SD
KF5503/31								
50 mg	50	40.2 ± 51.0	46	72.8 ± 52.0	30	133 ± 76.0	34	159 ± 68.0
75 mg	40	25.2 ± 31.6	41	62.7 ± 67.1	25	111 ± 72.0	21	140 ± 73.7
100 mg	43	34.8 ± 53.1	42	86.3 ± 65.2	26	156 ± 84.7	25	180 ± 99.9
KF5503/32								
50 mg	103	53.0 ± 50.7	101	83.7 ± 44.9	80	70.7 ± 29.2	85	116 ± 49.4
75 mg	113	54.4 ± 55.5	109	72.4 ± 33.1	94	78.6 ± 35.9	97	132 ± 53.4
100 mg	103	63.7 ± 60.9	103	72.9 ± 37.7	88	80.4 ± 36.2	91	123 ± 49.7
KF5503/35								
50 mg	155	33.4 ± 41.2	152	63.3 ± 51.9	55	91.3 ± 52.4	56	154 ± 63.1
					65[a]	70.4 ± 40.2[a]	65[a]	129 ± 55.1[a]
75 mg	158	23.6 ± 34.5	156	55.7 ± 39.1	54	83.9 ± 43.3	54	136 ± 62.5
					70[a]	75.3 ± 34.6[a]	74[a]	129 ± 49.2[a]
100 mg	155	28.7 ± 47.3	154	58.5 ± 39.0	69	95.8 ± 45.2	71	155 ± 67.0
					53[a]	86.1 ± 54.8[a]	55[a]	136 ± 58.6[a]
KF5503/37								
75 mg	81	81.7 ± 55.5	75	79.3 ± 36.5	44	67.3 ± 32.3	46	136 ± 51.6
					28[a]	61.8 ± 20.5[a]	30[a]	141 ± 54.4[a]

a) Day 3.

h = hour(s); n = number of subjects; SD = standard deviation

Special populations

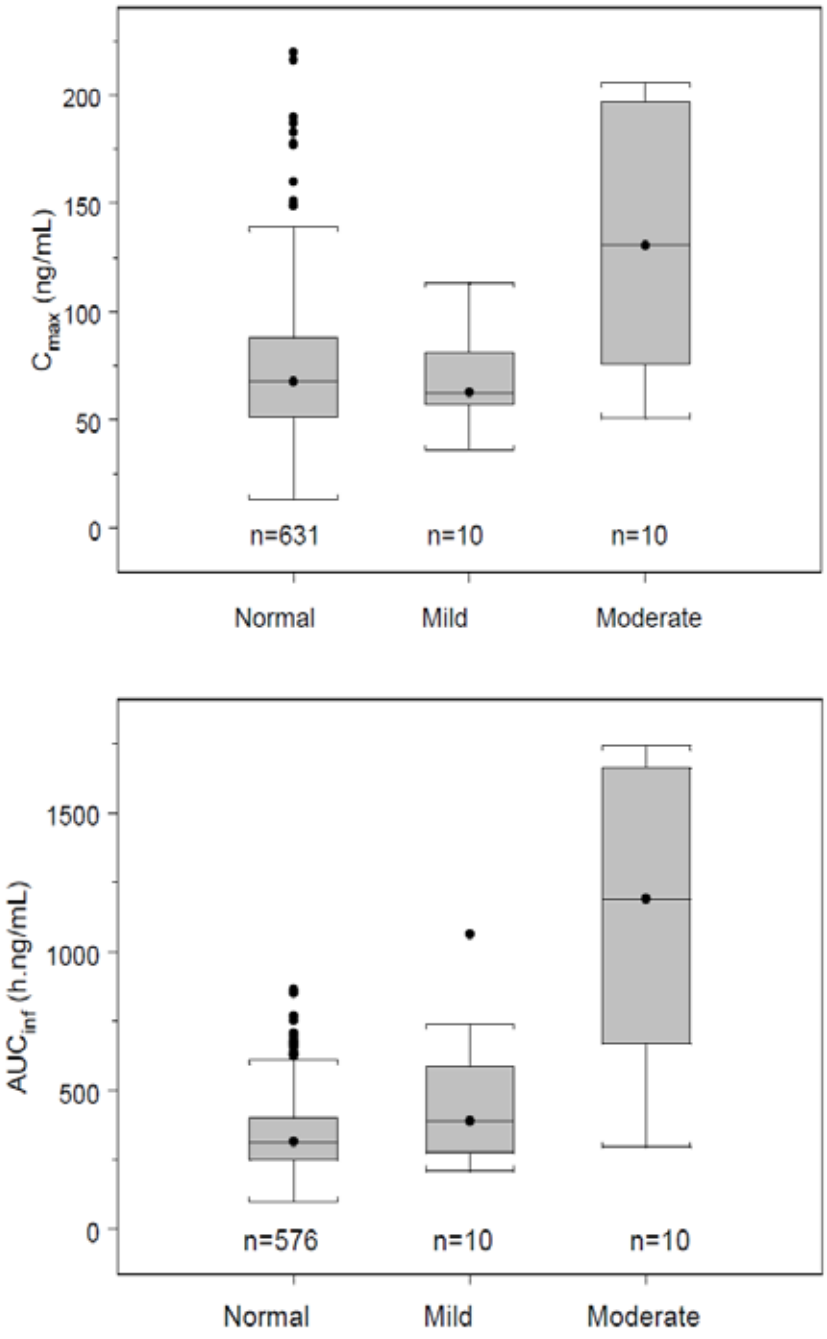
Effect of hepatic impairment

The effects of mild and moderate hepatic impairment on the pharmacokinetics of tapentadol were investigated in a single-dose study (HP5503/16). Dose proportionality in tapentadol pharmacokinetics has been established in healthy subjects over the relevant dose range but has not been investigated in hepatic impaired subjects. Therefore, to compare results from the hepatic impairment study with other Phase I trials, pharmacokinetic parameters were dose-normalised to the 80 mg dose used in the hepatic impairment study.

In the cross-study comparison, total systemic exposure (AUC_∞ [mean ± SD]) to tapentadol was approximately 1.4-fold and 3.5-fold higher in subjects with mild (477 ± 266 ng·h/mL) and moderate hepatic (1171 ± 516 ng•h/mL) impairment, respectively, compared to subjects with normal (334 ± 114 ng·h/mL) hepatic function.

The elimination half-life of tapentadol increased with decreasing hepatic function, such that subjects with moderate hepatic impairment exhibited the longest $t_{1/2}$ (mean ± SD) of 6.2 ± 1.5 hours compared to those with normal hepatic function (4.3 ± 0.76 hours) or mild hepatic impairment (5.1 ± 0.9 hours). The dose normalised C_{max} of tapentadol was almost similar in subjects with normal hepatic function (72.0 ± 29.0 ng/mL) and mild (66.9 ± 22.4 ng/mL) hepatic impairment but was 1.8-fold increased in subjects with moderate hepatic impairment (132 ± 58.6 ng/mL) (see Figure 4).

Figure 4: Normalised (to 80 mg) tapentadol C_{max} and AUC_{∞} in healthy subjects and subjects with varying degree of hepatic impairment (HP5503/16, dataset for cross-study comparison)



n = number of observations

Source: post-hoc evaluation (data on file)

Overall, these data indicate that tapentadol can be safely administered to subjects with mild hepatic impairment without dose adjustment. Subjects with moderate hepatic impairment should use tapentadol with caution. It is proposed that pain treatment of these subjects should be initiated at a dose of 50 mg with a dosing interval of no less than every 8 hours (a maximum of 3 doses in 24 hours). Subjects with severe hepatic impairment were not studied.

Effect of renal impairment

Tapentadol

The effects of mild, moderate and severe renal impairment on the pharmacokinetics of tapentadol were investigated in a single-dose study (HP5503/15). Dose proportionality for tapentadol pharmacokinetics has been established in healthy subjects over the relevant dose range but has not been investigated in subjects with renal impairment. Therefore, to compare results from the renal impairment study with other Phase I trials, pharmacokinetic parameters were dose-normalised to the 80 mg dose used in the renal impairment study.

The dose normalized C_{max} was similar in all groups (see Figure 5). Also, the total systemic exposure (AUC_{∞}) was similar regardless of renal function. In subjects with mild to moderate renal impairment, the average elimination half-life for tapentadol was in the range of 5.1 hours to 5.4 hours, which is 18% to 26% higher than the half-life observed in healthy subjects (4.3 hours). This limited increase in $t_{1/2}$ is likely to have only a limited impact on accumulation of tapentadol after multiple dosing at steady-state.

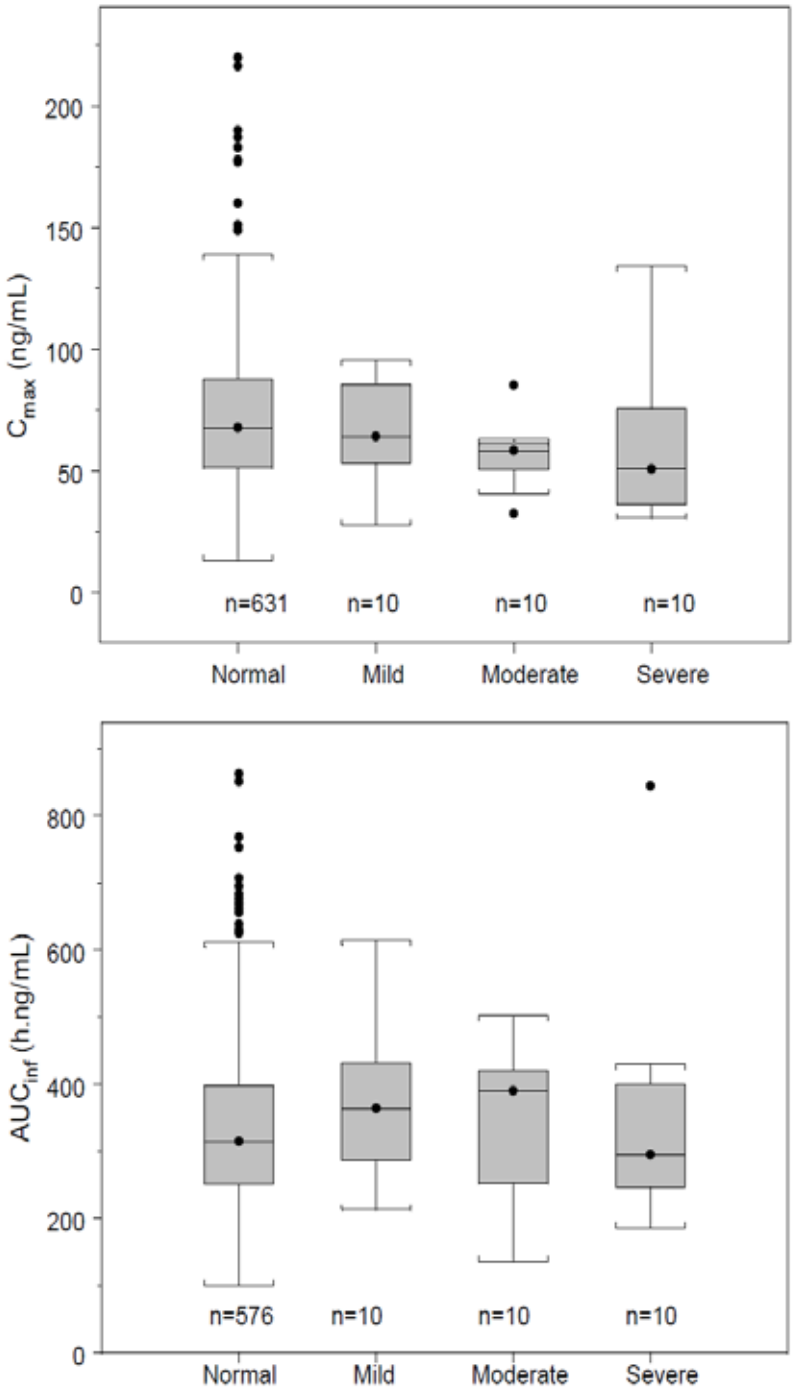
No dose modifications based on renal function status alone is warranted.

Tapentadol-O-glucuronide

Tapentadol-O-glucuronide is the major metabolite of tapentadol and it is almost exclusively excreted in the urine. A clear impact of renal function on the pharmacokinetics of the glucuronide was observed compared to its parent drug. Tapentadol-O-glucuronide elimination half-life and AUC_{∞} increased with increasing degree of renal impairment. In the cross-study comparison, AUC and $t_{1/2}$ increase with an increased level of renal impairment, whereas values for t_{max} and C_{max} only clearly increased for subjects with severe renal impairment (see Table 19). In subjects with moderate and severe renal impairment, the elimination half-life of tapentadol-O-glucuronide compared to healthy control subjects increased 1.7-fold and 3.6-fold, respectively and AUC_{∞} was increased 2.7 times and 6.3 times, respectively (ratio of arithmetic means). The t_{max} in subjects with moderate renal impairment was in the same range as the healthy subjects and subjects with mild impairment. The C_{max} of tapentadol-O-glucuronide was 1.15-fold and 1.16-fold higher in subjects with mild and moderate renal impairment, respectively, as compared to C_{max} in normal subjects (ratios of arithmetic means). The impact on the pharmacokinetics of the glucuronide metabolite was more pronounced in the subjects with severe renal impairment and all pharmacokinetic parameters relating to exposure and t_{max} were increased in this subject group, showing the importance of renal function on the pharmacokinetics of the glucuronide metabolite.

Overall, these data indicate that tapentadol can be safely administered to subjects with mild or moderate renal impairment. Because of the accumulation potential of tapentadol-O-glucuronide in subjects with severe renal impairment, the use of tapentadol is not recommended in this population.

Figure 5: Dose normalised (to 80 mg) tapentadol C_{max} and AUC_{∞} in healthy subjects and subjects with varying degree of renal impairment



n = number of observations

Table 19: Dose normalised (to 80 mg) pharmacokinetic parameters for tapentadol-O glucuronide in healthy subjects and in subjects with various degree of impaired renal function (HP5503/15, dataset for cross-study comparison)

	Renal function			
Parameter [a]	Normal	Mild impairment	Moderate impairment	Severe impairment
t_{max}, h	1.50 (1.00 – 5.95) (n = 266)	1.50 (1.00 – 2.02) (n = 10)	1.51(1.00 – 6.00) (n = 10)	3.50 (1.50 – 9.00) (n = 10)
C_{max}, ng/mL	2731 ± 654 [25] (n = 266)	3134 ± 1094 [35] (n = 10)	3180 ± 875 [28] (n = 10)	3472 ± 734 [20] (n = 10)
AUC_{∞}, ng•h/mL	13495 ± 2638 [20](n = 212)	21258 ± 6486 [31] (n = 10)	36191 ± 11874 [33] (n = 10)	84942 ± 52258 [61] (n = 10)
$t_{1/2}$, h	3.9 ± 0.5 [13](n = 212)	5.1 ± 1.6 [32] (n = 10)	6.7 ± 2.0 [30] (n = 10)	14.2 ± 8.0 [30] (n = 10)

a) Data expressed as mean ± SD [%CV], except for t_{max} where median (range) is provided.
%CV = coefficient of variation in percent; n = number of observations ; SD = standard deviation.

Pharmacokinetics of tapentadol in men and women

No specific study was performed to investigate the effect of sex on the pharmacokinetics of tapentadol. The pooled pharmacokinetic data of tapentadol from Phase I studies was used to compare the pharmacokinetics of tapentadol in healthy, fasted men and women. The effect of sex on tapentadol pharmacokinetics was also evaluated in a population pharmacokinetic analysis. The clearance after oral tapentadol was just marginally higher in men than in women after adjusting the calculated estimates for all covariates that could impact the clearance of tapentadol.

Hence, dose adjustment is not warranted based on sex.

Effect of age on the pharmacokinetics of tapentadol

The pharmacokinetics of tapentadol in the elderly population has been explored in a specific clinical pharmacology study comparing the pharmacokinetics of tapentadol in healthy young adults and elderly subjects. A cross-study comparison of data from Phase I studies is presented in Table 20.

Generally, the overall systemic exposure to tapentadol (AUC_{∞}) is similar in elderly subjects compared to young adults and mid-aged subjects. Maximum serum concentrations show a limited tendency to decrease in these subpopulations, suggesting that age-related changes in physiology have little impact on the pharmacokinetics of tapentadol following oral administration.

The influence of age on tapentadol pharmacokinetics was further explored using population pharmacokinetic analysis. Age was not identified as a clinically significant factor for the clearance of tapentadol; hence, dose adjustment based upon age is not warranted.

Table 20: Dose normalised (to 100 mg) pharmacokinetic parameters for tapentadol in young, mid-aged and elderly subjects (dataset for cross-study comparison)

Parameter [a]	Young adult 18 y – 45 y	Mid aged 46 y – 64 y	Elderly ≥65 y
t_{max}, h	1.22 (0.50 – 6.27)	1.50 (0.75 – 4.00)	1.26 (1.00 – 2.00)
	(n = 521)	(n = 94)	(n = 16)
C_{max}, ng/mL	91.0 ± 36.3	86.5 ± 37.1	79.8 ± 23.4
	[40] (n = 521)	[43] (n = 94)	[29] (n = 16)
AUC_{∞}, ng·h/mL	418 ± 141	415 ± 156	415 ± 113
	[34] (n = 466)	[38] (n = 94)	[27] (n = 16)
$t_{1/2}$, h	4.2 ± 0.8	4.4 ± 0.6	4.6 ± 0.5
	[19] (n = 466)	[14] (n = 94)	[10] (n = 16)
CL_R, mL/min	108 ± 40.2	99.8 ± 36.3	76.8 ± 20.0
	[38] (n = 39)	[36] (n = 23)	[26] (n = 16)
CRCL, mL/min[a]	115 ± 22.5	97.8 ± 18.3	77.7 ± 13.3
	[20] (n = 579)	[19] (n = 107)	[17] (n = 21)

Data expressed as mean ± SD [%CV], except for t_{max} where median (range) is provided; CRCL was calculated using the Cockcroft-Gault equation.

Age ranges are defined by those set in the study in elderly subjects Module 5.3.3.3 HP5503/30.

a) Calculated post-hoc according to Cockcroft and Gault (1976)

%CV = coefficient of variation in percent; n = number of observations; SD = standard deviation; y = years; CRCL = creatinine clearance.

Effects of body weight

No clinical pharmacology studies were conducted to evaluate the effects of body weight on the pharmacokinetics of tapentadol. A population pharmacokinetic analysis of tapentadol indicated that body weight might have an influence on the pharmacokinetics of tapentadol. With increasing body weight, it was observed that both the oral clearance and central volume of distribution of tapentadol increased slightly. However, no dose modification based on body weight is warranted.

Effects of race

No clinical studies were conducted to directly compare the effects of race on the pharmacokinetics of tapentadol. In healthy Japanese men, the pharmacokinetics of tapentadol is similar to that observed in the Phase I data (HP5503/48). The population pharmacokinetic model predicted that the clearance of tapentadol in Black subjects, Hispanic-Latinos and other combined non-White racial groups was approximately 17%, 11% and 15% lower, respectively, compared to that predicted in White subjects. The race effect is of no clinical relevance; hence dose adjustment is not required.

Interactions

At concentrations close to those in clinical practice, non-steroidal anti-inflammatory drugs (NSAIDs), certain azole drugs and chloramphenicol were able to slightly inhibit the glucuronidation of tapentadol in *in vitro* systems. Probenecid and naproxen showed the highest inhibitory potential of 45% and 27%, respectively, towards the glucuronidation of tapentadol *in vitro*.

Concomitant administration of probenecid 500 mg twice daily resulted in an increased C_{max} for tapentadol by 30% and the tapentadol exposure (AUC) was increased by 57%. These data indicate that tapentadol metabolism was affected by probenecid. There was no evidence of any substantial changes in the renal elimination of tapentadol or its major metabolite (tapentadol-O-glucuronide) that could have resulted from the presence of probenecid.

Probenecid, a typical transport inhibitor, did not reduce urinary output of tapentadol-O-glucuronide.

There was a 17% increase of the AUC of tapentadol on co-administration of naproxen (500 mg twice daily for 2 days) with a single oral dose of tapentadol. There was no significant effect on the C_{max} of tapentadol.

Acetylsalicylic acid (at 325 mg once per day for 2 days) did not significantly affect the pharmacokinetics of tapentadol.

Paracetamol enhanced the rate of glucuronidation of tapentadol *in vitro*, however, no relevant effect of paracetamol co-administration on the pharmacokinetics of tapentadol or tapentadol-O-glucuronide was observed in healthy subjects

Changes in gastrointestinal transit time induced by co-administered drugs (for example, metoclopramide) could possibly affect the absorption of drugs. Metoclopramide, however, did not affect the pharmacokinetics of tapentadol, indicating that gastrointestinal transit time has no influence on the absorption of tapentadol (HP5503/19).

Omeprazole, which changes the gastric pH, did not affect the pharmacokinetics of tapentadol to a clinically relevant extent (HP5503/20).

A population pharmacokinetic analysis showed no evidence that concomitant administration of ibuprofen, Vicodin (hydrocodone combined with paracetamol), metoclopramide, paracetamol and ketorolac affect the pharmacokinetics of tapentadol.

Evaluator's overall conclusions on pharmacokinetics

- Following a single oral dose of tapentadol IR, the serum concentrations of tapentadol rise quickly to reach a maximum concentration at around 1.25 hours (range 0.50 hours to 6.27 hours) after intake.
- Oral absorption of tapentadol is almost complete as evidenced by the urinary excretion of 99% of an oral dose of radioactively labelled medication.
- Under fasted conditions, the absolute oral bioavailability of tapentadol is approximately 32% due to a high first pass metabolism.
- Plasma protein binding of tapentadol is approximately 20% and protein binding is independent of drug concentration.
- Tapentadol is mainly metabolised by glucuronidation and to a smaller extent by sulfation and Phase1 oxidative pathways. The serum concentrations of the main metabolite tapentadol-O-glucuronide, which has no analgesic activity, are considerably (24-fold) higher than those of tapentadol.
- *In-vitro* studies did not reveal a potential of tapentadol to either inhibit or induce cytochrome P450 enzymes.
- Total serum clearance of tapentadol is 1530 ± 177 mL/min (or 91.9 ± 10.6 L/h) and the terminal elimination half-life (after oral administration) is on average 4.3 ± 0.8 hours. The tapentadol-O-glucuronide metabolite exhibits a similar terminal elimination half-life.
- Elimination of tapentadol occurs almost exclusively as drug-conjugates, with 96% of the administered oral dose excreted in urine as metabolites. Approximately 3% of the administered oral dose is excreted in the urine as unchanged drug.

- The pharmacokinetics of tapentadol following multiple doses of tapentadol IR are predictable from single-dose pharmacokinetic data and are associated with a low degree of inter-subject variability (around 34%) for systemic exposure (AUC).
- Steady-state serum concentration levels are attained within 1 day (about 5 times the half-life) in most subjects. Following multiple dosing every 6 hours, the accumulation ratio for tapentadol ranged from 1.4 to 1.7 and is predictable from single-dose pharmacokinetics. The mean accumulation ratio ranged from 1.7 to 2.0 for the major metabolite tapentadol-O-glucuronide in subjects with normal renal function.

Special populations

• Exposure to tapentadol is similar for young adult (18 years to 45 years of age) and elderly (≥65 years of age) subjects. The effect of age on the pharmacokinetics of tapentadol is considered to be of no clinical significance. It is considered appropriate that dose adjustment based upon age is not warranted.

• There is no clinically relevant difference in the pharmacokinetics of tapentadol in men and women.

• Exposure and peak serum concentrations of tapentadol were increased in subjects with mild or moderate hepatic impairment, whereas the maximum concentrations of the metabolite, tapentadol-O-glucuronide, were decreased in subjects with moderate liver impairment. The ratios of tapentadol pharmacokinetic parameters for subjects with mild or moderate hepatic impairment in comparison to subjects with normal hepatic function were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. Subjects with severe hepatic impairment were not studied.

It is considered that dose adjustment should be made for patients with moderate hepatic impairment and that tapentadol should not be used in patients with severe hepatic impairment. This is in line with recommendations in the proposed Product Information (PI).

• Exposure and peak serum concentrations of tapentadol were similar in subjects with mild, moderate or severe renal impairment. In contrast, increased exposure to tapentadol-O-glucuronide was observed with an increasing degree of renal impairment. In subjects with mild, moderate and severe renal impairment, the AUC_{∞} of tapentadol-O-glucuronide was 1.5-fold, 2.5-fold and 5.5-fold higher as compared to subjects with normal renal function, respectively.

It is considered that tapentadol should not be used in patients with severe renal impairment. This is in line with recommendation in the proposed PI.

• Healthy subjects and subjects with acute pain have similar pharmacokinetics of tapentadol.

Extrinsic factors

• No absorption-related drug-drug interactions were observed with tapentadol IR when gastric pH or upper gastro-intestinal motility was changed by concomitant administration of omeprazole or metoclopramide respectively.

• The C_{max} and AUC of tapentadol increased by 16% and 25%, respectively, when tapentadol IR was dosed with a high-fat high-calorie meal. The effect of concomitant food intake on the pharmacokinetics of tapentadol is considered to be of no clinical significance and tapentadol IR may be given with or without food.

• In clinical pharmacokinetic drug-drug interaction studies with the probe drugs naproxen) and probenecid, increases in tapentadol AUC of 17% and 57%, respectively, were observed. These increases in exposure to tapentadol require no specific measures for the use of tapentadol in combination with naproxen or probenecid. The pharmacokinetic parameters of tapentadol were not changed when paracetamol or acetylsalicylic acid were administered concomitantly.

Introduction Tapentadol IR Pharmacodynamics

The evaluation of the pharmacodynamics of tapentadol included static and dynamic pupillometry, the assessment of a potential effect on the QT and QTc intervals, the orocaecal transit time, the effect on sex hormone concentrations, an assessment of the potential for drug liking and experimental pain models using laser- and mechano-somatosensory evoked potentials.

Mechanism of action

Tapentadol hydrochloride has been developed for the relief of moderate to severe acute pain. The centrally active analgesic agent has an apparent dual-mode of action.

Tapentadol is a mu-opioid receptor agonist with a K_i (mean ± SD) of 0.16 ± 0.04 μM, compared to morphine with a mean Ki of 0.009 ± 0.0035 μM, for the human mu-opioid receptor. In the guanosine 5′-O-(3-thiotriphosphate) (GTPγS) assay using membranes from cells expressing recombinant human μ-opioid receptors, the potency (mean EC50 ± SD) of tapentadol is 0.67 ± 0.15 μM, compared to 0.022 ± 0.003 μM for morphine. Tapentadol also inhibits, *in vitro*, the reuptake of noradrenaline via the noradrenaline transporter. Both mechanisms are likely to contribute to the analgesic effects of the compound.

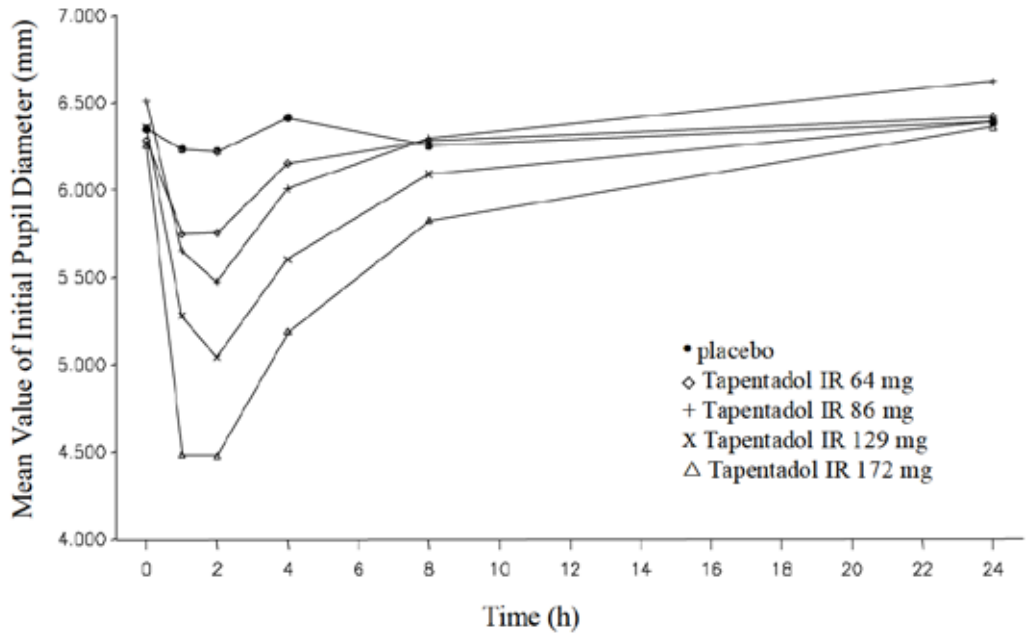
Results of individual studies

HP5503/03: Pharmacodynamic effects of pupillometry after single oral administration of tapentadol at 4 escalating doses (Phase I)

Study HP5503/03 was a randomised, escalating single-dose, double-blind, placebo-controlled study to evaluate the pharmacodynamic effects of tapentadol on static and dynamic pupillometric parameters as biomarkers for central mu-opioid agonistic action. This study also assessed the pharmacokinetics and dose linearity of tapentadol Thirty three healthy subjects (both men and women) in the age range of 18 years to 44 years old were enrolled, of which 32 subjects completed the study. Subjects received tapentadol 64, 86, 129 and 172 mg or placebo. Static and dynamic pupillometry was performed before and 1, 2, 4, 8 and 24 hours after intake.

Results: Tapentadol induced a dose and time-dependent effect on pupillometric parameters (that is, the initial diameter), which is typically observed following mu-opioid agonist dosing (see Figure 6). A maximum decrease in initial pupil diameter was evident at 1 hour to 2 hours after intake, which coincides with the time of maximum serum concentrations of tapentadol, with a subsequent gradual return to baseline value after 8 hours to 24 hours. Hence, pupillometry can be used as a surrogate to measure mu-opioid agonist activity.

Figure 6: Effects of different doses of tapentadol and placebo on initial pupil diameter (HP5503/03)

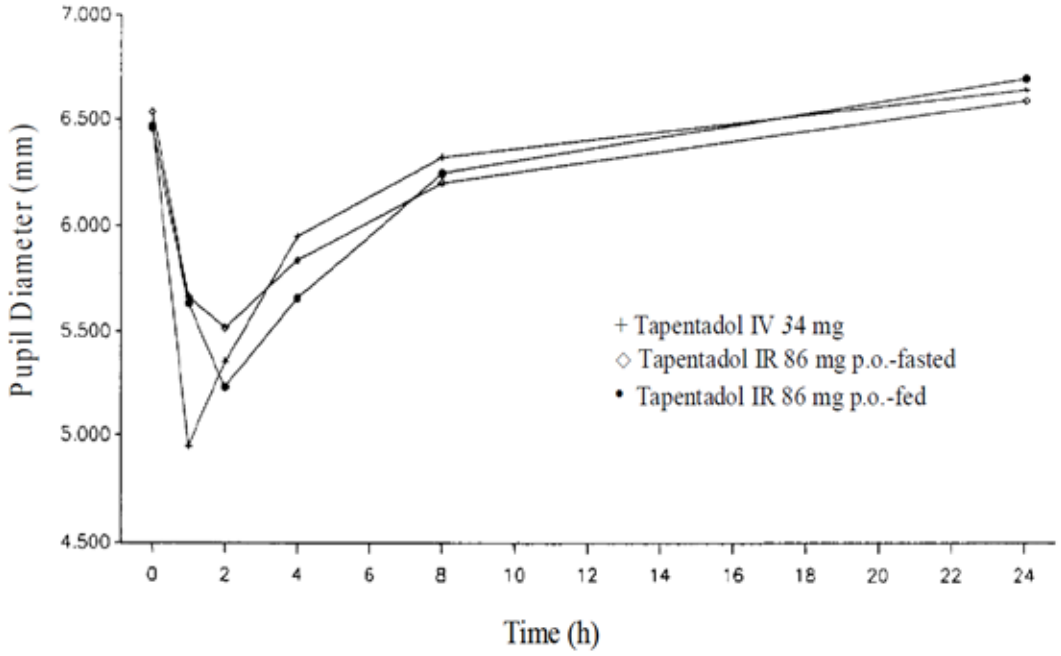


HP5503/04: An assessment of the pharmacodynamic effects of tapentadol on pupillometric parameters (Phase I)

Study HP5503/04 was a randomised, single-centre, single-dose, 3- way cross over Phase I study in 24 healthy men. The primary objective of this study was to evaluate the basic pharmacokinetic parameters of tapentadol in healthy men. In addition, the central mu-opioid activity of tapentadol was to be characterised by means of static pupillometry (initial pupil diameter). Subjects received the following treatments: an intravenous infusion of 34 mg tapentadol over 15 minutes, an oral administration of 86 mg tapentadol IR in the fasted state or an oral administration of 86 mg tapentadol after a continental breakfast. Static and dynamic pupillometry was performed before and 1, 2, 4, 8 and 24 hours after administration.

Results: Tapentadol exposure led to pharmacodynamic effects typical for mu-opioid agonist type drugs. Pupillometric measurements showed a time-dependent decrease in initial pupil diameter (see Figure 7) and time of constriction. The maximum decrease in initial pupil diameter was observed after 34 mg intravenous infusion of tapentadol at 1 hour after start of dosing (first observation point). The effect gradually returns to baseline values 8 to 24 hours after dosing. After oral administration of 86 mg tapentadol, the maximum observed effects are observed slightly later, about 2 hours after dosing, which parallels the time concentration profile of tapentadol IR. In the presence of food, the observed effects were slightly increased, reflecting the higher serum concentrations of tapentadol in the presence of food.

Figure 7: Time course of effects on initial pupil diameter after different administrations of tapentadol to healthy men (Study HP5503/04)



HP5503/09: Effect of tapentadol at 43 mg or 86 mg dose on orocaecal transit time and sex hormones (Phase I)

Study HP5503/09 was a randomised, single-centre, single-dose, double-blind, placebo- and morphine-controlled, 4-way cross-over study to determine the effect of tapentadol IR 43 mg and tapentadol IR 86 mg, or a presumed equianalgesic dose of morphine sulfate IR 40 mg on OCTT. OCTT was determined by lactulose hydrogen breath test. This study also assessed the concentrations of sex hormones (luteinizing hormone, testosterone) and the basic pharmacokinetic parameters of tapentadol in 24 healthy men in the age range of 26 years to 49 years. Blood samples for the determination of sex hormones were taken predose and 2 hours, 4 hours and 6 hours after study drug administration.

Results: OCTT: The non-parametric analysis revealed a less pronounced effect on OCTT following treatment with tapentadol IR 43 mg than with morphine sulfate IR 40 mg (point estimate: 83.93%), whereas treatment with tapentadol IR 86 mg resulted in a comparable effect on OCTT as morphine sulfate IR 40 mg (point estimate: 99.96%). Comparing the pair-wise treatment ratios of 43 mg and 86 mg tapentadol IR, respectively, to placebo showed a dose-dependent increase of OCTT from 148.73% to 197.75% (see Table 27 below).

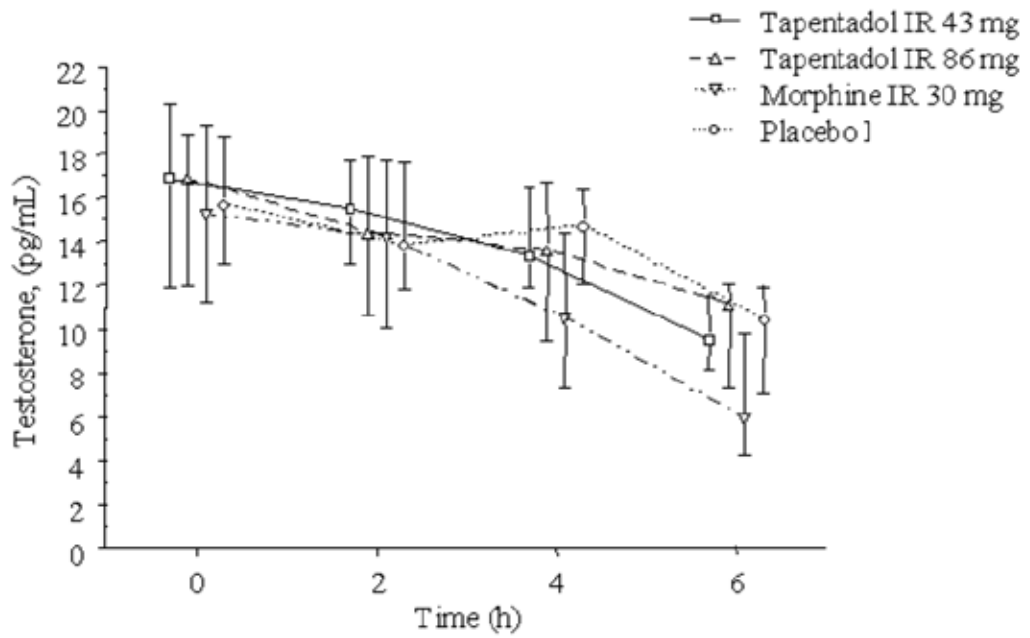
Sex hormones: Total testosterone and free testosterone decreased from predose up to 6 hours after administration in all treatment periods including the placebo arm (see Figure 8). The decrease was more pronounced after intake of morphine sulfate IR, with several testosterone concentrations below the reference range at 6 hours post-dose, whereas there was no difference in testosterone serum concentrations after intake of 43 mg or 86 mg tapentadol IR and placebo.

Table 27: Point estimates for the ratio of the orocaecal transit time median values including the non-parametric 95% confidence interval (HP5503/09) (per protocol set [N = 23])

Comparison	Ratio, %	95% CI
Tapentadol 43 mg/placebo	148.73	117.30 – 200.00
Tapentadol 43 mg/morphine sulfate IR 40 mg	83.93	69.01 – 100.67
Tapentadol 86 mg/placebo	197.75	153.41 – 243.97
Tapentadol 86 mg/morphine sulfate IR 40 mg	99.96	86.02 – 120.88

CI = confidence interval

Figure 8: Medians and quartiles of free testosterone following either single dose tapentadol, morphine sulfate IR or placebo (HP5503/09)



The normal range in healthy men is: age 18 to 39 years: 8.8 to 27 pg/mL; age 40 years to 59 years: 7.2 pg/mL to 23 pg/mL

Luteinizing hormone serum concentrations remained constant over time from predose up to 6 hours after intake of 43 mg or 86 mg tapentadol or placebo (medians for the three treatments at 6 hours post-dose ranged from 3.6 mIU/mL to 3.9 mIU/mL). By contrast, luteinizing hormone serum concentrations were clearly decreased at 4 and 6 hours after administration of morphine sulfate IR 40 mg. The median serum luteinizing hormone concentration at 6 hours after intake of morphine sulfate IR 40 mg is clearly decreased to 1.7 mIU/mL, which is at the lower limit of the reference range for men aged 20 to 70 years old (range 1.5 mIU/mL-9.5 mIU/mL).

HP5503/13: Effect on pupillometry and sex hormones following ascending single and multiple doses of tapentadol IR (Phase I)

Study HP5503/13 was a single-centre, randomised, double-blind, placebo-controlled, four-period dose-escalation study (tapentadol IR 75 mg to a planned upper dose of 250 mg, 6 hourly for 6 doses) in healthy men and women. Sixteen men and 16 women were included and 22 subjects remained by the time the study was terminated for operational reasons. Static pupillometry was assessed by measurement of the initial pupil diameter. Measurements were performed at regular time-points from pre-dose up to 54 hours after the first study drug administration. Testosterone and luteinizing hormone were measured for all men in this study pre-dose and 24 hours after dosing.

The study was terminated prematurely with the highest administered dose of 175 mg. The sponsor stopped the study before continuing with the next dose level (200 mg every 6 hours) because, according to the FDA, exposure in non-clinical toxicology studies was insufficient to support the safety of continued dose escalation in the clinical study until the agency had the opportunity to review the pharmacokinetic data from completed studies with tapentadol. The requested information was submitted to the FDA and the study remained suspended. It was decided to terminate the study as too much time had elapsed, which prevented reconstitution of the cohorts (which would have required major protocol amendments) and due to the desire not to restart dose titration from the initial dose level in new cohorts. Moreover, with the highest administered dose (175 mg every 6 hours), it was concluded that sufficient data was available to continue the development of tapentadol.

Results:

***Pupillometry*:** After administration of placebo, the mean initial pupil diameter, defined as the pupil diameter before presentation of the light stimulus, demonstrated minimal changes over the 54-hour assessment period. Following administration of the first dose of tapentadol IR, the mean maximum decrease in the initial diameter occurred at 2 or 4 hours in all treatments. The effect of tapentadol on initial pupil diameter was dose-related with the greatest effect after administration of tapentadol IR 175 mg. A maximum decrease occurred between 26 and 28 hours after the first dose (2 or 4 hours after the fifth dose), returning to baseline at 54 hours (approximately 24 hours after the last administration of study drug) in all tapentadol dose groups. There were no apparent differences between men and women in the pupillometric variables.

Sex hormone concentrations: The data revealed no clear trends in luteinizing hormone changes with respect to tapentadol IR dose. There was a slight increase in testosterone concentrations from baseline to the 24-hour time-point in the placebo group (mean increase of 0.86 nM/L). Testosterone concentrations decreased in all tapentadol IR dose groups in a dose-related manner up to the 150 mg dose, with mean decreases of 0.22 nM/L for tapentadol IR 75 mg, 3.19 nM/L for tapentadol IR 100 mg, 3.94 nM/L for tapentadol IR 125 mg, 7.37 nM/L for tapentadol IR 150 mg and 6.31 nM/L for tapentadol IR 175 mg. Upon analysis of differences within individual subjects, the results showed that concentrations of testosterone at 24 hours were consistently lower after administration of tapentadol IR compared with placebo.

HP5503/14: Drug liking of tapentadol IR compared to placebo and hydromorphone IR in opiate-experienced non-dependent subjects (Phase I)

Study HP5503/14 was a single-centre, single-dose, double-blind, double-dummy, placebo-controlled, randomised, 7-way cross-over study to evaluate the drug liking of tapentadol at doses of 50, 100 and 200 mg, compared to placebo and hydromorphone IR 4 mg, 8 mg and 16 mg in opiate-experienced but non-dependent recreational drug users. Pharmacodynamic assessments included Overall Drug Liking (Visual analog scale), Subjective Drug Value (questioning), Subjective Effects Visual analogue scale, Observer-rated single-dose questionnaire, Subject-rated Opiate Agonist Scale, Addiction Research Center Inventory, Divided Attention Test and Choice Reaction Time Test.

Results:

Pharmacodynamics: The drug liking, as demonstrated by the subjective effects following single-dose administration of tapentadol IR 50 mg, 100 mg and 200 mg, was shown to be different from that of placebo and similar to calculated equianalgesic doses of hydromorphone IR (4 mg, 8 mg and 16 mg) based on the pharmacodynamic assessments

performed in healthy men and women who were opiate-experienced but non-dependent recreational drug users. The following pharmacodynamic findings support this conclusion.

The mean peak Overall Drug Liking Score over 24 hours post-dose (primary endpoint) for all of the tapentadol IR dosages (50 mg, 100 mg and 200 mg), were significantly different from placebo. These scores were not different from the calculated equianalgesic doses of hydromorphone IR (4 mg, 8 mg and 16 mg).

Results for the secondary endpoints, whether positive, negative, sedative or other effects (Visual analogue scale – Any Drug Effect, Subjected-Rated Opioid Agonist Scale, Divided Attention Test, Choice Reaction Time and Observer-Rated Single-Dose Questionnaire), were consistent with the findings for the primary endpoint.

Single doses of tapentadol IR showed similar subjective effects to calculated equianalgesic doses of hydromorphone IR (tapentadol IR and hydromorphone IR were both distinct from placebo and their calculated equianalgesic doses were not different from each other).

The mean positive effect scores tended to reach the highest values at 1 to 2 hours post-dose for the tapentadol IR and hydromorphone IR groups, whereas the highest mean negative effect scores were observed at 2 to 6 hours post-dose for the tapentadol IR and hydromorphone IR groups. The delayed negative effects were similar between the calculated equianalgesic doses of tapentadol IR and hydromorphone IR.

In the Choice Reaction Time and Divided Attention tests, there was a tendency for subjects on the highest doses of both tapentadol IR and hydromorphone IR to have longer response latencies and decreased visual-motor coordination.

Overall, tapentadol IR showed a similar drug liking to that of estimated equianalgesic doses of hydromorphone IR in a study in opioid-experienced healthy subjects.

HP5503/25: Effect on QTc intervals in healthy subjects receiving multiple dosing tapentadol IR at therapeutic and supratherapeutic doses (Phase I)

Study HP5503/25 was a single-centre, double-blind, randomised, placebo- and positive-controlled, 4-way cross-over study in healthy subjects aged 25 to 64 years old. The primary objective of the study was to assess the effect of tapentadol on the 12 lead ECG QT interval duration corrected for heart rate (QTc) in healthy men and women receiving multiple doses of tapentadol IR at therapeutic (100 mg) and supratherapeutic (150 mg) doses. The secondary objectives were to evaluate the incidence of QT/QTc changes from baseline greater than 30 and 60 milliseconds, post-dose QTc values greater than 450, 480 and 500 milliseconds, changes in other ECG intervals (RR, QRS, PR) and to evaluate the pharmacokinetics of serum tapentadol and serum tapentadol-O-glucuronide. The pharmacokinetic analysis set was 68 subjects.

Tapentadol IR was tested at doses of 100 mg and 150 mg tapentadol every 6 hours on Day 1 and on Day 2 to achieve steady-state (total of 5 doses each). Moxifloxacin 400 mg was used as a positive control for the evaluation of QT/QTc to establish assay sensitivity. Serial 12-lead ECGs were taken immediately before and up to 12 hours after the last administration of study drug (steady-state) in the morning of Day 2 in each treatment period. Blood samples for the determination of tapentadol and tapentadol-O-glucuronide were collected from predose up to 36 hours after the first dose.

Results:

Pharmacokinetics: A summary of the mean serum pharmacokinetic parameters for tapentadol on Day 2 is presented in Table 28 below. Peak tapentadol serum concentrations

were reached at about 1.5 hours post-dose. The terminal half-life averaged 3.7 hours in both treatments, conforming to the results from previous studies with the tapentadol IR formulation.

Table 28: Pharmacokinetic parameters of tapentadol at steady-state (HP5503/25)

Parameter [b]	n	Tapentadol IR 100 mg	Tapentadol IR 150 mg
$t_{max,ss}$, h	58	1.45 (0.87 – 6.00)	1.49 (0.40 – 6.02)
$C_{max,ss}$, ng/mL	58	129 ± 42.0	197 ± 89.1
C_{trough}, ng/mL	55	55.2 ± 25.2	93.3 ± 50.7
$C_{avg,ss}$, ng/mL	58	78.4 ± 24.3	122 ± 48.0
AUC_{τ}, ng•h/mL	58	465 ± 146	729 ± 282
$t_{1/2}$, h	53[a]	3.7 ± 0.9	3.7 ± 0.9
CL_{ss}/F, mL/min	58	3969 ± 1351	3820 ± 1176

a) tapentadol IR 150 mg, $t_{1/2}$: n = 52; b) Data expressed as mean ± SD, except for t_{max} where median (range) is provided

n = number of subjects; SD = standard deviation

Pharmacodynamics: The upper limits of the 90% confidence interval for the difference in mean ΔQTcF[24] between tapentadol IR 100 mg and placebo were below 10 ms for all time-points. The same was seen for the difference in means between tapentadol IR 150 mg and placebo (see Table 29).

No effect of therapeutic (100 mg) and supratherapeutic (150 mg) doses of tapentadol IR on the QT interval were shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology). Thus, tapentadol IR is deemed non-inferior to placebo with regard to QTc prolongation. The assay sensitivity of the study was validated by the expected QTc prolongation observed after moxifloxacin treatment.

Table 29: Pairwise comparison from modelling of change from baseline in QTc intervals – Fridericia correction (HP5503/25: Pharmacodynamics analysis set)

[24] QT_c: The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated. The correction here was made using *Fridericia's formula.*

Time	Tapentadol IR 100 mg minus placebo			Tapentadol IR 150 mg minus placebo		
	LS Mean	SE	90% CI	LS Mean	SE	90% CI
24 H	-3.9	1.72	(-6.76; -1.11)	-4.1	1.71	(-6.87; -1.24)
24 H 30 min	-2.0	1.72	(-4.83; 0.83)	-2.2	1.71	(-4.98; 0.65)
25 H	-3.2	1.72	(-6.00; -0.34)	-1.9	1.71	(-4.77; 0.87)
25 H 30 min	-0.9	1.72	(-3.68; 1.97)	-0.1	1.71	(-2.91; 2.72)
26 H	2.5	1.72	(-0.34; 5.34)	2.4	1.71	(-0.38; 5.26)
26 H 30 min	-0.5	1.72	(-3.29; 2.37)	-2.1	1.72	(-4.89; 0.75)
27 H	-0.2	1.72	(-3.06; 2.60)	0.4	1.71	(-2.46; 3.17)
28 H	-0.6	1.72	(-3.38; 2.28)	-0.6	1.71	(-3.41; 2.22)
30 H	2.7	1.72	(-0.10; 5.55)	-0.7	1.71	(-3.51; 2.12)
33 H	-1.8	1.72	(-4.62; 1.03)	-2.2	1.71	(-5.03; 0.60)
36 H	-0.6	1.72	(-3.45; 2.21)	-2.3	1.71	(-5.09; 0.54)

Note: 24 hours refers to the last dose of study drug on Day 2.

LS Means and CIs are based on mixed model.

CI = confidence interval; LS Mean = least square mean; SE = standard error of the mean; H min = time in hours and minutes

HP5503/50: Dose-response relationship of tapentadol IR in a pain model -using laser- and mechano-somatosensory evoked potentials in healthy male subjects. (Phase I)

Study HP5503/50 was a single-centre, single-dose, double-blind, placebo-controlled, randomised, 4-way cross-over study in healthy male subjects aged between 25 and 51 years old. The primary objective of the study was to establish a dose-response relationship after administration of single oral doses of tapentadol IR (50 mg, 75 mg and 100 mg) tablets or placebo in a human pain model using CO_2- Laser-Somatosensory Evoked Potentials (LSEP) on Ultraviolet-B-irradiated skin in healthy male subjects. To support the objective-quantitative high resolution algesimetry from LSEPs, the subjective impression of 'Post Laser Pain' on UVB-irradiated skin was recorded by the subject via Visual Analogue Scale (VAS) (100 mm) scoring at 3 dose levels of tapentadol, compared to placebo. Peak-to-Peak (PtP) amplitudes of the N1 and P2 components of the LSEPs and Mechano- Somatosensory Evoked Potentials (MSEPs) were measured, derived from Vertexelectroencephalography (EEG) leads at 3 dose levels of tapentadol, compared to placebo in different skin conditions (UVB-irradiated and capsaicin irritated skin). LSEPs from UVB-irradiated and LSEPs and MSEPs from capsaicin-irritated skin were taken after single-dose administration of the study drug in each of the treatment periods at the following time-points: +30 minutes (only LSEPs) and at 1, 2, 3, 4, 5 and 6 hours. The laser and mechanical impact stimulus intensity were set to the thresholds on normal skin; determined at screening visit and kept constant during each study period. The mean of 12 artifact-free EEG segments after laser stimuli of 60 ms (UV) and 80 ms (capsaicin) duration were used. Warm-up, baseline and wind-up sessions were run before study drug administration on normal and capsaicin-sensitized skin.

Results:

In the UVB-irradiated skin as well as in the capsaicin-irritated skin, there was a development of hyperalgesia over time versus baseline due to the "acute" application of UVB-irradiation and capsaicin exposure. This was apparent both for the objective effect variables (LSEP and MSEP) and for the subjective effect variable (VAS). A single dose of tapentadol IR at 50, 75 and 100 mg induced a statistically significant reduction versus placebo in at least one of the main target variables, that is, the total PtP-amplitude of LSEP or VAS 'Post Laser Pain' from UVB-sensitized skin (see Table 30).

The effect of tapentadol on the P2-component was more pronounced than the effect of tapentadol on the N1-component. A predominant suppression of the P2-component mainly reflected an effect on central (spinal and/or cortical) pain processing.

A dose-response relationship after administration of single oral doses of tapentadol IR at 50, 75 and 100 mg was observed in a human pain model. A linear trend was observed between the different doses and this was statistically significant.

Table 30: Least Squares Means with corresponding 95% CIs for primary endpoints PtP-amplitude of LSEP and VAS 'Post Laser Pain' on UV_B-irradiated skin

Treatment	PtP-amplitude (µV) LSEP UV-sensitized skin	VAS (mm) Post Laser Pain
Placebo	28.6 [24.2 ; 32.9]	36.8 [28.2 ; 45.4]
Tapentadol IR 50 mg	25.5 [21.2 ; 29.8]	34.5 [25.9 ; 43.1]
Tapentadol IR 75 mg	25.7 [21.4 ; 30.0]	32.7 [24.1 ; 41.3]
Tapentadol IR 100 mg	23.2 [18.8 ; 27.5]	32.0 [23.4 ; 40.6]

Evaluator's overall conclusions on pharmacodynamics

• In a thorough QT study, no effect on the QT interval was shown of therapeutic (100 mg) and supra-therapeutic (150 mg) doses of tapentadol IR. Tapentadol had no relevant effect on other electrocardiogram (ECG) parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

• After tapentadol IR administration, the initial pupil diameter, a biomarker for mu-opioid receptor agonist activity, changed in a dose dependent manner and changes were well correlated to the pharmacokinetics of tapentadol.

• After multiple doses of tapentadol IR, testosterone serum concentrations decreased in an apparent dose related manner, but most of the testosterone values remained within the normal range.

• Tapentadol IR showed a similar drug liking to that of estimated equianalgesic doses of hydromorphone IR in a study in opioid experienced non-dependent healthy subjects.

• A statistically significant dose-response relationship was seen after administration of single oral doses of 50 mg, 75 mg and 100 mg of tapentadol IR in an experimental pain model using CO_2-laser-somatosensory evoked potentials on ultraviolet (UV) B-irradiated skin in healthy male subjects.

Efficacy

To the date of this submission more than 4000 subjects had received tapentadol IR in Phase I, Phase II and Phase III clinical studies. In the Phase II and Phase III studies, the doses of tapentadol IR ranged from 21 mg to 172 mg given as single or multiple doses. Several Phase II double-blind, placebo or active controlled studies were designed to provide guidance for the development of the pivotal clinical Phase III studies, including single-dose studies of acute pain following third molar tooth surgery (extraction) (KF5503/02 and KF5503/04) or bunionectomy (KF5503/05) and two multiple-dose studies following bunionectomy (KF5503/21 and KF5503/22).

There were four confirmatory and well-controlled clinical studies conducted to assess the efficacy of tapentadol IR for the relief of moderate to severe pain in three settings: KF5503/32 and KF5503/37, bunionectomy in an in-patient setting; KF5503/35, abdominal pain post-hysterectomy in an in-patient setting; and KF5503/33, end-stage degenerative joint disease of the hip or knee in an out-patient setting. A further study (KF5503/31) in subjects

who had undergone unilateral hip replacement surgery was terminated early due to slow recruitment and high discontinuation rates.

The proposed indication for tapentadol IR is for the relief of moderate to severe acute pain with 50 mg, 75 mg and 100 mg doses given every 4 to 6 hours as needed.

Support for the use of the Phase III studies in post-operative pain models as pivotal studies for a general indication of moderate to severe acute pain was obtained from a Scientific Advice Meeting with the European Medicines Agency (EMEA/CHMP/SAWP/266045/2006).

The Phase II studies have been divided into Phase IIa studies where single doses were given to evaluate dose response and Phase IIb studies where multiple doses were given to the subjects. The Phase IIa studies provided early evidence for the analgesic efficacy of tapentadol IR and support for the designs of the later studies. Doses chosen in the Phase IIb studies were based on those from the Phase IIa studies. All studies were performed with oral formulations except for KF5503/01 which used an intravenous formulation.

Phase IIa studies

The sponsor has conducted early Phase II studies in pain following abdominal surgery (KF5503/01), in third molar tooth surgery (KF5503/02 and KF5503/04) and in pain following bunionectomy (KF5503/05).

Phase IIb studies

The sponsor has conducted two Phase IIb studies in pain following bunionectomy (KF5503/21 and KF5503/22).

Phase III efficacy studies

The sponsor has conducted five Phase III efficacy studies in pain following bunionectomy (KF5503/32 and KF5503/37), in pain following an abdominal hysterectomy (KF5503/35), in pain following unilateral hip replacement (KF5503/31) and in pain due to end-stage degenerative joint disease (KF5503/33) to assess the efficacy of tapentadol IR in the relief of moderate to severe pain.

All five studies used a fixed dose with a flexible administration regimen of every 4 to 6 hours. All confirmatory Phase III studies had predefined subgroup analyses for baseline pain severity with 'moderate' defined as≥4 and < 6 on the 11 -point numerical rating scale (NRS) (or ≥4.5 and <6 in KF5503/33 only) and 'severe' defined as ≥6 on the 11-point NRS.

In addition, a double-blind, out-patient study (KF5503/34) was performed to evaluate the safety of tapentadol IR, the efficacy data of which are only used to discuss the persistency of analgesia.

Study evaluations

Table 31: Summary of principal efficacy evaluations in Phase II studies

	Abdominal pain	Molar tooth surgery pain		Bunionectomy pain		
Evaluation	**KF5503/01**	**KF5503/02**	**KF5503/04**	**KF5503/05**	**KF5503/21**	**KF5503/22**
PI	X	X	X	X	X	X
SPI					24 (Day 2, 3[a], 4)[e]	
PID	X	X	X	X	X	X
PEAKPID	X	X		X		X
SPID	8	8	4, 8	4, 8	24 (on Day 2, 3, 4)[e]	4, 8, 12
PRID		X	X	X		X
SPRID		X	X	X		4, 8, 12[a]
PAR	X	X	X	X	X	X
TOTPAR	8	4, 8[a]	4, 8[a]	4, 8[a]	24 (on Day 2, 3, 4)[e]	4, 8, 12
PEAKPAR	X	X	X	X		X
Time to PEAKPAR	X	X	X	X		
Global evaluation	X	X	X	X	X	X
Time to pain relief[b]	Perceptible[c]	Perceptible, meaningful, confirmed perceptible[d]	Perceptible, meaningful, confirmed perceptible[d]	Perceptible, meaningful, confirmed perceptible[d]	Perceptible, meaningful, confirmed perceptible[d]	Perceptible, meaningful, confirmed perceptible
Responder rates						X
Time to rescue	X	X	X	X	X	X

Note: time of assessment is given in hours for SPID and TOTPAR

a) Primary endpoint

b) Based on stopwatch method.

c) Perceptible pain relief was denoted 'onset of anlgesia' in the KF5503/01 integrated clinical study report

d) Confirmed perceptible pain relief was denoted 'onset of pain relief' in KF5503/02, KF5503/04, and KF5503/05 integrated clinical study reports, post-hoc parameter in KF5503/02

e) Over 24 hours on evaluation Day 2, Day 3, and Day 4

PAR = pain relief; PEAKPAR = peak pain relief; PRID = pain relief and intensity difference; PI = pain intensity; SPI = sum of pain intensity; PID = pain intensity difference; PEAKPID = peak pain intensity difference; SPID = sum of pain intensity difference; SPRID = sum of pain relief and intensity difference; TOTPAR = total pain relief; IR = immediate release

For each Phase III study, the time-point for the primary efficacy evaluation was determined during the double-blind treatment period (at 48 hours for the 72-hour double-blind treatment periods of KF5503/31, KF5503/32 and KF5503/37, at 24 hours for the 72-hour double-blind treatment period of KF5503/35 and at 5 days for the 10-day double-blind treatment period of KF5503/33. In KF5503/35, the primary endpoint was assessed at 24 hours because post-operative pain intensity after abdominal hysterectomy was expected to still be within the range of moderate to severe at this time, but to decrease markedly afterwards, whereas in the course of post-operative bunionectomy pain, the natural decrease in pain intensity is comparably slower. The Sum of Pain Intensity Difference (SPID) at 48 hours was, however, defined as a key secondary endpoint in KF5503/35. The secondary efficacy variables were selected to provide a comprehensive assessment of the total effect, duration of effect and overall response to the proposed dosing regimens. A tabular summary of the efficacy evaluations on the Phase III studies is provided in Table 32.

Table 32: Summary of efficacy evaluations in Phase III studies

	Abdominal hysterectomy	Bunionectomy pain		Hip replacement pain	End-stage degenerative joint disease	90-day safety
Evaluation	**KF5503/35**	**KF5503/32**	**KF5503/37**	**KF5503/31**	**KF5503/33**	**KF5503/34**
PI [c]	6, 12, 24, 48, 72	12, 24, 48, 72	6, 12, 24, 48, 72	12, 24, 48, 72	X	X
PID	6, 12, 24, 48, 72		6, 12, 24, 48, 72			
SPID	6, 12, 24 [a], 48 [b], 72	12, 24, 48[a], 72	6, 12, 24, 48[a], 72	12, 24, 48[a], 72	2, 5[a], 10 days	
SPRID	6, 12, 24, 48, 72	12, 24, 48, 72	6, 12, 24, 48, 72	12, 24, 48, 72	2, 5, 10 days	
PAR [c]	6, 12, 24, 48, 72		6, 12, 24, 48, 72			
TOTPAR	6, 12, 24, 48, 72	12, 24, 48, 72	6, 12, 24, 48, 72	12, 24, 48, 72	2, 5, 10 days	
PGIC [d]	24, 72, End of DB	End of DB	24, 48, 72, End of DB	End of DB	End of DB	X
Time to pain relief	Meaningful, perceptible, confirmed perceptible[e]	Meaningful, perceptible, confirmed perceptible	Meaningful, perceptible, confirmed perceptible[e]			
Responder rates	≥30 , ≥50%	≥30 , ≥50%	≥30 , ≥50%	≥30 , ≥50%	≥30 , ≥50%	
Time to rescue	X	X	X	X	X	

In KF5503/33, the 5-day TOTPAR includes all observations of PAR, and SPID includes all observations of PID, collected from the evening of Day 1 to the morning of Day 6.

Note: time of assessments in hours apart from KF5503/33 where the times are given in days

a) Primary endpoint.

b) Key secondary endpoint.

c) In studies KF5503/31, KF5503/32, KF5503/35, and KF5503/37, pain intensity and pain relief were also assessed at baseline (ie, the qualification assessment) and at 0.5, 1.0, 1.5, 2.0 hours, and every 2 hours thereafter until the next dose. For subsequent doses, pain intensity assessments were made pre-dose and every 2 hours thereafter until the next dose.

d) End of double-blind evaluation was 12 hours after the last dose.

e) Confirmed perceptible pain relief was denoted 'onset of pain relief' in KF5503/02, KF5503/04, and KF5503/05 integrated clinical study reports, post-hoc parameter in KF5503/02.

PAR = pain relief; PI = pain intensity; PID = pain intensity difference; SPID = sum of pain intensity difference; SPRID = sum of pain relief and intensity difference; TOTPAR = total pain relief; PGIC = patient global impression of change; DB = double-blind; IR = immediate release

Pain intensity

On the basis of the recent Initiative on Methods, Measurement and Pain Assessment in Clinical Studies Recommendations for Core Outcome Measures in Chronic Pain Studies, the 11-point NRS was chosen as the efficacy outcome measure for the confirmatory Phase III studies (Dworkin *et al.* 2005[25]). In addition, the NRS is a standard and widely used tool for the assessment of pain intensity (Diaz *et al*. 2006[26]). Subjects rate pain intensity (PI) on this scale from 0 = 'no pain' to 10 = 'pain as bad as you can imagine'.

Pain relief

On the basis of the recent Initiative on Methods, Measurement and Pain Assessment in Clinical Studies Recommendations for Core Outcome Measures in Chronic Pain Studies, the 5-point pain relief scale was chosen as the efficacy outcome measure for the pivotal studies. PAR was assessed by subjects answering the question 'How much relief have you had from your starting pain?' or 'How much relief have you had from your starting pain at rest or while moving from the supine to the sitting position?' Subjects rated PAR using a 5-point scale (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete).

Patient global impression of change

The 7-point patient global impression of change (PGIC) was chosen as a complementary assessment of efficacy based on work by Farrar and the recent Initiative on Methods, Measurement and Pain Assessment in Clinical Studies group paper (Diaz *et al*. 2006, Farrar *et al*. 2001[27]). This is a commonly accepted and validated outcome measure for clinical pain studies. PGIC was assessed by completing the statement 'Since I began study drug, my overall status is:' Subjects verbally rated their overall impression of treatment with 1 of 7 possible responses (very much improved, much improved, minimally improved, no change, minimally worse, much worse, very much worse).

Times to perceptible, meaningful and confirmed perceptible pain relief

A double stopwatch method, a commonly used and accepted technique to measure confirmed perceptible pain relief, has been reported as being a reasonable estimate of the time to onset of analgesic effect (Desjardins 1996[28]).

Pain intensity difference

To examine the change from baseline in pain intensity, Pain Intensity Difference (PID) was calculated as follows:

PID = baseline pain intensity – current pain intensity (1)

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[25] Dworkin RH, Turk DC, Farrar JT *et al.* (2005). Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain* 113:9-19.

[26] Diaz JA, Cuervo C, Valderrama AM et al. (2006). Valdecoxib provides effective pain relief following acute ankle sprain. *J Int Med Res* 2006;34:456-67

[27] Farrar JT, Young JP, Jr, LaMoreaux L, Werth JL, Poole RM. (2001). Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain.* 94:149–158.

[28]Desjardins PJ, Black PM, Balm TK *et al.* (1996) Onset of analgesia: further validation of a new stopwatch method. *Clin Pharmacol Ther* 59:130.

PID was calculated at each assessment time-point.

Sum of pain intensity difference

In the Phase III studies, the primary endpoint was the SPID over time, measured at 24 hours for KF5503/35, 48 hours for KF5503/31, KF5503/32 and KF5503/37 and 5 days for KF5503/33.

The SPID was defined as follows:

$SPID = \Sigma W_i \times PID_i$ where the sum includes all observations of PID collected from baseline to particular fixed time-points and W_i is the time elapsed from the previous observation (PID_{i-1}) to the current observation (PID_i). For $SPID_{24}$ and $SPID_{48}$, the sum includes all observations of PID collected up to the 24 or 48 hour fixed assessment time-points, respectively,.

$SPID_{48}$ was defined as the primary endpoint for KF5503/31, KF5503/32 and KF5503/37 and $SPID_{24}$ was defined as the primary endpoint for KF5503/35. For each study, the calculation of SPID used all available data prior to the first intake of any additional analgesic medication.

Statistical methodology

No pooling of efficacy data for the pivotal studies was performed due to differences in the pain models used, differences in the time-points of the primary endpoints used as well as differences in the study designs (that is, allowed/did not allow the use of rescue medication).

The Intent-to-Treat population was defined as all randomised subjects who took at least one dose of tapentadol IR and if applicable active control or placebo and had a non-missing baseline pain assessment. This set was the primary analysis set used for all efficacy analyses.

The per-protocol analysis set was a subset of the Intent-to-Treat population in all studies. It included subjects who were compliant with the protocol (without major protocol deviations). Major protocol deviations leading to exclusion from the per-protocol analysis set were defined per study and are specified in the respective statistical analysis plans.

In KF5503/31, KF5503/32, KF5503/35 and KF5503/37, Day 1 was defined as the day of the first double-blind dose (that is, in the morning following the day of surgery) and was used as the reference time-point in computing relative days in the study. In KF5503/33, the first double-blind dose date was used as the reference start date in computing relative study days. For efficacy summaries, the double-blind treatment period was defined from the date of the first dose of study drug to the date of the last dose.

In general for the studies, the baseline value was defined as the last non-missing observation assessed prior to the first dose for analyses of the double-blind period.

Statistical hypothesis for the primary objective

The null hypothesis was that there was no difference between each of the tapentadol IR dose groups and the placebo group based on the primary efficacy variable ($SPID_{48}$ for KF5503/32 and KF5503/37, $SPID_{24}$ for KF5503/35 and 5-day SPID KF5503/33). The alternative hypothesis was that at least one of the tapentadol IR dose groups differed from placebo. The overall Type I error rate was controlled within each study at the 0.05 level for the primary analysis by applying the Hochberg procedure to adjust for multiple comparisons of multiple dose groups of tapentadol IR to placebo (not applicable to KF5503/37).

Primary efficacy analyses

The SPID (over 48 hours for KF5503/31, KF5503/32 and KF5503/37, over 24 hours for KF5503/35 and over the first 5 days of treatment for KF5503/33) was the primary efficacy variables.

The primary efficacy analysis on the primary endpoint was an analysis of covariance (ANCOVA) with the factors of treatment, centre (pooled centre for KF5503/31, KF5503/33 and KF5503/35) and baseline pain intensity as covariate. All pair-wise treatment differences were estimated based on the least-square means of the difference. The Hochberg's procedure was used to adjust the p-values for multiple comparisons of all tapentadol IR groups versus the placebo group, where applicable.

Per pre-planned analysis for each study, additional imputation methods (Baseline Observation Carried Forward [BOCF], Worst Observation Carried Forward [WOCF] and modified last observation carried forward (LOCF) (for KF5503/33) were also applied to calculate the primary efficacy variable.
Treatment effects were examined using the primary analysis method. For KF5503/35, the Hochberg procedure was used to maintain the overall significance level at 5% in a pre-planned approach; for the other studies, adjustment using the Hochberg procedure was performed in a post-hoc manner, where applicable.

Study KF5503/31 was terminated early due to slow recruitment and a high discontinuation rate. Therefore, the sample sizes were lower than planned. As a consequence, the analysis on the primary endpoint has to be considered as being exploratory in nature.

Subgroup analysis

Descriptive statistics were provided for the primary efficacy variable by subgroups (sex, racial/ethnic group, age group, baseline pain intensity category and early second dose, where applicable).Subgroup analysis based on the baseline pain intensity category (moderate or severe) was performed on the primary efficacy variable (using the primary imputation strategy, LOCF) using an analysis of variance (ANOVA) model including treatment and centre (pooled centre for KF5503/33 and KF5503/35) as factors.

The subgroups for pain intensity were defined as follows:

• Baseline pain intensity category (11-point NRS: moderate ≥4 to <6; severe ≥6 for KF5503/32, KF5503/35 and KF5503/37 and moderate ≥4.5 to <6; severe ≥6 for KF5503/33).

Secondary efficacy analyses

The key secondary endpoint of KF5503/35 was the $SPID_{48}$. In order to control the overall Type I error rate for the primary and key secondary analyses at the 0.05 level, a hierarchical testing approach was applied. Only those doses of tapentadol IR which demonstrated a statistically significant difference to placebo on the primary endpoint analysis were included in the analysis of the key secondary endpoint. The overall Type I error rate for the comparison of each dose of tapentadol IR versus placebo on the key secondary endpoint was controlled at the 0.05 level by applying the Hochberg procedure. Efficacy was additionally tested between the tapentadol IR treatment groups and placebo based on SPID at non-primary time-points, total pain relief (TOTPAR), the sum of combined pain relief and pain intensity (SPRID), time to first additional pain medication, continuous responder rates, PGIC and time to confirmed perceptible pain relief (except for KF5503/33). For KF5503/32, KF5503/33, KF5503/35 and KF5503/37, a prioritisation of these secondary objectives was performed relative to the primary (key secondary in KF5503/35) endpoint using the following order: compare treatment effect of tapentadol IR doses with placebo on the time to first additional pain medication during the double-blind period using only those doses that demonstrated a statistically significant difference to placebo on the primary endpoint (key secondary in KF5503/35). The Hochberg procedure was then used to control the overall Type I error rate for multiple comparisons of tapentadol IR to placebo on the time to first additional pain medication. Other secondary endpoints were considered supportive only and each

comparison of tapentadol IR versus placebo was performed at a two-sided 0.05 significance level.

For KF5503/31, the number of subjects available for evaluation was low following slow recruitment and high discontinuation rates leading to the subsequent closure of the study, therefore, no analyses of the secondary efficacy endpoints will be presented in this document.

Distribution of responder rates using pain intensity

Responder rates were based on percent improvement from baseline in pain intensity using an 11-point NRS. The responder rate for a given percent improvement value was defined as the proportion of subjects who had a value above that threshold value.

The responder rates were calculated at 24 hours (KF5503/35), 48 hours (KF5503/31, KF5503/32 and KF5503/37) and at the end of Day 5 (KF5503/33). Subjects without a pain value at these time-points (subjects who discontinued prior to this assessment) were assigned the worst possible score (0 [no improvement]). In addition, subjects in KF5503/35 and KF5503/37 who used additional analgesics prior to the specified time-point were also assigned the worst possible score. Responder rates for achieving ≥30% and 50% improvement in pain intensity from baseline were compared using the Cochran-Mantel-Haenszel test controlling for centre (KF5503/32 and KF5503/37) or pooled centre (KF5503/31, KF5503/33 and KF5503/35). In addition, the distribution (by changing the threshold value) of responder rates were determined for each treatment group and compared using the Gehan test for KF3305/32 and KF5503/33 and the log-rank test for KF5503/35 and KF5503/37. Because the Gehan test puts more weight on the response rates for lower percentage change improvement from baseline, the distributions of responder rates for both studies KF5503/32 and KF5503/33 were also compared in a post-hoc manner using the log-rank test which assigns equal weights to tall values and therefore, does not depend on the pattern of the distributions. Similar calculations were performed for percent change from baseline at the 12-, 24- and 72-hour time-points (KF5503/32 and KF5503/37), on Day 2 and Day 10 (KF5503/33) and at the 12-, 48- and 72-hour time-points (KF5503/35).

Additional pain intensity and pain relief variables

At each analysis time-point (for KF5503/32: Hour 12, 24, 48 and 72; for KF5503/33: Day 2, Day 5 and Day 10; for KF5503/35 and KF5503/37: Hour 6, 12, 24, 48 and 72), TOTPAR, SPID (at the non-primary and the non-key secondary for KF5503/35, time-point) and SPRID were analysed separately using an ANCOVA model with factors of treatment, centre (pooled centre for KF5503/33 and KF5503/35) and baseline pain intensity as the covariate. The least-significant difference procedure was used to perform pair-wise treatment comparisons. For KF5503/31, the SPID at Hour 12, 24, 48 and 72 was additionally presented. Descriptive statistics for all pain relief (PAR), pain intensity (PID), PRID (= PAR + PID), TOTPAR, SPID and SPRID variables were provided by time-point for each treatment group. The results for PAR and PID variables were also plotted over time.

Times to perceptible, meaningful and confirmed perceptible pain relief

The distributions of the time to onset of perceptible pain relief and meaningful pain relief were estimated by the Kaplan-Meier method and compared using log-rank statistics with centre (pooled centre for KF5503/35) as a stratification factor. Time to confirmed perceptible pain relief was equivalent to the stopwatch time of first perceptible pain relief if the subject also experienced meaningful pain relief.

Active comparator versus placebo

To validate the sensitivity of the study assays, comparison of oxycodone IR or morphine IR versus placebo was performed on the primary endpoint (using LOCF, BOCF and WOCF imputation), SPID at non-primary time-points and TOTPAR and SPRID at each time-point for KF5503/32, KF5503/33, KF5503/35 and KF5503/37. Similarly, treatment comparisons based on the time to first rescue medication use and distribution of responder rates were also performed.

Phase II - Dose-response studies

Study KF5503/01 (Abdominal pain)

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient dose ranging study of an intravenous formulation of tapentadol (8.6 to 69 mg) given as a 15-minute infusion to approximate the kinetic profile of an orally administered formulation in male subjects after abdominal surgery. The active comparator was morphine 10 mg. A post-operative pain score of ≥40 mm on a visual analogue scale (VAS) was required for inclusion. The primary variable was the SPID over 8 hours ($SPID_8$).

Subject population

A tabular summary of subject selection criteria for Phase II studies is provided in Table 33 below:

Table 33: Summary of subject selection criteria of Phase II studies

	KF5503/01	KF5503/02	KF5503/04	KF5503/05	KF5503/21	KF5503/22
Age range (years)	18 to 65	18 to 45	18 to 45	18 to 65	18 to 65	18 to 75
Baseline pain						
- VAS (0 mm to 100 mm)	≥40 mm	≥50 mm	≥50 mm	≥45 mm	-	≥40 mm
- NRS (11-point)	-	-	-	-	≥4	-
- VRS (4-point)	-	Moderate or severe	Moderate or severe	Moderate or severe	Moderate or severe	Moderate or severe
Sex	Male	Male and female [a]	Male and female	Male and female	Male and female	Male and female
Pain cause	Abdominal surgery	Third molar tooth surgery	Third molar tooth surgery	Bunionectomy	Bunionectomy	Bunionectomy

a) Not specified in protocol

NRS = Numerical rating scale; VAS = visual analogue scale; VRS = visual rating scale

Results

The intravenous infusion of 69 mg tapentadol over 15 minutes showed greater analgesic relief on $SPID_8$ and other efficacy parameters (pain intensity, pain relief, pain intensity difference (PEAK PID), TOTPAR, time to onset of perceptible pain relief (1 stopwatch method, denoted time to onset of analgesia in the integrated clinical study report), time to first intake of rescue medication and overall assessment by the subject) compared with placebo over 8 hours. Tapentadol 69 mg also provided numerically greater analgesic relief than morphine 10 mg intravenously. Lower doses of tapentadol (17 mg and 34 mg) also showed an analgesic effect compared to placebo in some of the efficacy parameters (for example SPID).

Dose-ranging Study KF5503/02 (Third molar tooth surgery)

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient dose ranging study that investigated the analgesic efficacy of tapentadol IR (43 mg to 172 mg) as a single dose for control of pain after third molar tooth surgery. The active controls were ibuprofen 400 mg and tramadol 150 mg. A post-operative pain score of

≥50 mm on a VAS and at least moderate pain on a 4-point VRS was required for inclusion. The primary variable was $TOTPAR_8$.

Results

All single doses of tapentadol IR (43, 64, 86, 129 and 172 mg) were statistically superior to placebo based on the primary efficacy variable, TOTPAR over 8 hours ($TOTPAR_8$) (see Table 34). Analgesic superiority to placebo was also demonstrated by secondary efficacy variables, including time to maximum pain relief, time to onset of confirmed perceptible pain relief (2 stopwatch method, denoted time to pain relief in the integrated clinical study report) and time to first rescue medication. Efficacy results of the tramadol group were similar to results obtained in the lower tapentadol IR dose groups (43 mg, 64 mg and 86 mg) for the first 4 hours of the observation period and similar to results in the higher dose groups (129 mg and 172 mg) for the 8 hours observation period.

Table 34: Results for total pain relief over 8 hours ($TOTPAR_8$; LOCF) (Third molar tooth surgery: KF5503/02, Full Analysis Set)

	Tapentadol IR					Tramadol IR	Ibuprofen	
	43 mg	**64 mg**	**86 mg**	**128 mg**	**172 mg**	**150 mg**	**400 mg**	**Placebo**
N	49	49	51	52	50	51	49	49
Mean (SD)	8.2 (7.6)	11.7 (8.8)	10.7 (9.5)	13.9 (8.6)	14.9 (7.8)	12.3 (9.7)	15.3 (10.1)	4.5 (7.8)
Unadjusted p-value versus placebo	0.005	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	-

p-value for pair-wise comparison to placebo

SD = standard deviation; N = number of subjects; LOCF = last observation carried forward; IR = immediate release

Dose-ranging Study KF5503/04 (Third molar tooth surgery)

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient dose ranging study that investigated the analgesic efficacy of tapentadol IR (21 mg to 172 mg) as a single dose for control of pain after third molar tooth surgery. The active controls were ibuprofen 400 mg and morphine IR 60 mg. A post-operative pain score of ≥50 mm on a VAS and at least moderate pain on a 4-point VRS was required for inclusion. The primary variable was the $TOTPAR_8$.

Results

In this study of acute pain following third molar tooth surgery, single doses of tapentadol IR 64 mg, 86 mg and 172 mg were statistically superior to placebo based on the primary efficacy variable, $TOTPAR_8$ (see Table 35). There was a dose-related effect of tapentadol IR on $TOTPAR_8$ and similar potency observed between tapentadol IR 172 mg and morphine IR 60 mg. The analyses of derived variables based on PAR and/or PID scores and percentage of subjects experiencing 50% pain relief, also showed that the response to treatment increased with increasing dose of tapentadol IR.

Table 35: Results for total pain relief over 8 hours ($TOTPAR_8$; LOCF) (Third molar tooth surgery: KF5503/04, Full Analysis Set)

	Tapentadol IR					Morphine	Ibuprofen	
	21.5 mg	43 mg	64 mg	86 mg	172 mg	IR 60 mg	400 mg	Placebo
N	49	50	50	48	49	51	51	51
Mean (SD)	6.3 (8.4)	7.9 (8.1)	9.7 (8.5)	11.6 (8.2)	15.3 (7.5)	13.8 (10.3)	17.7 (9.9)	4.7 (7.3)
Unadjusted p-value versus placebo	Not calculated	0.063	0.004	<0.001	<0.001	<0.001	<0.001	-

p-value for pair-wise comparison to placebo

SD = standard deviation; N = number of subjects; LOCF = last observation carried forward; IR = immediate release

Phase IIa Study KF5503/05 (Bunionectomy)

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient study that examined the efficacy, safety and pharmacokinetics of single oral doses of tapentadol IR (21 mg to 172 mg) for the relief of moderate to severe post-operative pain following a bunionectomy. The active comparators were morphine IR 60 mg and ibuprofen 400 mg. For inclusion, a baseline pain intensity of ≥45 mm on a VAS and at least moderate pain on a 4-point VRS within 6 hours of surgery was required. The primary variable was the $TOTPAR_8$.

Results

The mean $TOTPAR_8$ was statistically significantly greater ($p \leq 0.01$), indicating a greater analgesic effect, for tapentadol IR 43 mg, 64 mg, 86 mg and 172 mg, morphine IR 60 mg and ibuprofen 400 mg compared with placebo (see Table 36). The mean $TOTPAR_8$ score for tapentadol IR 172 mg was numerically superior to the mean score for morphine IR 60 mg. Tapentadol IR showed a dose-related increase in analgesia over the entire range of doses studied. The statistically significant ($p \leq 0.001$) difference between ibuprofen 400 mg and placebo and between morphine IR 60 mg and placebo validated the sensitivity of the bunionectomy pain model. Based on the primary endpoint in this study, the analgesic effect of a tapentadol IR dose lying between 86 mg and 172 mg is assumed to be similar to the effect of morphine IR 60 mg. The analyses of efficacy following a single dose of tapentadol IR suggested that the minimally effective dose is 43 mg.

Table 36: Results for total pain relief over 8 hours ($TOTPAR_8$; LOCF) (Bunionectomy: KF5503/05, Full Analysis Set)

	Tapentadol IR					Morphine	Ibuprofen	
	21 mg	43 mg	64 mg	86 mg	172 mg	IR 60 mg	400 mg	Placebo
N	66	64	64	65	66	63	64	65
Mean (SD)	2.9 (4.6)	4.1 (5.7)	4.4 (5.0)	4.8 (5.3)	8.1 (6.8)	6.7 (7.5)	8.0 (8.4)	1.5 (2.9)
Unadjusted p-value versus placebo	0.166	0.014	0.007	0.002	<0.001	<0.001	<0.001	

p-value for pair-wise comparison to placebo

SD = standard deviation; N = number of subjects; LOCF = last observation carried forward; IR = immediate release

Phase IIb Study KF5503/21

This was a randomised, double-blind, parallel-group, multiple-dose study assessing the analgesic efficacy and safety of two dose levels of tapentadol IR (50 mg and 100 mg) compared to oxycodone 10 mg and placebo in subjects following orthopaedic surgery (bunionectomy). Subjects took tapentadol IR, oxycodone IR, or placebo every 4 to 6 hours (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first study drug administration 'early second dose']) for up to 72 hours. For inclusion, a baseline pain intensity of ≥4 on the 11-point (0 to 10) pain intensity NRS with a 1-point increase and at least moderate pain on a 4-point VRS, was required. The primary variable

was the Sum of Pain Intensity over 24 hours (SPI_{24}) on Day 3 (commencing the morning of Study Day 3 (06:00 h), approximately 40 hours to 44 hours after surgery, until 06:00 h the next day) based on the VRS.

Results

Primary endpoint SPI_{24} (Day 3)

The mean SPI_{24} on evaluation Day 3 based on the VRS was lower in the three active treatment groups than in the placebo group. However, based on the pre-defined primary analysis, there were no statistically significant differences between either of the tapentadol IR treatment groups, or oxycodone IR and placebo. This pre-defined analysis inappropriately included rescue medication as a factor in the ANOVA model. However, as stated by the FDA the use of rescue medication is also a treatment-dependent outcome and not a baseline characteristic so that inclusion of this variable as a factor makes the treatment effect in the model non-interpretable. Therefore, a post-hoc analysis using an ANOVA model without the factor 'use of rescue medication' was performed and indeed, the pair-wise comparison between each dose of tapentadol IR and placebo showed a statistically significant difference ($p \leq 0.0133$) (see Table 37).

Table 37: Results for sum of pain intensity over 24 hours (SPI_{24}; LOCF) based on a verbal rating scale on evaluation Day 2, Day 3 and Day 4 (Bunionectomy: KF5503/21: Full Analysis Set)

		Tapentadol IR		Oxycodone
Characteristic	**Placebo**	**50 mg**	**100 mg**	**IR 10 mg**
Evaluation Day 3				
N	67	67	65	65
Mean (SD)	41.90 (17.67)	33.58 (19.67)	29.16 (15.22)	35.68 (17.18)
p-value versus placebo [a,b]	–	0.0133	0.0001	–
95% CI		[–15.1;–1.5]	[–19.4;–5.8]	
Evaluation Day 2				
N	67	67	68	67
Mean (SD)	53.85 (13.73)	41.23 (16.10)	36.94 (15.63)	43.25 (16.46)
p-value versus placebo [a]	–	<0.0001	<0.0001	<0.0001
Evaluation Day 4				
N	67	67	64	63
Mean (SD)	30.07 (18.00)	24.89 (18.44)	23.42 (15.20)	25.03 (15.51)
p-value versus placebo [a]	–	0.0773	0.0284	0.0754

a) Based on a post-hoc ANOVA model with factors of treatment, center and baseline pain intensity. Oxycodone IR group was excluded from the model for primary analysis. Dunnett's method for adjustment of multiple comparisons of tapentadol IR versus placebo was used.

b) ANOVA model with factors of treatment, center, baseline pain intensity and use of rescue medication had yielded non significant results. FDA commented that rescue medication as factor makes treatment effect non-interpretable in this model. Therefore, ANOVA without rescue medication was performed post-hoc.

N = number of subjects; SD = standard deviation; CI = confidence interval; ANOVA = analysis of variance; LOCF = last observation carried forward; IR = immediate release

Time to rescue medication use

In the placebo group, 98.5% of the subjects took first-line rescue medication (paracetamol/acetaminophen). In the active treatment groups, the percentages of patients who took first-line rescue medication were lower but comparable across the groups: 80.6% in the tapentadol IR 50 mg group, 76.5% in the tapentadol IR 100 mg group and 80.6% in the oxycodone IR 10 mg group. The percentage of subjects using rescue medication decreased over time. The difference between the placebo group and the active treatment groups for first-line rescue medication use was highest on evaluation Day 2 (98.5% of subjects versus 72.1% to 76.1%) and lowest on evaluation Day 4 (49.3% versus 37.3% to 41.3%). The results for

the intake of second-line (ibuprofen or ketorolac) and third-line (Lortab) rescue medications were similar to those for the intake of first-line medication.

Overall, the median time to first dose of rescue medication in the placebo group (3 hours 12 minutes) was shorter than in the active treatment groups (tapentadol IR 50 mg: 7 hours 31 minutes; tapentadol IR 100 mg: 8 hours 31 minutes; and oxycodone IR 10 mg: 4 hours 41 minutes). Using the log-rank test, there was a statistically significant difference between each of the active treatment groups and the placebo group ($p < 0.001$) in time to first rescue medication use. The time to first dose of rescue medication was also numerically longer for each of the tapentadol IR groups than for the oxycodone IR 10 mg group.

Time to pain relief

The median time to onset of confirmed perceptible pain relief (denoted onset of pain relief in the integrated clinical study report) was longer in the placebo group (2 hours 40 minutes) than in the active treatment groups (tapentadol IR 50 mg 43 minutes, tapentadol IR 100 mg 31 minutes, oxycodone IR 10 mg 31 minutes).

Phase IIb Study KF5503/22

This was a randomised, double-blind, parallel-arm, placebo and active controlled dose-ranging study of the efficacy and safety of multiple doses of tapentadol IR for post-operative pain following bunionectomy surgery. Subjects were randomised to 6 treatment groups with study drug administered at 0 hours, 4 hours and 8 hours for the following dosing regimens:

1. Placebo, placebo and placebo (placebo treatment group).

2. 80 mg, 80 mg and 80 mg tapentadol IR (tapentadol IR 80 mg treatment group).

3. 120 mg, 120 mg and 120 mg tapentadol IR (tapentadol IR 120 mg treatment group).

4. 120 mg, 60 mg and 60 mg tapentadol IR (tapentadol IR 120/60 mg treatment group).

5. 160 mg, 80 mg and 80 mg tapentadol IR (tapentadol IR 160/80 mg treatment group).

6. 10 mg, 10 mg and 10 mg oxycodone IR (oxycodone IR 10 mg treatment group, the active control).

For inclusion, a pain intensity (0 to 100 mm VAS) ≥40 mm and at least moderate pain on a 4-point VRS after at least 10 hours following the start of surgery and within 9 hours of discontinuation of a popliteal block or permitted systemic analgesics during post-operative surgical period was required.

Results

Primary endpoint - $SPRID_{12}$

The primary efficacy variable, $SPRID_{12}$ (VRS) showed statistically significant improvement in pain for all tapentadol IR treatment groups compared to placebo (all p-values <0.001, Dunnett's procedure). The mean $SPRID_{12}$ values were 38.4, 35.8, 33.6 and 32.3 in the tapentadol IR 120 mg, tapentadol IR 160/80 mg, tapentadol IR 120/60 mg and tapentadol IR 80 mg groups, respectively, compared to 11.5 with placebo (see Table 39). Oxycodone IR 10 mg (mean $SPRID_{12}$: 26.4) also showed a statistically significant difference from placebo ($p < 0.001$), thus validating the assay sensitivity of this study design.

Sum of total pain relief and pain intensity difference at non-primary time-points

Statistically significant improvement ($p < 0.001$) was observed in the sum of total pain relief and pain intensity difference over 4 and 8 hours ($SPRID_4$ and $SPRID_8$) in all tapentadol IR treatment groups compared with the placebo group (see Table 38) and was consistent with the

primary efficacy variable, $SPRID_{12}$. Mean $SPRID_4$ and $SPRID_8$ values were numerically higher for all tapentadol IR treatment groups compared with the oxycodone IR 10 mg group.

Table 38: Sum of total pain relief and sum of pain intensity difference at 12 hours ($SPRID_{12}$ using a VRS; LOCF) (Bunionectomy: KF5503/22: Intent-to-Treat population)

		Tapentadol IR				Oxycodone IR
	Placebo	80 mg	120 mg	120/60 mg	160/80 mg	10 mg
	(N = 79)	(N = 77)	(N = 77)	(N = 82)	(N = 78)	(N = 79)
0-12 hours						
Mean (SD)	11.5 (17.59)	32.3 (23.80)	38.4 (21.88)	33.6 (22.45)	35.8 (21.91)	26.4 (21.58)
Median	8.7	35.2	42.2	34.3	38.4	29.1
(range)	(-12,72)	(-12,81)	(0,82)	(0,80)	(-12,70)	(-12,77)
Primary analysis versus placebo						
p-value [a]		<0.001	<0.001	<0.001	<0.001	
LS-means		20.7	26.8	22.0	24.3	
(95% CI)		[12.22;29.23]	[18.29;35.29]	[13.63;30.36]	[15.78;32.73]	
Assay sensitivity analysis versus placebo						
p-value [b]						<0.001
LS-means						14.8
(95% CI)						[8.08;21.62]

Note: Placebo = placebo/placebo/placebo;
tapentadol IR 80 mg = tapentadol IR 80 mg/80 mg/80 mg;
tapentadol IR 120 mg = tapentadol IR 120 mg/120 mg/120 mg;
tapentadol IR 120/60 mg = tapentadol IR 120 mg/60 mg/60 mg;
tapentadol IR 160/80 mg = tapentadol IR 160 mg/80 mg/80 mg;
oxycodone IR 10 mg = oxycodone IR 10 mg/10 mg/10 mg

Higher value in SPRID indicates greater pain relief.

a) Based on analysis of variance model with factors of treatment, center, and baseline pain intensity. The oxycodone IR 10 mg group was excluded from the model for primary analysis. P-values and CI associated with Dunnett procedure.

b) Based on analysis of variance model with factors of treatment, center, and baseline pain intensity. All treatment groups are included. No adjustment of p-values for multiplicity.

N = number of subjects; SD = standard deviation; CI = confidence interval; LS = least square; VRS = verbal rating scale; LOCF = last observation carried forward; IR = immediate release

Table 39: Sum of total pain relief and pain intensity difference (SPRID using a VRS; LOCF) at 4 hours and 8 hours (Bunionectomy: KF5503/22: Intent-to-Treat population)

		Tapentadol IR				Oxycodone IR
	Placebo (N=79)	80 mg (N=77)	120 mg (N=77)	120/60 mg (N=82)	160/80 mg (N=78)	10 mg (N=79)
0 – 4 hours						
Mean (SD)	5.3 (6.88)	10.6 (7.82)	13.0 (6.81)	11.8 (7.31)	12.5 (7.65)	9.5 (7.19)
Median	3.0	10.6	14.3	12.4	13.4	10.6
(range)	(-4,24)	(-4,26)	(0,26)	(0,26)	(-4,26)	(-4,24)
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001	<0.001
LS-means		5.3	7.7	6.5	7.2	4.2
(95% CI)		[2.98;7.57]	[5.38;9.97]	[4.24;8.76]	[4.93;9.50]	[1.92;6.48]
0 – 8 hours						
N	79	77	77	82	78	79
Mean (SD)	8.8 (12.56)	21.6 (15.65)	26.2 (14.47)	23.1 (14.94)	25.3 (14.86)	18.2 (14.11)
Median	6.5	23.1	28.5	22.6	26.8	20.9
(range)	(-8,48)	(-8,53)	(0,57)	(0,52)	(-8,48)	(-8,48)
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001	<0.001
LS-means		12.8	17.4	14.3	16.5	9.3
(95% CI)		[8.21;17.33]	[12.81;21.92]	[9.78;18.75]	[11.97;21.05]	[4.81;13.86]

Note: Placebo = placebo/placebo/placebo; Tapentadol IR 80 mg = Tapentadol IR 80 mg/80 mg/80 mg; Tapentadol IR 120 mg = Tapentadol IR 120 mg/120 mg/120 mg; Tapentadol IR 120/60 mg = Tapentadol IR 120 mg/60 mg/60 mg; Tapentadol IR 160/80 mg = Tapentadol IR 160 mg/80 mg/80 mg; oxycodone IR 10 mg = oxycodone IR 10 mg/10 mg/10 mg

Higher value in SPRID indicates greater pain relief.

a) Based on analysis of variance model with factors of treatment, center, and baseline pain intensity. P-values and CI associated with Fisher's least-square means of the difference procedure.

N = number of subjects; SD = standard deviation; CI = confidence interval; LS = least square; VRS = verbal rating scale; LOCF = last observation carried forward; IR = immediate release

Additional non-primary derived pain scale variables

A statistically significant improvement in pain ($p < 0.001$) was shown for all tapentadol IR groups compared to placebo for $SPID_4$, $SPID_8$, $SPID_{12}$ and for $TOTPAR_4$, $TOTPAR_8$ and $TOTPAR_{12}$. All tapentadol IR groups showed improvement in pain compared to placebo for PID, PID based on VAS, PAR, PRID, PEAKPID, PEAKPID based on a VAS and peak pain relief (PEAKPAR).

Responder rates

The evaluation of responder rates in this study was an exploratory analysis. The percent improvement in pain intensity (VAS) of ≥30% from baseline was observed in a higher percentage of subjects with tapentadol IR treatment than with placebo or oxycodone IR at 12 hours (5.06% with placebo, 30.49% to 45.57% with tapentadol IR and 24.69% with oxycodone IR 10 mg). The tapentadol IR 120 mg group had the highest percentage of subjects who demonstrated ≥30% improvement (relative to baseline) compared to the other tapentadol treatment groups at this time-point (45.57% compared to 37.5% for tapentadol IR 80 mg, 30.49% for tapentadol IR 120/60 mg and 35.44% for tapentadol IR 160/80 mg).

Phase III - Main (pivotal) studies

Study KF5503/35 – Abdominal pain

Study design

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient study that examined the efficacy, safety and pharmacokinetics of multiple doses of 50 mg, 75 mg and 100 mg of tapentadol IR for the relief of moderate to severe post-operative pain following an abdominal hysterectomy. The active comparator was morphine IR 20 mg. Subjects took tapentadol IR or morphine IR every 4 to 6 hours for 3 days (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first study drug administration ['early second dose']). For inclusion, a baseline pain intensity of at least 4 on the 11-point (0 to 10) pain intensity NRS and at least moderate pain on a 4-point VRS rated within 30 minutes before randomisation was required. Use of any additional analgesic medication during the double-blind treatment period led to the subjects being discontinued from the study for lack of efficacy. The primary variable was $SPID_{24}$ and the key secondary variable was the $SPID_{48}$.

Demographics and baseline characteristics

The demographic data of the treatment groups were similar in KF5503/35. The treated subjects had a mean age of 47.5 years, with 98.4% being under 65 years old and the age ranging from 28 years to 78 years. The mean weight was 72.6 kg, mean height was 164.3 cm and the mean body mass index was 26.8 kg/m^2 (see Table 40). All subjects were women. For the Intent-to-Treat population, the mean baseline pain intensity based on the 11-point NRS was similar in all treatment groups. The proportion of subjects with moderate pain on the NRS (4 to <6) was 71.1% in the placebo group, 71.8% in the tapentadol IR 50 mg group, 67.7% in the tapentadol IR 75 mg group, 70.9% in the tapentadol IR 100 mg group and 75.0% in the morphine IR 20 mg group. Most other subjects had severe baseline pain intensity except for six subjects who had mild pain at baseline (see Table 41).

Subject disposition

In total, 854 subjects were randomised in 52 centres in 9 countries. All randomised subjects were allocated to one of the five treatment groups: 169 subjects to the placebo group, 168 subjects to the tapentadol IR 50 mg group, 171 subjects to the tapentadol IR 75 mg group, 176 subjects to the tapentadol IR 100 mg group and 170 subjects to the morphine IR 20 mg group. The majority of subjects (80.8%) completed the study. Fewer subjects in the placebo group (117 subjects [69.2%]) completed the 72-hour double-blind period compared to each of the active treatment groups (147 subjects [87.5%] on tapentadol IR 50 mg, 153 subjects [89.5%] on tapentadol IR 75 mg, 150 subjects [85.2%] on tapentadol IR 100 mg and 138 subjects [81.2%] on morphine IR 20 mg). The largest number of subjects discontinued from the study was observed in the placebo group (32.5%), primarily for lack of efficacy (24.3%) (see Table 42).

Table 40: Descriptive statistics for demographic parameters (Abdominal hysterectomy: KF5503/35: Safety Analysis Set)

			Tapentadol IR			Morphine	Tapentadol	
	Statistic	Placebo (N=169)	50 mg (N=168)	75 mg (N=171)	100 mg (N=176)	IR 20 mg (N=170)	IR Total (N=515)	Total (N=854)
Race/Ethnicity								
White	n (%)	169 (100)	168 (100)	171 (100)	176 (100)	170 (100)	515 (100)	854 (100)
Age (years)								
	Mean	47.2	47.0	47.1	47.5	48.5	47.2	47.5
	SD	5.83	5.56	5.37	6.43	6.75	5.81	6.03
	Min	31	28	30	33	31	28	28
	Max	70	68	66	78	74	78	78
Age groups								
< 65 years	n (%)	166 (98.2)	166 (98.8)	170 (99.4)	173 (98.3)	165 (97.1)	509 (98.8)	840 (98.4)
≥65 years	n (%)	3 (1.8)	2 (1.2)	1 (0.6)	3 (1.7)	5 (2.9)	6 (1.2)	14 (1.6)
Weight (kg)								
	Mean	73.0	71.9	72.5	72.2	72.6	72.2	72.5
	SD	12.68	13.53	13.29	12.68	11.74	13.15	12.77
		(N=169)	**(N=167)**	**(N=171)**	**(N=176)**	**(N=170)**	**(N=514)**	**(N=853)**
Height (cm)								
	Mean	164.4	165.0	164.0	163.9	164.4	164.3	164.3
	SD	5.77	5.29	5.84	5.33	5.32	5.51	5.52
Body mass index (kg/m^2)								
	Mean	27.0	26.3	26.9	26.9	26.9	26.7	26.8
	SD	4.54	4.49	4.63	4.50	4.36	4.54	4.50

N or n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum; IR = immediate release

Table 41: Descriptive statistics for baseline pain intensity at rest (NRS) (Abdominal hysterectomy: KF5503/35: Intent-to-Treat population)

		Tapentadol IR			Morphine	Tapentadol	
Statistic	Placebo (N=166)	50 mg (N=163)	75 mg (N=167)	100 mg (N=172)	IR 20 mg (N=164)	IR Total (N=502)	Total (N=832)
Baseline pain intensity at rest (NRS)							
N	166	163	167	172	164	502	832
Mean	5.1	5.1	5.2	5.1	5.0	5.1	5.1
SD	1.20	1.15	1.22	1.20	1.14	1.19	1.18
Min	3	4	3	2	3	2	2
Median	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Max	9	8	8	10	9	10	10
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Baseline pain intensity at rest (NRS)							
none (0)	0	0	0	0	0	0	0
mild (1 to <4)	1 (0.6)	0	1 (0.6)	3 (1.7)	1 (0.6)	4 (0.8)	6 (0.7)
moderate (4 to <6)	118 (71.1)	117 (71.8)	113 (67.7)	122 (70.9)	123 (75.0)	352 (70.1)	593 (71.3)
severe (≥6)	47 (28.3)	46 (28.2)	53 (31.7)	47 (27.3)	40 (24.4)	146 (29.1)	233 (28.0)

N = number of subjects; SD = standard deviation; Min = minimum; Max = maximum; NRS = numerical rating scale; IR = immediate release

Table 42: Frequency table of subject disposition (Abdominal hysterectomy: KF5503/35: All Screened Subjects)

		Tapentadol IR			Morphine	Tapentadol	
	Placebo	50 mg	75 mg	100 mg	IR 20 mg	IR Total	Total
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Screened							1014
Randomized	169 (100)	168 (100)	171 (100)	176 (100)	170 (100)	515 (100)	854 (100)
Treated	169 (100)	168 (100)	171 (100)	176 (100)	170 (100)	515 (100)	854 (100)
Completed 72 hour-DB Period	117 (69.2)	147 (87.5)	153 (89.5)	150 (85.2)	138 (81.2)	450 (87.4)	705 (82.6)
Completed study	114 (67.5)	144 (85.7)	151 (88.3)	146 (83.0)	135 (79.4)	441 (85.6)	690 (80.8)
Discontinued study	55 (32.5)	24 (14.3)	20 (11.7)	30 (17.0)	35 (20.6)	74 (14.4)	164 (19.2)
• Subject choice (subject withdrew consent)	5 (3.0)	3 (1.8)	2 (1.2)	4 (2.3)	2 (1.2)	9 (1.7)	16 (1.9)
• Lost to follow-up	0	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.8)	3 (0.6)	6 (0.7)
• Adverse event	6 (3.6)	7 (4.2)	8 (4.7)	14 (8.0)	11 [a] (6.5)	29 (5.6)	46 (5.4)
• Death	0	0	0	0	1 (0.6)	0	1 (0.1)
• Lack of efficacy	41 (24.3)	10 (6.0)	4 (2.3)	5 (2.8)	11 (6.5)	19 (3.7)	71 (8.3)
• Other	3 (1.8)	3 (1.8)	5 (2.9)	6 (3.4)	7 (4.1)	14 (2.7)	24 (2.8)

N = number of subjects; DB = double-blind

a) According to the adverse event data, 12 subjects (7.1%) had adverse events that led to study discontinuation, however, this was the primary reason for discontinuation from the study in only 11 subjects (6.5%).

Results

Primary endpoint – SPID24

In the Intent-to-Treat population, all active treatment groups showed a statistically significant difference to placebo for the SPID24 for all imputation methods (LOCF, BOCF and WOCF) (see Tables 43 and 44). The highest mean least-square means of the difference compared to placebo in SPID24 (Intent-to-Treat population, LOCF) was observed for the tapentadol IR 100 mg group with 23.3, followed by the tapentadol IR 75 mg group with 20.8 and the tapentadol IR 50 mg group with 18.1; the mean least-square means of the difference for the morphine IR 20 mg group compared to placebo was 20.6. Over the first 24 hours of the double-blind period, tapentadol IR 75 mg demonstrated a numerically similar pain relief to that of morphine IR 20 mg based on the primary endpoint, SPID24.

Table 43: Results for sum of pain intensity difference (SPID) at 24 hours using last observation carried forward (LOCF) (Abdominal hysterectomy: KF5503/35: Intent-to-Treat

population)

Time	Statistic	Placebo (N=166)	Tapentadol IR 50 mg (N=163)	Tapentadol IR 75 mg (N=167)	Tapentadol IR 100 mg (N=172)	Morphine IR 20 mg (N=164)
24 hours	N	166	163	167	172	164
	Mean	29.0	49.0	52.4	52.9	48.8
	SD	44.98	39.87	41.85	40.95	41.00
	LS-means (difference from Placebo)	-	18.1	20.8	23.3	20.6
	95% CI	-	[10.9;25.3]	[13.7;28.0]	[16.3;30.4]	[13.4;27.8]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001

LS = least square; SD = standard deviation; N = number of subjects; CI = confidence interval; IR = immediate release

Table 44: Results for sum of pain intensity difference at 24 hours ($SPID_{24}$) using baseline (BOCF) and worst (WOCF) observation carried forward (Abdominal hysterectomy: KF5503/35: Intent-to-Treat population)

Imputation	Statistic	Placebo (N=166)	Tapentadol IR 50 mg (N=163)	Tapentadol IR 75 mg (N=167)	Tapentadol IR 100 mg (N=172)	Morphine IR 20 mg (N=164)
BOCF	N	166	163	167	172	164
	Mean	32.2	50.2	53.6	52.6	49.6
	SD	37.32	34.53	37.20	34.64	34.98
	LS-means (difference from placebo)	-	16.3	19.1	20.0	18.5
	95% CI	-	[10.7;22.0]	[13.5;24.7]	[14.4;25.5]	[12.8;24.1]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001
WOCF	N	166	163	167	172	164
	Mean	25.9	47.5	51.4	49.7	47.0
	SD	45.36	39.95	42.62	42.13	40.30
	LS-means (difference from placebo)	-	19.7	23.1	23.4	21.9
	95% CI	-	[12.4;26.9]	[15.9;30.3]	[16.2;30.5]	[14.7;29.1]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001

BOCF = baseline observation carried forward; WOCF = worst observation carried forward; LS = least square; CI = confidence interval; SD = standard deviation; N = number of subjects; IR = immediate release

Key secondary endpoint - $SPID_{48}$

For the Intent-to-Treat population, all tapentadol IR treatment groups showed statistically significant improvement in pain relief compared to the placebo group for $SPID_{48}$ using all imputation methods (LOCF, BOCF and WOCF) (see Table 45). Over the first 48 hours of the double-blind period, tapentadol IR 100 mg (least square difference compared to placebo of 51.4) demonstrated a numerically higher pain relief compared to morphine IR 20 mg (46.9) which in turn demonstrated a numerically higher pain relief compared to tapentadol IR 75 mg (44.0) based on the key secondary endpoint, $SPID_{48}$ (Intent-to-Treat population, LOCF). However, there were no consistent trends for increasing efficacy with increasing dose of tapentadol. In Table 45 there were greater differences observed between placebo and tapentadol IR 50 mg than between placebo and tapentadol IR 100 mg. In addition, differences between the tapentadol doses lacked clinical significance.

Sum of pain intensity difference at other time-points 6 hours, 12 hours and 72 hours

The results for the analysis of SPID (Intent-to-Treat population, LOCF) at 6, 12 and 72 hours (see Table 46) were similar to the results of the primary ($SPID_{24}$) and key secondary endpoint ($SPID_{48}$) analyses . Statistically significant differences relative to placebo were observed for each dose of tapentadol IR at each time-point. Morphine IR also demonstrated a statistically significant improvement in pain relief compared to placebo at each time-point. However, once again there were no consistent trends to support increasing efficacy with increasing doses of tapentadol.

Table 45: Results for sum of pain intensity difference at 48 hours ($SPID_{48}$) using last (LOCF), baseline (BOCF) and worst (WOCF) observation carried forward (Abdominal hysterectomy: KF5503/35: Intent-to-Treat population)

			Tapentadol IR			
Imputation	**Statistic**	**Placebo (N=166)**	**50 mg (N=163)**	**75 mg (N=167)**	**100 mg (N=172)**	**Morphine IR 20 mg (N=164)**
LOCF	N	166	163	167	172	164
	Mean	71.1	112.4	120.6	123.5	116.6
	SD	101.17	87.32	87.35	83.50	87.10
	LS-means (difference from placebo)	-	37.1	44.0	51.4	46.9
	95% CI	-	[21.6;52.6]	[28.6;59.5]	[36.1;66.7]	[31.4;62.4]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001
BOCF	N	166	163	167	172	164
	Mean	79.5	114.9	123.5	118.3	114.5
	SD	76.95	71.45	75.14	69.24	71.97
	LS-means (difference from placebo)	-	31.9	39.3	38.3	37.0
	95% CI	-	[20.3;43.5]	[27.8;50.9]	[26.9;49.7]	[25.4;48.6]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001
WOCF	N	166	163	167	172	164
	Mean	60.6	107.3	117.5	111.4	107.9
	SD	104.37	88.32	90.57	87.40	86.27
	LS-means (difference from placebo)	-	42.6	51.9	50.3	48.6
	95% CI	-	[26.7;58.5]	[36.1;67.7]	[34.6;66.0]	[32.7;64.5]
	p-value	-	<0.0001	<0.0001	<0.0001	<0.0001

LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; SD = standard deviation; N = number of subjects

Table 46: Descriptive statistics for sum of pain intensity difference (SPID) at 6, 12, 72 hours using last observation carried forward (LOCF) (Abdominal hysterectomy: KF5503/35: Intent-to-Treat population)

			Tapentadol IR			Morphine
Time	Statistic	Placebo (N=166)	50 mg (N=163)	75 mg (N=167)	100 mg (N=172)	IR 20 mg (N=164)
6 hours	N	166	163	167	172	164
	Mean	8.5	11.3	12.5	11.2	10.3
	SD	8.84	7.98	11.99	10.97	9.04
12 hours	N	166	163	167	172	164
	Mean	14.6	23.3	24.8	24.2	22.1
	SD	19.40	17.51	20.09	19.92	19.56
72 hours	N	166	163	167	172	164
	Mean	124.6	189.9	201.2	205.5	195.6
	SD	164.33	139.03	135.00	127.15	133.39

N = number of subjects; SD = standard deviation; IR = immediate release

Additional non-primary derived pain scale variables

The TOTPAR was assessed at 6, 12, 24, 48 and 72 hours. At all time-points (except 6 hours), the difference to placebo for all tapentadol IR groups and the morphine IR 20 mg group was statistically significant (Intent-to-Treat population; LOCF). At the first time-point (6 hours), only the tapentadol IR 75 mg and 100 mg groups showed a statistically significant difference to placebo.

Time to rescue medication

Rescue medication was defined as any additional analgesic medication taken during the treatment period. Since rescue medication was not permitted during the study, subjects who used such medication were withdrawn due to lack of efficacy. Most subjects did not use additional analgesic medications. The highest proportion of subjects using such medications was seen in the placebo group (25.9%) and the lowest proportion in the tapentadol IR 100 mg group (5.2%) (Intent-to-Treat population; LOCF). For all tapentadol IR groups, the time to first additional analgesic medication was statistically significant compared to placebo ($p < 0.001$), with longer times to the need for additional analgesics for each dose of tapentadol IR. Additionally, the morphine IR 20 mg group was also statistically significantly different to placebo (p-value <0.001).

Responder rates

The number of subjects with a response ≥30% and ≥50% at 24 hours (Intent-to-Treat population, LOCF) was similar in the active treatment groups and statistically significant to placebo (all p-values for comparison to placebo ≤0.003 for ≥30% and <0.001 for ≥50%) (see Table 47). Similar results were observed for responder rate evaluations performed at 48 hours except that the percentage of subjects with a response was higher for each treatment group (Intent-to-Treat population, LOCF).

Time to pain relief

For the Intent-to-Treat population, 81.3% of subjects on placebo, 89.6% to 91.6% of subjects treated with tapentadol IR and 90.9% of subjects in the morphine IR 20 mg group demonstrated onset of confirmed, perceptible pain relief. The median time to confirmed perceptible pain relief was 0.4 hours in all treatment groups. Only the morphine IR 20 mg

group demonstrated a statistically significant difference relative to placebo (p-value = 0.01). The high number of subjects showing confirmed perceptible pain relief and the identical time to confirmed perceptible pain relief compared to active treatment groups is in line with the relatively high responder rates in the placebo group in this study.

Patient global impression of change

The percentage of subjects who rated their PGIC at 24 hours (Intent-to-Treat population) as at least 'minimally improved' was 68.1% on placebo, 85.3% on tapentadol IR 50 mg, 89.2% on tapentadol IR 75 mg, 83.7% on tapentadol IR 100 mg and 84.8% on morphine IR 20 mg. The distribution of responses at 24 hours was statistically significantly different from placebo (all p-values <0.001) for each of the active treatment groups.

At 72 hours, all active groups differentiated from placebo (all p-values ≤0.005). The highest number of subjects rating their pain as very much improved was seen in the tapentadol IR 100 mg group (70 subjects, 40.7%), followed by the tapentadol IR 75 mg group (65 subjects, 38.9%), the morphine IR 20 mg group (62 subjects, 37.8%), the tapentadol IR 50 mg group (54 subjects, 33.1%) and the placebo group (43 subjects, 25.9%).

Table 47: Distribution of responder rates at 24 hours and 48 hours using pain intensity at rest (NRS) per response threshold (Abdominal hysterectomy: KF5503/35: Intent-to-Treat population)

Time		Placebo (N=166) N (%)	Tapentadol IR 50 mg (N=163) N (%)	Tapentadol IR 75 mg (N=167) N (%)	Tapentadol IR 100 mg (N=172) N (%)	Morphine IR 20 mg (N=164) N (%)
24 hours	**Response (≥30%)**					
	Number of responders	89 (53.6)	116 (71.2)	121 (72.5)	126 (73.3)	115 (70.1)
	p-value[a]					
	- overall	0.0003				
	- pair-wise comparison versus Placebo		0.0012	0.0005	0.0002	0.0025
	Response (≥50%)					
	Number of responders	63 (38.0)	96 (58.9)	105 (62.9)	103 (59.9)	94 (57.3)
	p-value[a]					
	- overall	<0.0001				
	- pair-wise comparison versus Placebo		0.0001	<0.0001	<0.0001	0.0004
48 hours	**Response (≥30%)**					
	Number of responders	101 (60.8)	123 (75.5)	139 (83.2)	137 (79.7)	131 (79.9)
	p-value[a]					
	- overall	<.0001				
	- pair-wise comparison versus Placebo		0.0034	<0.0001	<0.0001	<0.0001
	Response (≥50%)					
	Number of responders	94 (56.6)	112 (68.7)	130 (77.8)	126 (73.3)	124 (75.6)
	p-value[a]					
	- overall	<0.0001				
	- pair-wise comparison versus Placebo		0.0228	<0.0001	0.0003	<0.0001

a) p-value versus placebo, based on Generalized Cochran-Mantel-Haenszel test for general association controlling for center. Subjects who discontinued or used additional analgesic medication prior to the time interval are considered non-responders.

NRS = numerical rating scale; N = number of subjects; IR = immediate release

Comment: All tapentadol IR treatment groups showed statistically significant improvement in pain relief compared to the placebo group for the primary variable, ($SPID_{24}$; regardless of missing value imputation method) and for the key secondary variable, $SPID_{48}$. Assay sensitivity was confirmed by the separation of the morphine IR 20 mg group from placebo in both the primary and key secondary variables. Overall, there were no consistent trends for increasing efficacy with increasing dose of tapentadol. In addition, differences between the tapentadol doses lacked clinical significance.

KF5503/32 - Bunionectomy

Study design

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo-controlled, in-patient study that examined the efficacy, safety and pharmacokinetics of multiple doses of 50 mg, 75 mg and 100 mg of tapentadol IR for the relief of moderate to

severe post-operative pain following a bunionectomy followed by a voluntary open-label extension. The active comparator was oxycodone IR 15 mg. Subjects took tapentadol IR, oxycodone IR or placebo every 4 to 6 hours for three days (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first administration ['early second dose']). For inclusion, a baseline pain intensity of ≥4 on the 11-point (0 to 10) pain intensity NRS rated within 30 minutes before randomisation was required. Use of any additional analgesic medication during the double-blind treatment period led to the subject being discontinued from the study for lack of efficacy. The primary variable was the $SPID_{48}$ based on the NRS.

Demographic and baseline characteristics

Demographics and baseline characteristics were balanced across the treatment groups (see Table 48). Most subjects were White (55%), Hispanic (22%), or Black (20%). Most of the subjects across the treatment groups were women (87%) and less than 65 years of age (94%) (overall mean age: 44.3 years). For time from stop of popliteal sciatic block to first dose of study drug, median times were similar between treatment groups, but the means diverged, primarily because of subjects whose popliteal blocks were discontinued early (two subjects in the placebo group, one subject in the tapentadol IR 50 mg group, two subject in the tapentadol IR 75 mg group, three subjects in the tapentadol IR 100 mg group and no subjects in the oxycodone IR 15 mg group). However, these subjects were given other systemic analgesics and were randomised at appropriate times as specified in the protocol. Some 75% of subjects were categorised as having severe baseline pain intensity (NRS pain intensity ≥6) and 25% as having moderate baseline pain intensity (NRS pain intensity ≥4 to <6); the distribution was similar among treatment groups (see Table 48). The median baseline pain intensity score was 7.0 in all groups, the mean baseline pain score ranged from 6.9 in the placebo and tapentadol IR 100 mg groups to 7.2 in the tapentadol IR 50 mg group.

Table 48: Demographic and baseline characteristics (Bunionectomy: KF5503/32: Intent-to-Treat population)

		Tapentadol IR			Oxycodone	
	Placebo (N = 120)	50 mg (N = 119)	75 mg (N = 120)	100 mg (N = 118)	IR 15 mg (N = 125)	Total (N = 602)
Sex, n (%)						
Male	12 (10)	18 (15)	13 (11)	19 (16)	15 (12)	77 (13)
Female	108 (90)	101 (85)	107 (89)	99 (84)	110 (88)	525 (87)
Racial/ethnic group, n (%)						
White	68 (57)	56 (47)	71 (59)	62 (53)	76 (61)	333 (55)
Black	23 (19)	27 (23)	19 (16)	24 (20)	25 (20)	118 (20)
Hispanic	26 (22)	32 (27)	24 (20)	30 (25)	23 (18)	135 (22)
Other	3 (3)	4 (3)	6 (5)	2 (2)	1 (1)	16 (3)
Age (Years) category, n (%)						
<65 years	111 (93)	113 (95)	114 (95)	111 (94)	119 (95)	568 (94)
≥65 years	9 (8)	6 (5)	6 (5)	7 (6)	6 (5)	34 (6)
Mean (SD)	44.3 (14.45)	41.5 (13.27)	44.8 (13.61)	44.4 (13.68)	46.4 (13.02)	44.3 (13.66)
Median	45.0	42.0	47.5	46.5	49.0	46.0
Range	(18;77)	(18;75)	(19;72)	(18;74)	(18;73)	(18;77)
Weight (kg)						
Mean (SD)	75.6 (17.28)	76.4 (19.00)	74.3 (16.96)	78.2 (18.92)	77.9 (17.14)	76.5 (17.87)
Median	69.5	71.8	71.4	74.6	74.5	72.0
Range	(46;129)	(49;148)	(47;135)	(48;127)	(48;150)	(46;150)
Baseline body mass index (kg/m^2)						
Mean (SD)	27.8 (6.00)	28.1 (5.77)	27.6 (6.17)	28.5 (5.85)	28.9 (6.03)	28.2 (5.96)
Median	26.6	27.7	26.8	28.0	27.6	27.4
Range	(16;46)	(19;48)	(16;53)	(19;44)	(19;55)	(16;55)
Baseline pain intensity score category based on NRS, n (%)						
Moderate (4 to <6)	31 (26)	25 (21)	32 (27)	33 (28)	27 (22)	148 (25)
Severe (≥6)	89 (74)	94 (79)	88 (73)	85 (72)	98 (78)	454 (75)
Time from anesthesia stop to first dose (hours)[a]						
Mean (SD)	2.91 (3.174)	2.41 (2.751)	2.50 (2.664)	2.72 (3.548)	1.93 (1.293)	2.49 (2.792)
Median	1.59	1.43	1.60	1.51	1.40	1.53
Range	(0.4;23.8)	(0.3;24.9)	(0.4;24.0)	(0.4;22.9)	(0.4;6.5)	(0.3;24.9)

a) In this study, anesthesia was defined as the popliteal block and does not include systemic analgesia used subsequent to the popliteal block.

N or n = number of subjects; NRS = Numerical rating scale; SD = standard deviation; IR = immediate release

Subject disposition

A total of 918 subjects were screened and 603 subjects were randomised. For the double-blind period, the 603 subjects were randomised to the five treatment groups in a 1:1:1:1:1 ratio (121 subjects in the placebo, 119 in the tapentadol IR 50 mg, 120 in the tapentadol IR 75 mg, 118 in the tapentadol IR 100 mg and 125 in the oxycodone IR 15 mg groups). Of the randomised subjects, 602 subjects received tapentadol IR, oxycodone IR, or placebo. One subject was enrolled and randomised to the placebo group but did not receive it because at entry the subject recorded a pain intensity of 2 and not in line with the inclusion requirement of ≥4 based on the NRS. The percentage of subjects who completed the double-blind period was lowest in the placebo group (50%) and higher in the tapentadol IR treatment groups (76% to 89%) with the percentage increasing with increasing tapentadol IR dose from 50 mg to 100 mg (see Table 49).

The placebo group had the highest percentage of subjects (49%) who discontinued due to 'lack of efficacy' (that is, took 'rescue medication', defined as any additional analgesic taken

during the double-blind treatment period) compared with the tapentadol IR groups. The percentage of subjects who discontinued due to 'lack of efficacy' decreased with increasing dose of tapentadol IR (19% with tapentadol IR 50 mg; 14% with tapentadol IR 75 mg; and 10% with tapentadol IR 100 mg).

Table 49: Completion and discontinuation information (Bunionectomy: KF5503/32: Safety Analysis Set)

		Tapentadol IR			Oxycodone
	Placebo (N = 120)	50 mg (N = 119)	75 mg (N = 120)	100 mg (N = 118)	IR 15 mg (N = 125)
Completion Status	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Completed	60 (50)	91 (76)	96 (80)	105 (89)	107 (86)
Withdrawn/discontinued	60 (50)	28 (24)	24 (20)	13 (11)	18 (14)
• Subject choice [a]	0	1 (1)	1 (1)	1 (1)	3 (2)
• Adverse event	1 (1)	4 (3)	6 (5)	0	2 (2)
• Lack of efficacy	59 (49)	23 (19)	17 (14)	12 (10)	11 (9)
• Other	0	0	0	0	2 (2)

Percentages were calculated with the number of subjects in each group as denominator.

Completion and discontinuation information was based on the study termination electronic Case Report Form page.

Lack of efficacy was defined as use of 'rescue medication', defined as any additional analgesic taken during the double-blind period.

a) Subject withdrew consent

N or n = number of subjects; IR = immediate release

Results

Primary endpoint – Sum of pain intensity difference at 48 hours

An overview of the primary efficacy results and selected secondary efficacy results from the double-blind period of KF5503/32 is shown in Table 50. For the Intent-to-Treat population, all tapentadol IR treatment groups showed a statistically significant (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain on the primary efficacy variable of $SPID_{48}$ compared with placebo with the LOCF imputation. There was a numerical trend of increasing efficacy with increasing tapentadol IR dose (mean $SPID_{48}$: 119.1, 139.1 and 167.2 in the tapentadol IR 50 mg, 75 mg, 100 mg groups, respectively). Oxycodone IR 15 mg (mean $SPID_{48}$: 172.3) also showed a statistically significant (nominal p-value <0.001) difference from placebo (mean $SPID_{48}$: 24.5), validating the study assay sensitivity.

Analyses of mean $SPID_{48}$ based on the BOCF and WOCF imputations showed similar results to those for the LOCF imputation; there were statistically significant differences for all active-treatment groups compared to placebo (all nominal p-values <0.001).

Table 50: Sum of pain intensity difference at 48 hours ($SPID_{48}$) (Bunionectomy: KF5503/32: Intent-to-Treat population)

	Placebo (N = 120)	Tapentadol IR 50 mg (N = 119)	Tapentadol IR 75 mg (N = 120)	Tapentadol IR 100 mg (N = 118)	Oxycodone IR 15 mg (N = 125)
SPID at Hour 48 (LOCF)					
Mean (SD)	24.5 (120.93)	119.1 (125.86)	139.1 (118.93)	167.2 (98.99)	172.3 (110.86)
Median (range)	43.4 (-278,274)	127.6 (-185,402)	131.3 (-199,462)	158.5 (-94,408)	170.6 (-190,431)
LS-means difference from placebo (95% CI)		88.2 [60.71;115.59]	113.5 [86.12;140.81]	141.4 [113.98;168.90]	142.4 [115.28;169.47]
Adjusted p-value versus placebo [a,b]		<0.001	<0.001	<0.001	--
Unadjusted p-value versus placebo [a]		--	--	--	<0.001
SPID at Hour 48 (BOCF)					
LS-means difference from placebo (95% CI)		65.4 [41.40;89.43]	82.2 [58.24;106.11]	106.5 [82.50;130.56]	109.4 [85.66;133.08]
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001
SPID at Hour 48 (WOCF)					
LS-means difference from placebo (95% CI)		87.1 [58.89;115.35]	113.4 [85.24;141.51]	142.3 [114.00;170.50]	141.0 [113.15;168.90]
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001

Higher value in SPID indicates greater pain relief.

a) Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity as a covariate.

b) P-values adjusted for multiplicity using Hochberg procedure.

SPID = sum of pain intensity difference; LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; IR = immediate release

Sum of pain intensity difference (at non-primary time-points)

At all non-primary time-points ($SPID_{12}$, $SPID_{24}$ and $SPID_{72}$), there was a statistically significant improvement in SPID values in all tapentadol IR treatment groups compared with placebo using the LOCF imputation (all nominal p-values <0.001) and a numerical trend of increasing mean values with increasing tapentadol IR dose (see Table 51). The results were consistent with the improvement in pain intensity difference for all tapentadol IR treatment groups for the primary efficacy variable, $SPID_{48}$.

Oxycodone IR 15 mg also showed a statistically significant difference from placebo (all nominal p-values <0.001) at all time-points, validating the study assay sensitivity. The mean SPID values over all time-points for the oxycodone IR 15 mg group were numerically similar to those for the tapentadol IR 100 mg group.

Table 51: Sum of pain intensity difference (SPID) at Hour 12, Hour 24 and Hour 72 (Bunionectomy: KF5503/32: Intent-to-Treat population)

		Tapentadol IR			Oxycodone
	Placebo	50 mg	75 mg	100 mg	IR 15 mg
	(N=120)	(N=119)	(N=120)	(N=118)	(N=125)
0-12 hours					
Mean (SD)	4.7 (25.66)	23.2 (25.08)	30.0 (25.46)	35.5 (22.34)	35.6 (25.73)
Median	7.2	25.6	25.0	32.0	35.0
(range)	(-62,71)	(-39,78)	(-31,106)	(-28,95)	(-46,105)
LS-means (difference from placebo)		17.0	24.9	30.6	29.7
(95% CI)		[11.07;23.01]	[18.95;30.85]	[24.61;36.56]	[23.82;35.60]
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001
0-24 hours					
Mean (SD)	5.2 (52.33)	46.6 (53.39)	60.5 (53.94)	73.3 (47.39)	73.3 (52.73)
Median	11.1	50.9	53.5	68.4	70.3
(range)	(-134,111)	(-87,164)	(-79,222)	(-47,200)	(-94,212)
LS-means (difference from placebo)		38.5	54.8	67.6	65.7
95% CI		[26.06;50.99]	[42.35;67.18]	[55.10;80.04]	[53.41;78.02]
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001
0-72 hours					
Mean (SD)	55.7 (201.87)	207.9 (207.57)	230.5 (189.36)	271.1 (154.57)	288.3 (170.67)
Median	72.3	223.6	230.9	250.6	301.5
(range)	(-422,484)	(-329,636)	(-319,702)	(-166,626)	(-286,657)
LS-means (difference from placebo)		141.7	173.0	213.4	223.9
(95% CI)		[97.77;185.69]	[129.17;216.79]	[169.39;257.37]	[180.46;267.28]
p-value versus placebo [a]		<0.001	<0.001	<0.001	<0.001

Higher value in SPID indicates greater pain relief.

a) Based on analysis of covariance model with factors of treatment, center, and baseline pain intensity. Unadjusted p-values

N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; IR = immediate release

Additional non-primary derived pain scale variables

For further secondary pain scale variables that were statistically tested (TOTPAR and SPRID), all tapentadol IR groups showed a statistically significant improvement (all nominal p-values <0.001) compared with the placebo group at all time-points (12, 24, 48 and 72 hours). For variables not statistically tested (PID, PAR, PRID), numerical trends indicating efficacy were observed. For $SPRID_{48}$ and $TOTPAR_{48}$ the 95% confidence intervals for the tapentadol IR 50 mg and 100 mg groups did not overlap, suggesting a good separation of pain scales between the respective dose-groups.

Responder rates

The proportions of subjects who showed ≥30% improvement in pain intensity from baseline at 48 hours was higher in the tapentadol IR treatment groups compared with placebo: 40.0% in the placebo group, 64.7%, 68.3% and 78.8% of subjects in the tapentadol IR 50 mg, tapentadol IR 75 mg and tapentadol IR 100 mg groups, respectively (all nominal p-values <0.001) (see Table 52). The proportion of subjects who showed ≥50% improvement in pain intensity at 48 hours were also higher in the tapentadol IR treatment groups compared with

placebo: 30.0% in the placebo group, 58.0%, 56.7% and 70.3% of subjects in the tapentadol IR 50 mg, tapentadol IR 75 mg and tapentadol IR 100 mg groups, respectively (all nominal p-values <0.001).

Table 52: Comparison of the distributions of responder rates using pain intensity at Hour 48 Bunionectomy: KF5503/32: Intent-to-Treat population)

		Tapentadol IR			Oxycodone
Parameter	Placebo (N = 120)	50mg (N = 119)	75mg (N = 120)	100mg (N = 118)	IR 15 mg (N = 125)
Hour 48					
Pain assessment ≥30% improved, n (%)	48 (40.0)	77 (64.7)	82 (68.3)	93 (78.8)	98 (78.4)
p-value versus placebo[a]		<0.001	<0.001	<0.001	<0.001
Pain assessment ≥50% improved, n (%)	36 (30.0)	69 (58.0)	68 (56.7)	83 (70.3)	91 (72.8)
p-value versus placebo[a]		<0.001	<0.001	<0.001	<0.001
Comparison of distribution of responders					
Gehan p-value (versus placebo)		<0.001	<0.001	<0.001	<0.001
Log-rank p-value (versus placebo)		<0.001	<0.001	<0.001	<0.001

Subjects who discontinued prior to the time interval are considered non-responders.

a) Based on Generalized Cochran-Mantel-Haenszel test for general association controlling for center

N or n = number of subjects; IR = immediate release

Time to rescue medication

For this analysis, rescue medication was defined as any additional analgesic medication taken during the treatment period. Since rescue medication was not permitted during the double-blind treatment period, respective subjects who used such medications were withdrawn due to lack of efficacy. A lower percentage of subjects in the tapentadol IR treatment groups (10% to 19%) and the oxycodone IR group (9%) took additional analgesic medication compared with the placebo group (49%). The median time to first rescue medication could not be calculated for any active-treatment group, because less than 50% of subjects took rescue medication during the double-blind treatment period. However, there was a statistically significant difference in the distribution of time to first rescue medication for the tapentadol IR treatment groups relative to placebo (all log-rank p-values <0.001 using the Hochberg adjustment) with longer times to first rescue use for each dose of tapentadol IR versus placebo. The oxycodone IR 15 mg group was also significantly different from placebo (nominal p-value <0.001).

Time to pain relief

For onset of confirmed perceptible pain relief, all tapentadol IR treatment groups showed statistically significantly shorter times compared with placebo (nominal p-value = 0.005 for tapentadol IR 50 mg; nominal p-values <0.001 for the 75 mg and 100 mg tapentadol IR treatment groups. The median times to confirmed perceptible pain relief did not exhibit a dose-dependent relationship and were 46.0, 32.0 and 37.0 minutes for tapentadol IR 50 mg, tapentadol IR 75 mg and tapentadol IR 100 mg, respectively, but were shorter than the median time of 100.0 minutes for placebo-treated subjects. The median time to confirmed perceptible pain relief for oxycodone IR 15 mg was 31.0 minutes. The percentage of subjects who achieved confirmed perceptible pain relief was higher in all tapentadol IR treatment groups than in the placebo group and a numerical trend toward a dose-response for tapentadol IR was noted (78.2%, 83.3% and 87.3% for tapentadol IR 50, tapentadol IR 75 mg and tapentadol IR 100 mg, respectively, compared with 54.2% for the placebo group). The

percentage of subjects who achieved confirmed perceptible pain relief was 84.8% for oxycodone IR 15 mg.

Patient global impression of change

For the distribution of PGIC scores, there was a statistically significant improvement in each tapentadol IR treatment group compared with the placebo group (all nominal p-values <0.001). The percentage of subjects reporting 'much improved 'or 'very much improved' was higher in all tapentadol IR treatment groups (68% to 89%) compared with the placebo group (41%). A numerical trend of dose-response was observed for tapentadol IR (68%, 78% and 89% for tapentadol IR 50 mg, 75 mg and 100 mg, respectively). The corresponding percentage for the oxycodone IR 15 mg group (88%) was similar to that for the tapentadol IR 100 mg group (89%).

Comment: The data from this study support efficacy of tapentadol IR in the relief of acute pain during a 72-hour period following a bunionectomy. Tapentadol IR demonstrated statistically superior efficacy compared to placebo based on the primary ($SPID_{48}$; regardless of missing value imputation strategy used) and all secondary variables. In addition, there was a numerical trend of increasing efficacy with increasing tapentadol IR dose. Assay sensitivity was confirmed by the separation of the oxycodone IR 15 mg group from placebo in the primary variable.

KF5503/37 - Bunionectomy

Study design

This was a multicentre, randomised, double-blind, parallel-group, active- and placebo controlled, in-patient study that examined the efficacy, safety and pharmacokinetics of multiple doses of 75 mg tapentadol IR for the relief of moderate to severe post-operative pain following a bunionectomy. The active comparator was morphine IR 30 mg. Subjects took tapentadol IR, morphine IR or placebo every 4 to 6 hours for 3 days (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first study drug administration ['early second dose']). For inclusion, a baseline pain intensity of ≥4 on the 11-point (0 to 10) pain intensity NRS and at least moderate pain on a 4-point VRS rated within 30 minutes before randomisation was required. In case the study drug did not provide sufficient pain relief, subjects were allowed to take a fixed combination of paracetamol/acetaminophen 500 mg and hydrocodone 5 mg as a rescue. Intake of this additional analgesic medication during the double-blind period was not considered a reason to discontinue subjects from the study. The primary variable was the $SPID_{48}$ based on the NRS which was calculated up to the time of the first intake of additional analgesic medication.

Demographic and baseline characteristics

In total, there were 244 women (83.8%) and 47 men (16.2%) in the Safety Analysis Set of KF5503/37. The ratio of men to women was slightly higher in the morphine IR 30 mg group (24.0% to 76.0%), than in the placebo group (11.1% to 88.9%) and tapentadol IR 75 mg group (13.5% to 86.5%). The majority of subjects where White (54.6%, see Table 53). The treatment groups were similar with respect to their mean age (44.0 years, with 94.2% being under 65 years old and the age ranging from 18 years to 78 years), mean weight (74.2 kg), mean height (165.0 cm) and body mass index (27.2 kg/m^2). For the Intent-to-Treat population, the mean baseline pain intensity based on the 11-point NRS was similar in all treatment groups (overall mean of 7.1, see Table 54).

Table 53: Descriptive statistics for demographic parameters (Bunionectomy: KF5503/37: Safety Analysis Set)

Parameter	Statistic	Placebo (N = 99)	Tapentadol IR 75 mg (N = 96)	Morphine IR 30 mg (N = 96)	Total (N = 291)
Sex					
Male	n (%)	11 (11.1)	13 (13.5)	23 (24.0)	47 (16.2)
Female	n (%)	88 (88.9)	83 (86.5)	73 (76.0)	244 (83.8)
Race/Ethnicity					
White	n (%)	60 (60.6)	48 (50.0)	51 (53.1)	159 (54.6)
Black or of African descent	n (%)	18 (18.2)	22 (22.9)	18 (18.8)	58 (19.9)
Asian	n (%)	0	1 (1.0)	2 (2.1)	3 (1.0)
Other	n (%)	0	2 (2.1)	0	2 (0.7)
Hispanic or Latino	n (%)	20 (20.2)	23 (24.0)	24 (25.0)	67 (23.0)
American Indian or Alaska native	n (%)	1 (1.0)	0	0	1 (0.3)
Native Hawaiian or other pacific islander	n (%)	0	0	1 (1.0)	1 (0.3)
Age (years)	Mean	43.8	44.6	43.7	44.0
	SD	13.93	12.58	14.19	13.55
	Min	18	21	18	18
	Max	74	72	78	78
<65 years	n (%)	91 (91.9)	94 (97.9)	89 (92.7)	274 (94.2)
≥65 years	n (%)	8 (8.1)	2 (2.1)	7 (7.3)	17 (5.8)
Weight (kg)	Mean	73.4	73.7	75.3	74.2
	SD	16.05	15.35	17.20	16.18
Height (cm)	Mean	164.2	164.6	166.4	165.0
	SD	8.88	9.73	10.79	9.84
Body mass index (kg/m^2)	Mean	27.2	27.2	27.3	27.2
	SD	5.28	5.08	6.30	5.56

N or n = number of subjects; SD = standard deviation; Min = minimum; Max = maximum; IR = immediate release

Table 54: Descriptive statistics for baseline pain intensity based on NRS (Bunionectomy: KF5503/37: Intent-to-Treat population)

	Statistics	Placebo (N = 96)	Tapentadol IR 75 mg (N = 96)	Morphine IR 30 mg (N = 93)	Total [a] (N = 285)
Baseline pain intensity (NRS)					
	Mean	7.1	6.8	7.4	7.1
	SD	1.81	1.83	1.69	1.79
	Min	4	4	4	4
	Median	7.0	7.0	8.0	7.0
	Max	10	10	10	10
Moderate (4 to <6)	n (%)	24 (25.0)	24 (25.0)	15 (16.1)	63 (22.1)
Severe (≥6)	n (%)	72 (75.0)	72 (75.0)	78 (83.9)	222 (77.9)

a) Six subjects were excluded form the Intent-to-Treat population because no baseline pain intensity data was available.
NRS = Numerical rating scale; N or n = number of subjects; SD = standard deviation;
Min = minimum; Max = maximum; IR = immediate release

Subject disposition

In total, 426 subjects were screened and 291 subjects were randomised in 6 centres in the USA. All randomised subjects were treated with study drug: 99 subjects to the placebo group, 96 subjects to the tapentadol IR 75 mg group and 96 subjects to the morphine IR 30 mg

group. In the placebo group, 95 subjects (96.0%) completed the 72-hour double-blind treatment period compared to 94 subjects (97.9%) in the tapentadol IR 75 mg group and 90 subjects (93.8%) in the morphine IR 30 mg group (see Table 55). A low overall number of subject discontinuations was observed in this study most likely due to the fact that subjects were allowed to take rescue medication if they required it. The number of subjects discontinued from the study was similar among treatment groups (4.0% in the placebo group, 2.1% in the tapentadol IR 75 mg group and 6.3% in the morphine IR 30 mg group). Of the 12 subjects who discontinued, 6 subjects discontinued because of adverse events, 4 subjects because of lack of efficacy and two subjects discontinued because they withdrew their consent.

Table 55: Completion and discontinuation information (Bunionectomy: KF5503/37: Overall)

Status	Placebo N (%)	Tapentadol IR 75 mg N (%)	Morphine IR 30 mg N (%)	Total N (%)
Screened				426
Randomized	99 (100)	96 (100)	96 (100)	291 (100)
Treated	99 (100)	96 (100)	96 (100)	291 (100)
Completed 72-hour double-blind period	95 (96.0)	94 (97.9)	90 (93.8)	279 (95.9)
Withdrawn from 72-hour double-blind period	4 (4.0)	2 (2.1)	6 (6.3)	12 (4.1)
• Subject choice (subject withdrew consent)	1 (1.0)	0	1 (1.0)	2 (0.7)
• Adverse event	1 (1.0)	2 (2.1)	3 (3.1)	6 (2.1)
• Lack of efficacy	2 (2.0)	0	2 (2.1)	4 (1.4)
Completed study	95 (96.0)	94 (97.9)	90 (93.8)	279 (95.9)
Withdrawn from study	4 (4.0)	2 (2.1)	6 (6.3)	12 (4.1)
• Subject choice (subject withdrew consent)	1 (1.0)	0	1 (1.0)	2 (0.7)
• Adverse event	1 (1.0)	2 (2.1)	3 (3.1)	6 (2.1)
• Lack of efficacy	2 (2.0)	0	2 (2.1)	4 (1.4)

N = number of subjects; IR = immediate release

Results

Primary endpoint – Sum of pain intensity difference at 48 hours

An overview of the primary efficacy results from the double-blind period of KF5503/37 is shown in Table 56. For the Intent-to-Treat population, tapentadol IR 75 mg demonstrated a statistically significant improvement in pain relief compared to placebo based on the primary endpoint and using the LOCF imputation strategy (least-square mean difference to placebo of 70.8; p-value <0.001). Similar results were observed when using the alternative imputation strategies of BOCF and WOCF. These results were further substantiated by an additional sensitivity analysis in which all pain intensity assessments collected up to 4 hours after each dose of allowed additional analgesic were imputed using LOCF. Morphine IR 30 mg also demonstrated a statistically significant improvement in pain relief compared to placebo based on the primary endpoint (least-square mean difference to placebo of 109.4; p-value < 0.001) thereby confirming the assay sensitivity of the study.

Table 56: Results for sum of pain intensity difference at 48 hours ($SPID_{48}$) using last (LOCF), worst (WOCF) and baseline (BOCF) observation carried forward (Bunionectomy: KF5503/37; Intent-to-Treat population)

Imputation	Statistics	Placebo (N = 96)	Tapentadol IR 75 mg (N = 96)	Morphine IR 30 mg (N = 93)
LOCF	N	96	96	93
	Mean	-17.5	46.2	102.5
	SD	111.27	130.83	153.26
	LS-means [a]	-	70.8	109.4
	(95% CI)	-	[35.9;105.6]	[74.2;144.6]
	Raw p-value	-	<0.0001	<0.0001
BOCF	N	96	96	93
	Mean	19.9	62.2	112.8
	SD	57.19	89.64	127.57
	LS-means [a]	-	44.8	88.2
	(95% CI)	-	[18.2;71.4]	[61.4;115.1]
	Raw p-value	-	0.0010	<0.0001
WOCF	N	96	96	93
	Mean	-37.9	23.7	88.4
	SD	104.88	126.19	155.05
	LS-means [a]	-	67.6	116.9
	(95% CI)	-	[32.9;102.3]	[81.8;152.0]
	Raw p-value	-	0.0002	<0.0001

a) Difference from placebo

CI = confidence interval; N = number of subjects; SD = standard deviation; LS = least square; LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; IR = immediate release

Sum of pain intensity difference (at non-primary time-points)

The results for the SPID at 6, 12, 24 and 72 hours confirmed the results of the primary endpoint (SPID at 48 hours). In the Intent-to-Treat population, both active treatment groups showed a statistically significant difference to placebo for the SPID at all time-points (see Table 57). Similar efficacy was observed between the tapentadol IR 75 mg and morphine IR 30 mg groups based on the least-square mean differences to placebo through 12 hours of treatment; after 12 hours there was a numerical separation between the groups, with morphine IR showing greater pain relief.

Additional non-primary derived pain scale variables

The results for TOTPAR and SPRID at all time-points confirmed the results for the primary efficacy endpoint (all p-values <0.001). The difference in SPRID between morphine IR 30 mg and placebo was larger than the difference between tapentadol IR 75 mg and placebo from 48 hours onwards. The differences to placebo in TOTPAR were similar between tapentadol IR 75 mg and morphine IR 30 mg at all time-points.

Table 57: Results for sum of pain intensity difference (SPID) at 6, 12, 24, 72 hours using last observation carried forward (LOCF) (Bunionectomy: KF5503/37: Intent-to-Treat population)

Time	Statistics	Placebo (N = 96)	Tapentadol IR 75 mg (N = 96)	Morphine IR 30 mg (N = 93)
Hour 6	N	96	96	93
	Mean	-1.2	8.0	8.0
	SD	13.10	13.51	15.59
	LS-means [a]	-	9.9	8.1
	(95% CI)	-	[6.2;13.6]	[4.4;11.8]
	Raw p-value	-	<0.001	<0.001
Hour 12	N	96	96	93
	Mean	-4.7	14.4	17.9
	SD	24.82	28.89	32.12
	LS-means [a]	-	20.6	20.1
	(95% CI)	-	[13.2;28.0]	[12.6;27.6]
	Raw p-value	-	<0.001	<0.001
Hour 24	N	96	96	93
	Mean	-10.7	22.3	41.3
	SD	51.28	60.17	68.96
	LS-means [a]	-	36.4	46.7
	(95% CI)	-	[20.7;52.0]	[30.9;62.6]
	Raw p-value	-	<0.001	<0.001
Hour 72	N	96	96	93
	Mean	-19.1	78.4	174.1
	SD	179.48	212.05	242.00
	LS-means [a]	-	108.2	177.1
	(95% CI)	-	[51.9;164.5]	[120.3;234.0]
	Raw p-value	-	<0.001	<0.001

a) Difference from placebo

N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; IR = immediate release

Responder rates

The proportion of subjects with a response at 48 hours ≥30% was 12.5% in the placebo group, 30.2% in the tapentadol IR group (p = 0.0025) and 51.6% in the morphine IR group (p <0.001) (see Table 58). Similar results were obtained for the≥30% and ≥50% response rates at time-points 12 hours, 24 hours and 72 hours.

Table 58: Distribution of responder rates at 48 hours using pain intensity at rest (NRS) per response threshold (Bunionectomy: KF5503/37: Intent-to-Treat population) (M2.7.3, p76)

	Statistics	Placebo (N = 96)	Tapentadol IR 75 mg (N = 96)	Morphine IR 30 mg (N = 93)
Response (≥30%)				
Number of responders	N (%)	12 (12.5)	29 (30.2)	48 (51.6)
p-value				
Overall		<0.0001		
Pair-wise comparison versus placebo			0.0025	<0.0001
Response (≥50%)				
Number of responders	N (%)	10 (10.4)	25 (26.0)	42 (45.2)
p-value				
Overall		<0.0001		
Pair-wise comparison versus placebo			0.0048	<0.0001

N = number of subjects; NRS = numerical rating scale; IR = immediate release

Time to rescue medication

Subjects in all treatment groups used additional analgesic medication. More subjects in the placebo group (85.4%) used additional analgesic medications compared to the tapentadol IR 75 mg (64.6%) and morphine IR 30 mg (49.5%) groups. The median time to first intake of additional analgesic medication was shorter in the placebo group at 4.8 hours than in the tapentadol IR group at 8.2 hours (Intent-to-Treat population). The mean time to first rescue medication for the morphine IR 30 mg group was 8.8 hours. For both active treatment groups, the distribution of the time to first additional analgesic medication was placebo ($p < 0.001$).

Time to pain relief

The percentage of subjects in the placebo group who experienced confirmed perceptible pain relief was 46.9% compared to 82.3% of subjects in the tapentadol IR 75 mg group and 64.5% of subjects in the morphine IR 30 mg group. The median time to confirmed perceptible pain relief was faster in both active treatment groups than in the placebo group (4.8 hours in the placebo group, 0.6 hours in the tapentadol IR 75 mg group and 0.9 hours in the morphine IR 30 mg group). The difference to placebo was statistically significant for both tapentadol IR 75 mg ($p < 0.001$) and for morphine IR 30 mg ($p = 0.036$).

The time to onset of confirmed perceptible pain relief for tapentadol IR 75 mg (median: 0.6 hours) was numerically faster than for morphine IR 30 mg (median: 0.9 hours). In addition, the number of subjects in the morphine IR group (62.4%) that required a second dose within 3 hours after the first dose was higher than the corresponding number of subjects in the tapentadol IR 75 mg group (47.9%).

Patient global impression of change

For the distribution of PGIC scores, there was a statistically significant improvement in both active treatment groups compared with the placebo group (all nominal p-values <0.0001). In the active treatment groups, at 24 hours, more than 50% of the subjects graded their pain as much or very much improved compared with 37.5% of subjects on placebo. Similar outcomes were observed at 48 h and 72 h, although no statistically significant difference to placebo was observed for tapentadol IR 75 mg at 48 hours.

Supportive studies

KF5503/31 – Hip replacement

Study design

This was a multicentre, randomised, double-blind, parallel-group, placebo- and active-controlled study to evaluate the efficacy and safety of multiple doses of 50 mg, 75 mg and 100 mg tapentadol IR in the treatment of acute pain from total hip replacement surgery followed by a voluntary open-label extension. The active comparator was oxycodone IR 10 mg. Subjects took tapentadol IR, oxycodone IR, or placebo every 4 hours to 6 hours for 3 days (with the option of taking the second dose as early as 1 hour but no later than 6 hours after the first administration ['early second dose']). For inclusion, a baseline pain intensity of ≥4 on the 11-point (0 to 10) pain intensity NRS rated within 30 minutes before randomisation was required. Use of any additional analgesic medication during the double-blind treatment period led to the subject being discontinued from the study for lack of efficacy. The primary variable was the $SPID_{48}$ based on the NRS. This study was terminated early due to slow recruitment and a high discontinuation rate. As a consequence, for efficacy only the analysis on the primary endpoint will be presented and the results should be considered as being exploratory in nature.

Demographic and baseline characteristics

Most demographic and baseline characteristics were balanced across the treatment groups (see Table 59). Most subjects in the study were White (93%) and 54% of subjects were women. The average age of the study population was 63 years. In total, 79% of subjects were categorised as having moderate baseline pain intensity (NRS pain intensity ≥4 and <6) and 21% as having severe baseline pain intensity (≥6); the overall mean score was 4.8. A higher percentage of subjects reported severe baseline pain intensity in the placebo, tapentadol IR 50 mg and tapentadol IR 75 mg groups (23%, 30% and 27%, respectively) compared with the tapentadol IR 100 mg and oxycodone IR 10 mg groups (11% and 16%, respectively). Some 25 to 32% of subjects reported prior opioid experience at screening defined as any opioid analgesic used within 30 days prior to the study entry.

Table 59: Demographic and baseline characteristics (Hip replacement: KF5503/31: Safety Analysis Set)

		Tapentadol IR			Oxycodone	
	Placebo	50 mg	75 mg	100 mg	IR 10 mg	Total
	(N=75)	(N=77)	(N=71)	(N=75)	(N=67)	(N=365)
Sex,						
Male (n [%])	31 (41)	38 (49)	39 (55)	34 (45)	26 (39)	168 (46)
Female (n [%])	44 (59)	39 (51)	32 (45)	41 (55)	41 (61)	197 (54)
Racial/ethnic group						
White (n [%])	71 (95)	67 (87)	70 (99)	69 (92)	61 (91)	338 (93)
Black (n [%])	2 (3)	5 (6)	0	5 (7)	6 (9)	18 (5)
Hispanic (n [%])	2 (3)	2 (3)	1 (1)	0	0	5 (1)
Other (n [%])	0	3 (4)	0	1 (1)	0	4 (1)
Age						
Mean (years [SD])	64.0 (11.23)	62.2 (12.20)	62.8 (9.24)	63.3 (10.30)	61.3 (12.39)	62.7 (11.11)
Median (years)	65.0	64.0	62.0	64.0	63.0	64.0
Range (years)	(30;83)	(28;84)	(43;80)	(32;80)	(20;80)	(20;84)
<65 years (n [%])	36 (48)	40 (52)	37 (52)	39 (52)	39 (58)	191 (52)
≥65 years (n [%])	39 (52)	37 (48)	34 (48)	36 (48)	28 (42)	174 (48)
Baseline pain intensity score based on NRS						
Mean (SD)	5.0 (1.40)	5.1 (1.32)	4.8 (1.05)	4.6 (0.84)	4.8 (1.24)	4.8 (1.20)
Median	5.0	5.0	4.0	4.0	4.0	4.0
Range	(4;10)	(4;10)	(4;8)	(4;8)	(4;10)	(4;10)
Moderate (4 to <6) (n [%])	58 (77)	54 (70)	52 (73)	67 (89)	56 (84)	287 (79)
Severe (≥6) (n [%])	17 (23)	23 (30)	19 (27)	8 (11)	11 (16)	78 (21)
Weight (N)	75	77	71	75	66	364
Mean (kg [SD])	84.2 (17.48)	87.0 (19.49)	87.8 (20.62)	85.3 (20.15)	83.0 (20.96)	85.5 (19.70)
Median (kg)	81.6	86.2	84.8	82.8	79.9	83.9
Range (kg)	(53;132)	(57;159)	(47;159)	(40;137)	(40;131)	(40;159)
Baseline BMI (N)	75	77	71	75	66	364
Mean (kg/m^2 [SD])	29.7 (5.13)	30.4 (6.40)	29.7 (5.85)	29.4 (5.95)	29.2 (6.08)	29.7 (5.87)
Median (kg/m^2)	28.8	28.8	29.5	28.2	28.0	28.5
Range (kg/m^2)	(22;45)	(20;62)	(20;49)	(16;49)	(17;44)	(16;62)
PCA stop to first dose (N)	75	77	70	74	67	363
Mean (hour [SD])	1.74 (1.375)	1.83 (1.079)	2.01 (1.311)	2.02 (1.478)	1.79 (1.218)	1.88 (1.297)
Median (hour)	1.50	1.58	1.64	1.75	1.50	1.58
Range (hour)	(-4.2;5.8)	(0.0;6.3)	(-1.0;6.2)	(-1.3;6.2)	(-0.4;6.0)	(-4.2;6.3)

PCA = patient controlled analgesia; N or n = number of subjects; NRS = Numerical rating scale; SD = standard deviation; IR = immediate release; BMI = body mass index

Subject disposition

A total of 590 subjects were screened and 367 subjects were randomised. For the double-blind period, the 367 subjects were randomised to the 5 treatment groups in a 1:1:1:1:1 ratio (75 subjects in the placebo, 77 in the tapentadol IR 50 mg, 71 in the tapentadol IR 75 mg, 75 in the tapentadol IR 100 mg and 69 in the oxycodone IR 10 mg groups). Of the randomised subjects, 365 subjects received tapentadol IR, oxycodone IR or placebo. Two subjects were enrolled and randomised to the oxycodone IR 10 mg group but did not receive it. The percentage of subjects who completed the double-blind period was lowest in the placebo group (32%) and higher in the active-treatment groups (40% to 54%) (see Table 60).

Table 60: Completion and discontinuation information (Hip replacement: KF5503/31: Safety Set)

	Placebo	Tapentadol IR			Oxycodone	Total
		50 mg	75 mg	100 mg	IR 10 mg	
	(N=75)	(N=77)	(N=71)	(N=75)	(N=67)	(N=365)
Completion Status	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Completed	24 (32)	35 (45)	31 (44)	30 (40)	36 (54)	156 (43)
Withdrawn	51 (68)	42 (55)	40 (56)	45 (60)	31 (46)	209 (57)
Subject choice (subject withdrew consent)	6 (8)	4 (5)	8 (11)	6 (8)	6 (9)	30 (8)
Adverse event	2 (3)	8 (10)	7 (10)	15 (20)	5 (7)	37 (10)
Lack of efficacy	42 (56)	22 (29)	22 (31)	21 (28)	17 (25)	124 (34)
Other	1 (1)	8 (10)	3 (4)	3 (4)	3 (4)	18 (5)

Note: Percentages were calculated with the number of subjects in each group as denominator.

Completion and discontinuation information was based on the study termination electronic Case Report Form page.

Lack of Efficacy was defined as use of additional analgesic medication during the double-blind treatment period

N or n = number of subjects; IR = immediate release

Results

Primary endpoint – Sum of pain intensity difference at 48 hours

For the Intent-to-Treat population, all tapentadol IR treatment groups showed a statistically significant (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain on the primary efficacy variable of $SPID_{48}$ compared with placebo using the LOCF imputation for subjects who discontinued. All tapentadol treatment groups showed similar efficacy (see Table 61). Oxycodone IR 10 mg also showed a statistically significant (nominal p-value <0.001) difference from placebo, validating the study assay sensitivity.

Table 61: Sum of pain intensity difference at Hour 48 ($SPID_{48}$) using last observation carried forward (LOCF) (Hip replacement: KF5503/31: Intent-to-Treat population)

		Tapentadol IR			Oxycodone
	Placebo	50 mg	75 mg	100 mg	IR 10 mg
	(N=68)	(N=70)	(N=64)	(N=68)	(N=60)
N	68	70	64	68	60
Mean (SD)	-18.6 (130.74)	73.9 (123.89)	54.4 (128.22)	49.3 (136.92)	57.6 (125.73)
Median (range)	-28.9 (-284,342)	99.8 (-235,295)	73.7 (-238,368)	93.4 (-287,335)	77.9 (-285,354)
LS-means (difference from placebo)		91.4	81.5	81.5	82.4
(95% CI)		[49.77;133.07]	[38.66;124.29]	[39.21;123.80]	[38.96;125.88]
Raw p-value		<0.001	<0.001	<0.001	<0.001
Adjusted p-value using Hochberg		<0.001	<0.001	<0.001	<0.001

The summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief.

This study was terminated early due to slow recruitment and a high discontinuation rate. As a consequence, the results have to be considered as being exploratory in nature.

LOCF = last observation carried forward; SPID = sum of pain intensity difference; N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; IR = immediate release

KF5503/33 - End-stage degenerative joint disease

Study design

A multicentre, randomised, double-blind, parallel-group, active- and placebo-controlled, out-patient study to evaluate the efficacy and safety of multiple doses of 50 mg or 75 mg of tapentadol IR for the relief of moderate to severe pain in subjects with end-stage degenerative joint disease of the hip or knee. The active comparator was oxycodone IR 10 mg. Subjects took tapentadol IR, oxycodone IR or placebo every 4 to 6 hours during waking hours for 10 days. For inclusion, subjects were required to have the following during the last 3 days of pain assessments during the run-in period: 1) a mean NRS pain intensity score ≥5 (after rounding 4.5 and above to an integer) and 2) a minimum single pain intensity assessment score of ≥3. Use of any additional analgesic medication during the double-blind treatment period led to the subject being discontinued from the study for lack of efficacy. However, these subjects were permitted to continue use of their prior, stable non-opioid analgesic regimens during the study. The primary variable was the 5-day SPID based on the NRS.

Demographic and baseline characteristics

Demographics and baseline characteristics were balanced across the treatment groups (see Table 62). Most subjects were White (91%). Fifty-one percent of the subjects across all treatment groups were men and 61% were <65 years of age (overall mean age: 61.2 years). The percentage of subjects taking non-opioid-analgesic concomitant medications during the double-blind period was similar across treatment groups (83% in the placebo, 83% in the tapentadol IR 50 mg, 83% in the tapentadol IR 75 mg and 80% in the oxycodone IR groups). In total, 69% of subjects were categorised as having severe baseline pain intensity (NRS pain intensity ≥6) and 31% were categorised as having moderate baseline pain.

Subject disposition

A total of 1101 subjects were screened and 674 subjects were randomised: 172 subjects to placebo, 161 subjects to tapentadol IR 50 mg, 169 subjects to tapentadol IR 75 mg and 172 subjects to oxycodone IR 10 mg group (1:1:1:1 ratio). Of these subjects, 8 subjects did not take study drug (3 subjects in the placebo group, four subjects in the tapentadol IR 50 mg group and one subject in the tapentadol IR 75 mg group). These subjects were excluded from all efficacy analyses. The percentage of subjects who completed the double-blind period was highest in the placebo group (90%) and lower in the tapentadol IR treatment groups with the percentage decreasing with increasing tapentadol IR dose from 50 mg to 75 mg (82% to 74%, respectively) (see Table 63). The main reason for withdrawal in the tapentadol groups was adverse events.

Table 62: Demographic and baseline characteristics (End-stage degenerative joint disease: KF5503/33: Intent-to-Treat population)

	Placebo (N = 169)	Tapentadol IR 50 mg (N = 153)	Tapentadol IR 75 mg (N = 166)	Oxycodone IR 10 mg (N = 171)	Total (N = 659)
Sex					
Male (n [%])	80 (47)	79 (52)	88 (53)	88 (51)	335 (51)
Female (n [%])	89 (53)	74 (48)	78 (47)	83 (49)	324 (49)
Racial/ethnic group					
White (n [%])	158 (93)	138 (90)	148 (89)	156 (91)	600 (91)
Black (n [%])	9 (5)	5 (3)	6 (4)	10 (6)	30 (5)
Hispanic (n [%])	0	5 (3)	7 (4)	3 (2)	15 (2)
Other (n [%])	2 (1)	5 (3)	5 (3)	2 (1)	14 (2)
Age					
Mean (years [SD])	61.3 (10.08)	60.6 (10.16)	60.8 (10.04)	62.1 (9.05)	61.2 (9.83)
Median (years)	62.0	60.0	61.5	62.0	62.0
Range (years)	(20;79)	(31;79)	(34;78)	(41;79)	(20;79)
<65 years (n [%])	104 (62)	91 (59)	103 (62)	101 (59)	399 (61)
≥65 years (n [%])	65 (38)	62 (41)	63 (38)	70 (41)	260 (39)
Weight					
Mean (kg [SD])	98.4 (24.96)	96.4 (25.02)	97.2 (22.03)	96.1 (22.95)	97.0 (23.71)
Median (kg)	93.8	92.5	95.1	93.0	93.4
Range (kg)	(48;175)	(54;200)	(54;181)	(54;181)	(48;200)
Pain intensity score based on NRS					
Moderate (4.5 to <6) (n [%])	48 (28)	43 (28)	52 (31)	60 (35)	203 (31)
Severe (≥6) (n [%])	121 (72)	110 (72)	114 (69)	111 (65)	456 (69)
Body mass index (N)	168	151	166	171	656
Mean (kg/m^2 [SD])	33.8 (7.71)	33.0 (8.02)	33.6 (7.79)	33.2 (6.86)	33.4 (7.58)
Median (kg/m^2)	32.1	31.2	32.8	32.2	32.0
Range (kg/m^2)	(19;60)	(21;76)	(21;64)	(20;52)	(19;76)

Notes: Percentages calculated with the number of subjects in each group as denominator

N or n = number of subjects; SD = standard deviation; NRS = numerical rating scale ; IR = immediate release

Table 63: Completion and discontinuation information: (End-stage degenerative joint disease: KF5503/33: Safety Analysis Set)

	Placebo (N = 169)	Tapentadol IR 50 mg (N = 157)	Tapentadol IR 75 mg (N = 168)	Oxycodone IR 10 mg (N = 172)
Completion Status	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Completed [a]	152 (90)	129 (82)	125 (74)	112(65)
Withdrawn [a]	17 (10)	28 (18)	43 (26)	60 (35)
Subject choice [c]	2 (1)	1 (1)	3 (2)	2 (1)
Lost to follow-up	0	0	1 (1)	1 (1)
Adverse event	7 (4)	21 (13)	31 (18)	52 (30)
Lack of efficacy [b]	6 (4)	2 (1)	2 (1)	2 (1)
Other	2 (1)	4 (3)	6 (4)	3 (2)

Note: Percentages calculated with the number of subjects in each group as denominator.

a) Completion and discontinuation information was based on the study termination electronic Case Report Form page.

b) Lack of efficacy is defined as use of 'rescue medication', defined as any additional analgesic taken during the double-blind treatment period.

c) Subject withdrew consent.

N = number of subjects; IR = immediate release

Results

Primary endpoint – Sum of pain intensity difference at 5 days

An overview of the primary efficacy results and selected secondary efficacy results from KF5503/33 is shown in Table 64. For the Intent-to-Treat population, both tapentadol IR treatment groups showed a significant (all p-values <0.001 adjusted for multiple comparisons using the Hochberg procedure) improvement in pain for the primary efficacy variable of 5-day SPID compared with placebo using LOCF Imputation. However, no numerical trend of increasing efficacy was observed with increasing tapentadol IR dose (mean 5-day SPID: 229.2 and 223.8 in the tapentadol IR 50 mg and tapentadol IR 75 mg groups, respectively). The mean total daily dose was different for the subjects in the tapentadol IR 50 mg and tapentadol IR 75 mg groups. For Day 2 through Day 5 of treatment, it was 186 mg in the tapentadol IR 50 mg group and 274 mg in the tapentadol IR 75 mg group.-Oxycodone IR 10 mg (mean 5-day SPID: 236.5) also showed a significant (nominal p-value <0.001) difference from placebo (mean 5-day SPID: 130.6) which validated the study assay sensitivity.

Analysis of mean 5-day SPID results based on BOCF imputation showed similar results to those observed using the LOCF imputation (even after post-hoc adjustment for multiple comparisons using the Hochberg procedure). Analysis of mean 5-day SPID results based on WOCF and modified LOCF imputations also showed similar results to those observed using the LOCF imputation. For the 5-day SPID, results in the oxycodone IR 10 mg group were numerically similar to those in the tapentadol IR groups.

Sum of pain intensity difference (at non-primary time-points)

At both non-primary time-points (2-day and 10-day SPID), there was a statistically significant improvement in SPID in both tapentadol IR treatment groups compared with placebo (all nominal p-values <0.001) based on the LOCF imputation (see Table 65). Across time-points, there was no clear trend of increasing mean values with increasing tapentadol IR dose (50 mg to 75 mg). The results were consistent with the improvement in pain intensity difference for both tapentadol IR treatment groups for the primary efficacy variable, the 5-day SPID. Oxycodone IR 10 mg also showed a statistically significant difference from placebo (all nominal p-values <0.001) at both time-points, validating the study assay sensitivity. The 2-day and 10-day SPID results also showed statistically significant improvements in pain compared with placebo for both tapentadol IR treatments based on the BOCF imputation. Oxycodone IR 10 mg also showed a statistically significant difference from placebo.

Table 65: Primary endpoint: 5-day sum of pain intensity difference (SPID): comparison with placebo (Hip replacement: KF5503/33: Intent-to-Treat population)

		Tapentadol IR		Oxycodone IR
	Placebo	50mg	75mg	10mg
	(N = 169)	(N = 153)	(N = 166)	(N = 171)
5-day SPID (LOCF)				
Mean (SD)	130.6 (182.77)	229.2 (228.92)	223.8 (217.76)	236.5 (222.82)
Median (range)	86.6 (-358,695)	164.1 (-480,881)	210.2 (-308,823)	206.7 (-268,884)
LS-means difference from placebo (95% CI)		101.2 [54.58;147.89]	97.5 [51.81;143.26]	111.9 [66.49;157.38]
Adjusted p-value versus placebo [a, b]		<0.001	<0.001	--
Unadjusted p-value versus placebo [a]		--	--	<0.001
5-day SPID (BOCF)				
LS-means difference from placebo (95% CI)		92.1 [48.18;136.09]	80.1 [37.02;123.18]	78.9 [36.08;121.71]
p-value [a]		<0.001	<0.001	--
5-day SPID (WOCF)				
LS-means difference from placebo (95% CI)		89.9 [44.32;135.38]	77.7 [33.07;122.31]	74.6 [30.30;118.99]
p-value [a,c]		<0.001	<0.001	<0.001

Higher value in SPID indicates greater pain relief.

a) Based on analysis of covariance model with factors of treatment, pooled center, and baseline pain intensity as a covariate.

b) P-values adjusted for multiplicity using Hochberg procedure.

c) P-values for tapentadol IR groups are adjusted for multiplicity using Hochberg procedure. Analysis of covariance model includes all treatment groups.

N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; LOCF = last observation carried forward; BOCF = baseline observation carried forward; WOCF = worst observation carried forward; SPID = sum of pain intensity difference; IR = immediate release

Table 66: Descriptive statistics and pair-wise comparison of sum of pain intensity difference (SPID) at Day 2 and Day 10 using last observation carried forward (LOCF) (End-stage degenerative joint disease: KF5503/33: Intent-to-Treat population)

		Tapentadol IR		Oxycodone
	Placebo	50 mg	75 mg	IR 10 mg
	(N = 169)	(N = 153)	(N = 166)	(N = 171)
Day 1- Day 2				
Mean (SD)	45.2 (74.64)	80.9 (82.01)	82.8 (81.66)	87.7 (90.46)
Median	29.1	74.6	62.6	75.4
(range)	(-237,275)	(-167,315)	(-120,301)	(-88,416)
LS-means difference from placebo	--	36.3	38.8	44.3
(95% CI)	--	[18.25;54.27]	[21.16;56.46]	[26.75;61.83]
Raw p-value	--	<0.001	<0.001	<0.001
Day 1- Day 10				
Mean (SD)	246.3 (346.78)	470.7 (445.34)	427.8 (418.90)	442.8 (421.25)
Median	179.5	389.2	392.8	394.2
(range)	(-678,1331)	(-880,1775)	(-568,1591)	(-538,1786)
LS-means difference from placebo	--	230.5	191.6	209.9
(95% CI)	--	[141.11;319.84]	[103.98;279.14]	[122.85;296.9]
Raw p-value	--	<0.001	<0.001	<0.001

The summary and analysis are based on the LOCF imputation method. Higher value in SPID indicates greater pain relief.

N = number of subjects; SD = standard deviation; LS = least square; CI = confidence interval; IR = immediate release

Additional non-primary derived pain scale variables

For further secondary pain scale variables that were statistically tested (TOTPAR and SPRID), both tapentadol IR treatment groups showed significant improvements (all nominal p-values <0.001) compared with the placebo group at all time-points (2-, 5- and 10-day). For variables not statistically tested (PID, PAR and PRID) numerical indications of efficacy were observed.

Responder rates

The proportion of subjects who showed ≥30% improvement in pain intensity from baseline at Day 5 was 30.2% in placebo, 43.1% in tapentadol IR 50 mg and 41.0% in tapentadol IR 75 mg (p-values 0.028 and 0.033, respectively) (see Table 67). The proportion of subjects who showed ≥50% improvement in pain intensity at Day 5 was also higher in the tapentadol IR treatment groups compared with placebo: 13.0% in placebo, 27.5% in tapentadol IR 50 mg and 25.9% in tapentadol IR 75 mg (p-values 0.003 and 0.002, respectively). The proportion of subjects who showed ≥30% improvement in pain intensity from baseline at Day 5 was 39.8% in the oxycodone IR 10 mg group (nominal p-value 0.091). The proportion of subjects who showed ≥50% improvement in pain intensity from baseline at Day 5 was 24.6% in the oxycodone IR 10 mg group (nominal p-value = 0.007).

The cumulative distribution of responder rates at 5 days were determined for each treatment group and compared using Gehan's (pre-specified) and log-rank (post-hoc) tests. A higher percentage of subjects in all active-treatment groups showed improvement in pain compared to placebo. A statistically significant difference was observed between the tapentadol IR 50 mg group and placebo in the distribution of responder rates based on pain intensity at Day 5 using the Gehan test (p-value = 0.011). There was no statistically significant difference observed between the tapentadol IR 75 mg group and placebo (p-value = 0.107, Gehan test).

Because the Gehan test gives more weight to the subjects with low percent changes from baseline pain intensity, a post-hoc analysis using log-rank test was performed which assigned equal weight to all percent changes from baseline values. The results showed that there were statistically significant differences between each of the tapentadol IR groups and placebo (nominal p-value <0.001 for tapentadol IR 50 mg and nominal p-value = 0.003 for tapentadol IR 75 mg). Similar patterns were observed in the results at Day 2 and Day 10.

Table 67: Comparison of the distributions of responder rates using pain intensity at Day 5 (End-stage degenerative joint disease: KF5503/33: Intent-to-Treat population)

	Placebo	Tapentadol IR		Oxycodone
		50mg	75mg	IR 10 mg
Parameter	(N = 169)	(N = 153)	(N = 166)	(N = 171)
Pain assessment ≥30% improved, n (%)	51 (30.2)	66 (43.1)	68 (41.0)	68 (39.8)
p-value versus placebo [a]		0.028	0.033	0.091
Pain assessment ≥50% improved, n (%)	22 (13.0)	42 (27.5)	43 (25.9)	42 (24.6)
p-value versus placebo [a]		0.003	0.002	0.007
Comparison of distribution of responders				
Gehan p-value (versus placebo)		0.011	0.107	0.626
Log-rank p-value (versus placebo)		<0.001	0.003	0.016

Subjects who discontinued prior to the time interval are considered non-responders.

a) Based on Generalized Cochran-Mantel-Haenszel test for general association controlling for pooled center

N or n = number of subjects; IR = immediate release

Time to rescue medication

In KF5503/33, subjects were allowed to continue non-opioid analgesic medication that they were taking on a stable dose for at least 28 days prior to the study. For the analysis of time to rescue medication, any additional analgesic medication taken during the treatment period was defined as rescue. Since rescue medication was not permitted during the double-blind treatment period, subjects who used such medications were withdrawn due to lack of efficacy. There were no statistically significant differences in distribution of time to rescue medication; likely a result of less than 5% of subjects in any treatment group (4% of subjects in the placebo group, 3% of subjects in each of the tapentadol IR groups and 1% of subjects in the oxycodone IR 10 mg group) taking rescue medication. The low use of rescue medication is likely to be attributed to the high number of subjects who used concomitant non-opioid analgesic medication during the double-blind treatment period (80% to 83% in all treatment groups).

Patient global impression of change

For the distribution of PGIC scores, there was a statistically significant improvement in each tapentadol IR treatment group compared with placebo (nominal p-values <0.001 for tapentadol IR 50 mg and tapentadol IR 75 mg). The percentage of subjects reaching the 'much improved' or 'very much improved' categories was higher in all tapentadol IR treatment groups (49% in the tapentadol IR 50 mg, 42% in the tapentadol IR 75 mg group) compared with the placebo group (21%). The corresponding percentage for the oxycodone IR 15 mg group (41%) was similar to that for the tapentadol IR 75 mg group.

Comment: The efficacy data from Study KF5503/33 of tapentadol IR in the relief of pain from end-stage degenerative joint disease of the knee or hip over 10 days were less robust than in the other studies. There was no numerical trend for a dose response observed. Tapentadol IR demonstrated superior efficacy compared with placebo on the primary (5-day SPID; regardless of missing value imputation method) and most secondary variables

(SPID at other time-points, TOTPAR, SPRID, patient global impression of change (PGIC) and proportion of subjects who showed 50% improvement in pain intensity). However efficacy results generally showed that oxycodone IR 15 mg had superior efficacy to tapentadol in this study. This study is considered supportive rather than pivotal in terms of efficacy.

Subgroup analyses

Baseline pain intensity

In KF5503/35 (abdominal hysterectomy), for SPID at both 24 hours and 48 hours, the least-square mean differences to placebo for subjects with moderate pain in the tapentadol IR and morphine IR treatment groups were statistically significant (all p-values <0.001).Severe pain based on NRS pain score categorization was reported by 28% of subjects at baseline. In these subjects, the least-square mean differences to placebo for $SPID_{24}$ for tapentadol IR 75 mg, tapentadol IR 100 mg and morphine IR 20 mg were statistically significant (all p-values <0.05). For subjects with severe pain, the SPID was numerically better in all active treatment groups than with placebo both at 24 hours and at 48 hours.

In both studies of post-bunionectomy pain (KF5503/32 and KF5503/37) over 75% of the subjects had severe pain at baseline. Efficacy was shown in these subgroups for all doses of tapentadol IR in both studies. In KF5503/32, 75% of subjects had severe pain at baseline. The mean $SPID_{48}$ values were higher for subjects with severe baseline pain intensity compared with those who had moderate baseline pain intensity. In subjects with moderate pain, the least-square mean differences to placebo for tapentadol IR 75 mg, tapentadol IR 100 mg and oxycodone IR 15 mg were statistically significant (all p-values <0.002). For tapentadol IR 50 mg the results were not significant. For subjects with severe pain, the least-square mean differences to placebo for all active groups, including tapentadol IR 50 mg, were statistically significant (all p-values <0.001).

Age, sex, race

No notable differences in efficacy were observed in analyses by age, sex and race.

Analysis of clinical information relevant to dosing recommendations

The dosing recommendation proposed for tapentadol IR is 50 mg, 75 mg, or 100 mg every 4 to 6 hours as needed. This dosing recommendation is based on the efficacy shown in the confirmatory Phase III studies. Both in-patient (following an abdominal hysterectomy, bunionectomy, or hip replacement) and out-patient (end-stage degenerative joint disease) subjects had pain relief over 3 and 10 days, respectively.

A clear numerical dose response was seen in the Phase II studies using single doses of tapentadol IR following third molar tooth surgery (KF5503/02 and KF5503/04) and in the single dose bunionectomy study (KF5503/05). A numerical dose response was also seen in the Phase IIb bunionectomy studies (KF5503/21and KF5503/22. A ceiling effect was not apparent within the dose range tested.

A clear numerical dose response was also seen in the Phase III bunionectomy study (KF5503/32). In this study, the dose relationship was present for efficacy across the tapentadol IR doses of 50 mg to 100 mg with all doses significantly different from placebo on the primary efficacy variable, $SPID_{48}$. A less clear, but numerically suggestive dose response was seen in the abdominal hysterectomy study (KF5503/35), possibly due to the greater number of subjects with moderate baseline pain giving less room for improvement and differentiation between doses and a higher placebo response. No dose response was seen in the KF5503/31 study which was ended early due to slow recruitment and high

discontinuation rates and also included a majority of subjects with moderate baseline pain. The findings in this study have to be considered as being exploratory in nature. In the end-stage degenerative joint disease study (KF5503/33), the mean total daily dose was different for the subjects in the tapentadol IR 50 mg and tapentadol IR 75 mg groups; however the efficacy of tapentadol IR 50 mg and tapentadol IR 75 mg was similar. The lack of a dose-response for efficacy between the dose groups might be attributed to the study design in which subjects were permitted to maintain a stable non-opioid analgesic therapy during the study (a total of 82% of subjects maintained their non-opioid analgesic regimen).

Comment: Overall the clinical evaluator concluded that there is evidence for a numerically increasing efficacy with increasing dose of tapentadol IR in most post-operative studies. The proposed dose range for initiation of treatment, 50 mg to 100 mg, for acute pain lies within the range of effective doses identified in Phase II and Phase III studies.

Persistence of efficacy and/or tolerance effects

KF5503/34

Study design

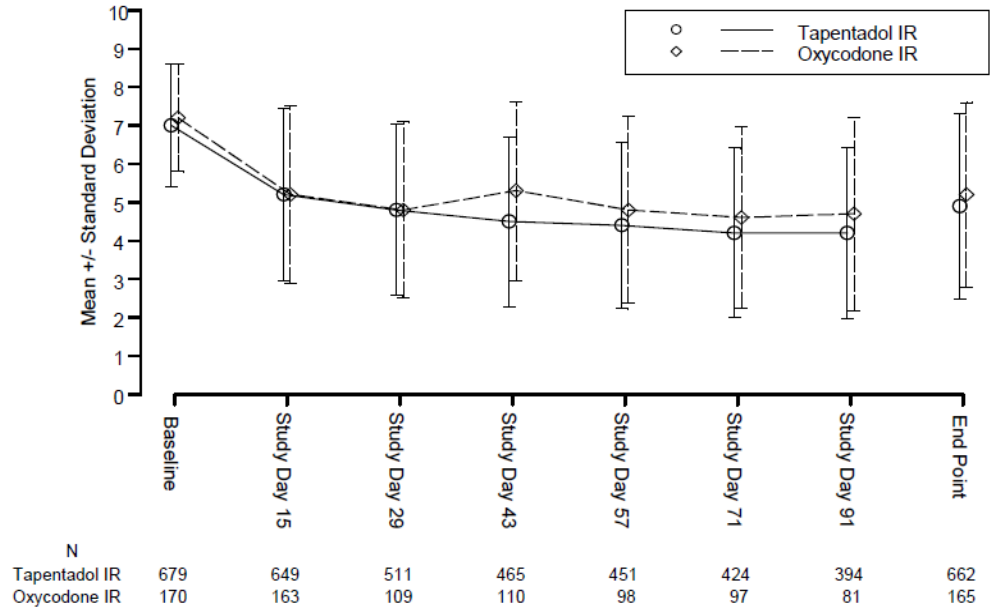
This was a study that examined multiple, flexible doses of 50 mg or 100 mg of tapentadol IR compared to oxycodone IR 10 mg or 15 mg taken every 4 to 6 hours as needed for 90 days in the relief of moderate to severe pain. This study was designed as a safety study and did not evaluate efficacy as a primary endpoint. It is, therefore, only discussed in terms of the persistency of analgesia.

KF5503/34 was a randomised, double-blind, active-control, parallel-group, multicentre, safety study of tapentadol IR in subjects with a clinical diagnosis (present for at least 3 months) of lower back pain or pain from osteoarthritis of the knee or hip. The primary objective of this study was to evaluate the safety profile of tapentadol IR with flexible doses of either 50 mg or 100 mg taken every 4 to 6 hours (600 mg maximum total daily dose), as needed, over an exposure of 90 days in comparison to oxycodone IR with flexible doses of either 10 mg or 15 mg. Although this was a safety study, pain intensity was assessed using the average pain over the last 24 hours on an 11-point NRS at each visit (Study Days 1, 15, 29, 43, 57, 71 and 91) over the 90-day double-blind treatment period and provided an assessment for the maintenance of effect over this extended period of time.

Results

Subjects in this study experienced moderate to severe pain due to lower back pain or osteoarthritis of the knee or hip that had been present for at least 90 days. Baseline pain in this study model was likely to be stable due to the nature of the pain. The mean pain intensity using an 11-point NRS was 7.0 at baseline and decreased (that is, showed improvement in pain) to a mean score of 4.9 at endpoint (the last non-missing observation assessed during the double-blind treatment period) with tapentadol IR (see Figure 9). This level of improvement was maintained from Day 29 with tapentadol IR. A numerically comparable improvement was observed with oxycodone IR (mean change in pain intensity from baseline to endpoint: -2.2 for tapentadol IR group and -1.9 for the oxycodone IR group).

Figure 9: Pain intensity score over time: 90-day safety study (KF5503/34: safety analysis set)



Note: subjects took tapentadol IR 50 mg or 100 mg or oxycodone IR 10 mg or 15 mg 4 hourly to 6 hourly depending on pain levels.

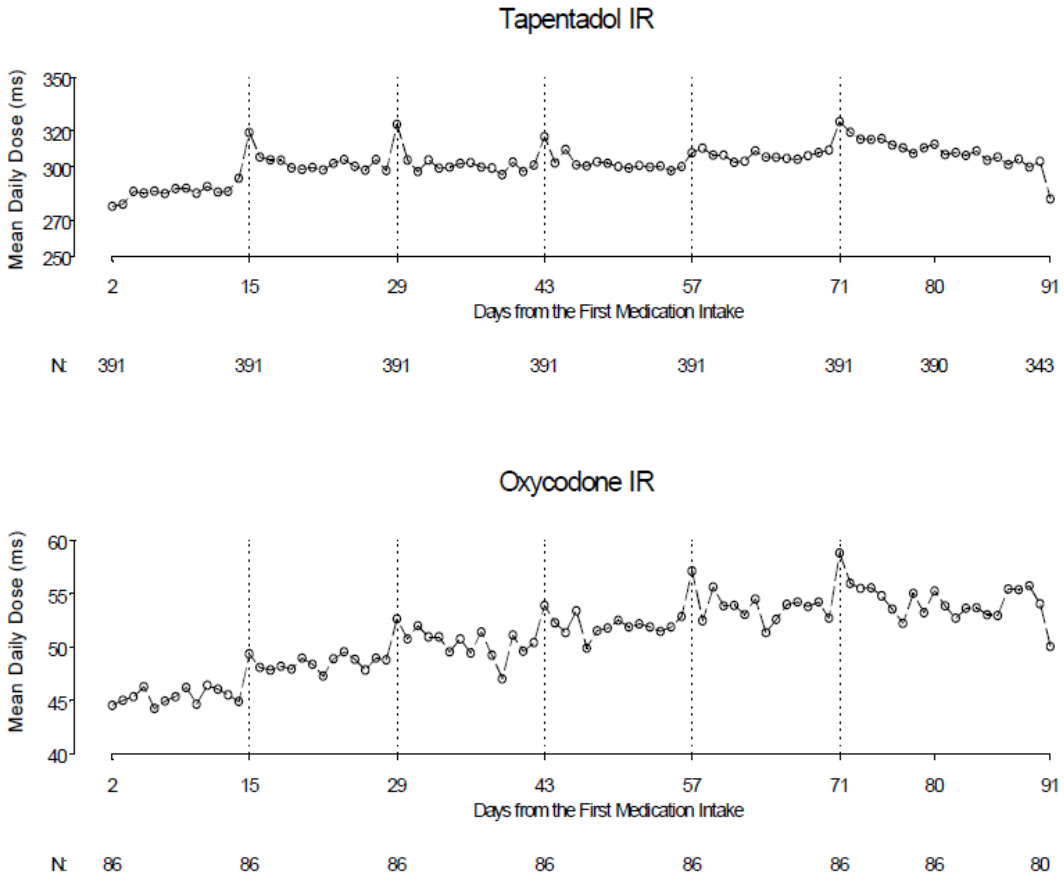
Endpoint is defined as subject completion or subject discontinuation.

IR = immediate release

The 90-day safety study showed a decrease in pain intensity over the period of the study with tapentadol IR, while the mean total daily dose increased on average by approximately 10% from Day 15 to Day 71, that is from 285 mg, the average of mean total daily dose over the treatment period up to Day 15, to 312 mg, the average of mean total daily dose over the treatment period between Day 57 to Day 71 (see Figure 10). The mean daily dose over time for subjects who completed the study in the tapentadol IR group increased only slightly from Day 15 to Day 71. A similar but more pronounced trend was seen from Day 15 to Day 71 in the oxycodone IR group (10 mg or 15 mg); the mean total daily dose increased on average, from 45 mg to 55 mg, approximately a 20% increase). For subjects who completed the study in the oxycodone IR group, the mean daily dose over time appeared to continuously increase between Days 15-71. It then remained relatively stable after Day 71.

Data supported maintenance of pain relief as shown by the stable reduced mean pain intensity accompanied by a mild increase in mean daily dose of tapentadol IR, compared with a larger increase in daily dose of oxycodone IR over a 90-day treatment period.

Figure 10: Mean daily dose over time for completed subjects: 90-day safety (KF5503/34: safety analysis set)



IR = immediate release

KF5503/33

The persistence of efficacy was described for periods of 10 days in Study KF5503/33. Subjects in this study experienced moderate to severe pain due to end-stage degenerative joint disease. Pain levels in this study model (assuming a stable non-opioid regimen) were likely to be stable due to the nature of the pain. During the 10-day exposure, the mean daily dose in the two tapentadol IR groups (50 mg and 75 mg) rose slightly from Day 2 to Day 10: from 187.5 mg to 205.8 mg and from 274.1 mg to 295.7 mg, respectively. In the oxycodone IR 10 mg group the mean daily dose rose from 32.8 mg to 37.9 mg. The results for PAR over time are similar to those for PID. Overall, higher PAR values were observed in the tapentadol IR treatment groups compared with placebo, indicating greater increase in pain relief.

Evaluator's overall conclusions on clinical efficacy

Efficacy of tapentadol IR was demonstrated in three pivotal Phase III confirmatory studies encompassing several different pain models (including a visceral pain model) for all doses employed in the studies (that is, 50 mg, 75 mg and 100 mg, respectively, taken every 4 to 6 hours). These studies examined subjects with moderate to severe pain (moderate was defined as ≥4 to <6 [≥4.5 to <6 in KF5503/33] and severe was defined as ≥6 on an 11-point NRS) following abdominal hysterectomy, following bunionectomy, following hip replacement (all three days of treatment) or due to end-stage degenerative joint disease (10 days of treatment

in an out-patient population). The subject populations enrolled in the studies were appropriate to support the proposed indication for treatment of moderate to severe pain.

The efficacy shown in the Phase III studies in post-bunionectomy pain was supported by three Phase II studies (one single-dose, two multiple dose) in the same model. Efficacy was also demonstrated in Phase II studies of third molar tooth surgery using single doses of tapentadol IR between 43 mg and 172 mg.

The efficacy data showed improvement of pain compared to placebo across several standard pain assessments and by using different missing value imputation methods (LOCF, BOCF and WOCF) for the primary variable. Results on secondary variables supported the robustness of the results obtained on the primary variables.

In addition, there was evidence for a numerically increasing efficacy with increasing dose of tapentadol IR in most post-surgical studies. There was no evidence for a ceiling effect in the broader dose range tested in Phase II studies (21.5 mg to 172 mg). The lack of a clear dose response in some Phase III studies may have been due to the model (including baseline pain severity), study design (for example, allowing concomitant medication use) or early termination.

Depending on the model and the number of subjects in the subgroups, efficacy was demonstrated both in subjects with moderate and in subjects with severe baseline pain.

Tapentadol IR showed a rapid onset of action (ranging from 24 minutes to 46 minutes) which was at least as fast as the onset observed for the active comparators oxycodone IR and morphine IR.

Maintenance of effect was shown for the complete treatment period, including a 10-day treatment period in the end-stage degenerative joint disease study. In addition, maintenance of pain reduction was shown for up to 90 days in the 90-day safety study. Although efficacy was not a primary objective of this study, there was a stable reduction in mean pain intensity after 15 days of treatment in the tapentadol IR treatment group (50 mg or 100 mg), that was similar to the active comparator, oxycodone IR (10 mg or 15 mg), a known opioid analgesic.

Comparison of responder rates and the similarity of the efficacy of tapentadol IR to the comparators used, confirmed the clinical relevance of the pain relief with tapentadol IR. The efficacy of tapentadol IR in the dose range of 50 mg to 100 mg appeared similar to that of oxycodone IR in the dose range of 10 mg to 15 mg in studies of pain following bunionectomy (KF5503/21, KF5503/22 and KF5503/32), hip replacement (KF5503/31) and end-stage degenerative joint disease (KF5503/33). Tapentadol IR 75 mg and morphine IR 20 mg had similar efficacy in the study of pain following abdominal hysterectomy (KF5503/35).

Based on the data from the Phase II and Phase III efficacy studies, the results suggest equianalgesic ratios in the range of 1:5 (KF5503/21) to 1:6.7 (KF5503/32) for oxycodone:tapentadol and 1:2.15 (KF5503/05) to 1:3.75 (KF5503/35) for morphine:tapentadol based on clinically prescribed doses of oxycodone and morphine (that is, oxycodone hydrochloride and morphine sulfate).

Overall, this evaluator considers that the data submitted for evaluation are adequate to support efficacy for tapentadol IR 50 mg, 75 mg and 100 mg, using a regimen of administration of 4 to 6 hours, in the treatment of moderate to severe pain.

Safety

Introduction Tapentadol IR

Results from Phase I and Phase II single dose studies will not be discussed in this report.

The Phase II/III Multiple-dose Double-blind Safety Analysis Set includes pooled data from the 10 double-blind, multiple-dose clinical studies/periods, including four Phase II clinical studies (KF5503/21, KF5503/22 and the multiple-dose periods of KF5503/04 and KF5503/08) and six Phase III clinical studies (KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35 and KF5503/37). A summary of subject disposition for subjects in the Phase II/III Multiple-dose Double-blind Safety Analysis Set is provided in Table 67. The percentage of subjects who discontinued was similar in the "all" tapentadol IR and placebo pooled analysis treatment groups.

The Phase III Open-label Extension Safety Analysis Set includes data from the open-label extension period of the Phase III studies, KF5503/31 and KF5503/32; it includes all randomized subjects who received at least one dose of the study drug during the specified treatment period. A total of 537 subjects were enrolled in the 9-day open-label extension periods of KF5503/32 and KF5503/31 and 509 subjects (94.8%) received at least one dose of tapentadol IR. Of these, four subjects (0.7%) discontinued because of TEAEs; three subjects (0.6%) withdrew consent; three subjects (0.6%) discontinued because of other reasons; and one subject (0.2%) was lost to follow-up. A total of 498 subjects (92.7%) completed the open-label extension period. Excluding subjects treated in Site 011006 in KF5503/31, 483 subjects are included in the Phase III Open-label Extension Safety Analysis Set.

Table 68: Disposition: Phase II/III Multiple-dose Double-blind Safety Analysis Set; randomised subjects

	Placebo (N = 799) n (%)	All Tapentadol IR (N = 2744) n (%)	All Oxycodone IR (N = 689) n (%)	All Morphine IR (N = 266) n (%)
Randomized	799 (100)	2744 (100)	689 (100)	266 (100)
Completed MD Phase	538 (67.3)	1913 (69.7)	429 (62.3)	225 (84.6)
Withdrawn in MD Phase	261 (32.7)	831 (30.3)	260 (37.7)	41 (15.4)
Withdrew consent	15 (1.9)	121 (4.4)	29 (4.2)	3 (1.1)
Entry criteria not met	0	0	–	–
Adverse event	17 (2.1)	276 (10.1)	115 (16.7)	14 (5.3)
Death	0	0	0	1 (0.4)
Lost to follow-up	0	30 (1.1)	14 (2.0)	3 (1.1)
Pregnancy	0	0	0	0
Lack of efficacy	220 (27.5)	303 (11.0)	86 (12.5)	13 (4.9)
Protocol violation	0	0	0	-
Other	9 (1.1)	102 (3.7)	16 (2.3)	7 (2.6)
Safety Analysis Set	788 (98.6)	2694 (98.2)	675 (98.0)	266 (100)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

'–' indicates reason was not applicable to any study/subject with this treatment group.

MD = multiple dose; IR = immediate release; N, n = number of subjects (total; per category).

Patient exposure

Phase II/3 Multiple-dose Double-blind Safety Analysis Set

A total of 2694 subjects were dosed with tapentadol IR in the Phase II/III Multiple-dose Double-blind Safety Analysis Set in one of the following dose groups: 0-30 mg (n = 22),

>30-60 mg (n = 706), >60-90 mg (n = 778) and >90 mg to 120 mg (n = 509) and flexible dose (n = 679).The number of subjects per treatment group and the duration of exposure are presented in Table 68 and mean daily doses are presented in Table 69.

For subjects in the "all" tapentadol IR pooled analysis treatment group, 577 subjects (21.4%, calculated manually) were treated for 11 days or more (including days on and off the study drug. The percentage of subjects with a treatment duration of 11 days or more was generally similar in the "all" tapentadol IR (21.4%, calculated manually) and "all" oxycodone IR (19.1%, calculated manually) pooled analysis treatment groups. Only one subject in the placebo group was treated for more than 10 days and only two subjects in the "all" morphine IR pooled analysis treatment group were treated for more than three days. Due to this short exposure to morphine IR or placebo, the incidence of TEAEs is potentially lower compared to tapentadol IR or oxycodone IR and may therefore be underestimated in this pooled analysis.

Table 69: Duration of exposure: Phase II/III Multiple-dose Double-blind Safety Analysis Set

	Placebo (N = 788)	All Tapentadol IR (N = 2694)	All Oxycodone IR (N = 675)	All Morphine IR (N = 266)
Treatment duration, days [a]				
N	788	2694	675	266
Mean (SD)	3.9 (3.19)	18.6 (31.82)	17.8 (30.98)	2.8 (0.60)
Median	3.0	3.0	4.0	3.0
Range	(1; 10)	(1; 105)	(1; 106)	(1; 4)
Treatment duration category, n (%)				
1 day	237 (30.1)	531 (19.7)	142 (21.0)	24 (9.0)
2 - 3 days	321 (40.7)	1056 (39.2)	195 (28.9)	240 (90.2)
4 - 10 days	230 (29.2)	537 (19.9)	211 (31.3)	2 (0.8)
11 - 45 days	0	121 (4.5)	25 (3.7)	0
> 45 days	0	449 (16.7)	102 (15.1)	0
Total duration, days [b]				
N	788	2694	675	266
Mean (SD)	3.9 (3.20)	18.9 (32.33)	18.1 (31.32)	2.8 (0.60)
Median	3.0	3.0	4.0	3.0
Range	(1; 12)	(1; 105)	(1; 111)	(1; 4)
Total duration category, n (%)				
1 day	237 (30.1)	531 (19.7)	141 (20.9)	24 (9.0)
2 - 3 days	320 (40.6)	1050 (39.0)	192 (28.4)	240 (90.2)
4 - 10 days	230 (29.2)	536 (19.9)	213 (31.6)	2 (0.8)
11 - 45 days	1 (0.1)	123 (4.6)	25 (3.7)	0
> 45 days	0	454 (16.9)	104 (15.4)	0

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

a) Calculated based on the accumulative number of days on the study drug during the treatment period.

b) Calculated based on the number of days between first and last dose of the study drug.

SD = standard deviation; IR = immediate release; N = number of subjects.

Table 70: Extent of exposure - mean daily dose: Phase II/III Multiple-dose Double-blind Safety Analysis Set

	Placebo (N = 788)	All Tapentadol IR (N = 2694)	All Oxycodone IR (N = 675)	All Morphine IR (N = 266)
Mean total daily dose (mg) (days on drug only) [a]				
N	788	2694	675	266
Mean (SD)	0 (0)	281.98 (124.452)	40.24 (20.872)	102.05 (27.158)
Median	0	266.67	35.00	93.33
Range	(0; 0)	(50.0; 800.0)	(10.0; 95.0)	(20.0; 160.0)
Mean total daily dose (mg) (days on/off drug) [b]				
N	788	2694	675	266
Mean (SD)	0 (0)	280.46 (124.864)	40.04 (20.920)	102.05 (27.158)
Median	0	264.84	35.00	93.33
Range	(0; 0)	(15.4; 800.0)	(2.5; 95.0)	(20.0; 160.0)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

a) Mean daily dose calculated based on the accumulative number of days on treatment during the treatment period.

b) Mean daily dose calculated based on the number of days between first and last dose of the study drug.

SD = standard deviation; IR = immediate release; N = number of subjects.

Phase III Open-label Extension Safety Analysis Set

A total of 483 subjects received at least one dose of tapentadol IR during the open-label extension period in the Phase III Open-label Extension Safety Analysis Set. The majority of subjects (317 of 483 subjects [calculated manually]) took the study drug for at least six days. In total, 65.0% of the subjects had a treatment duration of >6 to 9 days and no subject had a total duration of more than 9 days (including days without study drug intake). The median duration of treatment was 9 days and the mean duration of treatment was 7.0 days. The mean total duration was 8.9 days (including days without study drug intake) (see Table 70). Similar results were seen for the mean total daily dose: The median of the mean total daily dose based on accumulative days on the study drug (212.50 mg) was higher than the median of the mean total daily dose that included days both on and off the study drug (177.78 mg). The maximum mean total daily tapentadol IR dose was 600 mg.

Table 71: Duration of exposure: Phase III Open-label Extension Safety Analysis Set

	Flex TAP IR (N = 483)
Treatment duration, days [a]	
N	483
Mean (SD)	7.0 (2.67)
Median	9.0
Range	(1; 10)
Treatment duration category, n (%)	
≤3 days	78 (16.1)
>3-6 days	88 (18.2)
>6-9 days	314 (65.0)
>9 days	3 (0.6)
Total duration, days [b]	
N	483
Mean (SD)	8.9 (0.78)
Median	9.0
Range	(1; 9)
Total duration category, n (%)	
≤3 days	4 (0.8)
>3-6 days	5 (1.0)
>6-9 days	474 (98.1)
>9 days	0

Studies included: KF5503/31 and KF5503/32.

a) Calculated based on the accumulative number of days on treatment during the treatment period.

b) Calculated based on the number of days on study.

Flex TAP = Tapentadol IR flexible dose of 50 mg or 100 mg; SD = standard deviation; IR = immediate release; N = number of subjects.

Table 72: Extent of exposure mean daily dose: Phase III Open-label Extension Safety Analysis Set

	Flex TAP IR (N = 483)
Mean total daily dose (mg) (days on drug only) [a]	
N	483
Mean (SD)	234.78 (132.093)
Median	212.50
Range	(50.0; 600.0)
Mean total daily dose (mg) (days on/off drug) [b]	
N	483
Mean (SD)	199.74 (143.472)
Median	177.78
Range	(5.6; 600.0)

Studies included: KF5503/31 and KF5503/32.

a) Mean total daily dose calculated based on the accumulative number of days on treatment during the treatment period.

b) Mean total daily dose calculated based on the number of days between first and last dose of study drug.

Flex TAP = Tapentadol IR flexible dose of 50 mg or 100 mg; SD = standard deviation; IR = immediate release; N = number of subjects.

Adverse events

This section will describe treatment emergent adverse events (TEAEs) only.

Phase II/III Multiple-dose Double-blind Safety Analysis Set

In the Phase II/III Multiple-dose Double-blind Safety Analysis Set, the percentage of subjects with at least one TEAE was higher in the "all" tapentadol IR group (71.9%) compared with

the placebo group (47.8%) and was lower in the "all" tapentadol IR group (71.9%) compared with the "all" oxycodone IR group (84.0%). There were no deaths and the percentage of subjects with serious TEAEs was low (<1%) in the "all" tapentadol IR and placebo groups. One subject died in the "all" morphine IR group.

The percentage of subjects with TEAEs leading to discontinuation was higher in the "all" tapentadol IR group (10.1%) compared to the placebo group (2.2%) and was lower in the "all" tapentadol IR group (10.1%) compared to the "all" oxycodone IR group (16.7%). The difference between the "all" tapentadol IR and "all" oxycodone IR groups was largest for the percentage of subjects discontinuing due to gastrointestinal TEAEs (3.8% compared with 12.1%, respectively). In total, 6.8% of the subjects in the "all" oxycodone IR group and 2.0% of the subjects in the "all" tapentadol IR group discontinued due to nausea and 5.2% of the subjects in the "all" oxycodone IR group and 1.3% of the subjects in the "all" tapentadol IR group discontinued due to vomiting.

The most commonly reported (by ≥25% of subjects) TEAEs in the "all" tapentadol IR group were those affecting the gastrointestinal disorders System Organ Class (SOC) and the nervous system disorders SOC. The percentage of subjects with TEAEs affecting the gastrointestinal disorders SOC was higher in the "all" tapentadol IR group (43.3%) than in the placebo group (21.7%) and lower than in the "all" oxycodone IR group (64.0%). The percentage of subjects with TEAEs affecting the nervous system disorders SOC was higher in the "all" tapentadol IR group (37.2%) than in the placebo group (19.2%) and similar in the "all" oxycodone IR group (40.9%).

A summary of TEAEs by preferred term (PT) reported for ≥5% of subjects in the "all" tapentadol IR pooled analysis treatment group is provided in Table 70. The most commonly reported (by ≥5% of subjects) TEAEs in the "all" tapentadol IR group were nausea, dizziness, vomiting, somnolence, headache, constipation and pruritus. The percentage of subjects with TEAEs relating to gastrointestinal disorders (nausea, vomiting and constipation) was lower in the "all" tapentadol IR group compared with the "all" oxycodone IR. The percentage of subjects with dizziness was lower in the "all"

tapentadol IR group compared with the "all" oxycodone IR group. The percentage of subjects with somnolence or headache was similar between the two groups.

For this Safety Analysis Set, the results of the "all" morphine IR group have to be seen within the limitations of this pooling as described earlier. The overall percentage of subjects with at least one TEAE in the "all" morphine IR group was 69.5%. The most commonly reported (by ≥20% of subjects) TEAEs in the "all" morphine IR group were nausea (36.1% of the subjects) and vomiting (25.2%).

Table 73: TEAEs in at least 5% of subjects in any treatment group: Phase II/III Multiple-dose Double-blind Safety Analysis Set

System Organ Class / Preferred Term	Placebo (N = 788)	"All" Tapentadol IR (N = 2694)	"All" Oxycodone IR (N = 675)	"All" Morphine IR (N = 266)
Number (n (%)) of subjects with TEAE	377 (47.8)	1937 (71.9)	567 (84.0)	185 (69.5)
Gastrointestinal disorders	171 (21.7)	1166 (43.3)	432 (64.0)	138 (51.9)
Nausea	101 (12.8)	750 (27.8)	298 (44.1)	96 (36.1)
Vomiting	30 (3.8)	442 (16.4)	208 (30.8)	67 (25.2)
Constipation	25 (3.2)	210 (7.8)	133 (19.7)	26 (9.8)
Flatulence	17 (2.2)	49 (1.8)	5 (0.7)	15 (5.6)
Nervous system disorders	151 (19.2)	1003 (37.2)	276 (40.9)	81 (30.5)
Dizziness	56 (7.1)	552 (20.5)	167 (24.7)	30 (11.3)
Somnolence	22 (2.8)	348 (12.9)	87 (12.9)	27 (10.2)
Headache	77 (9.8)	263 (9.8)	69 (10.2)	37 (13.9)
General disorders and administration site conditions	61 (7.7)	344 (12.8)	110 (16.3)	37 (13.9)
Pyrexia	27 (3.4)	92 (3.4)	16 (2.4)	16 (6.0)
Skin and subcutaneous tissue disorders	37 (4.7)	294 (10.9)	135 (20.0)	54 (20.3)
Pruritus	7 (0.9)	119 (4.4)	70 (10.4)	23 (8.6)
Pruritus generalised	5 (0.6)	54 (2.0)	26 (3.9)	18 (6.8)
Investigations	55 (7.0)	163 (6.1)	35 (5.2)	30 (11.3)

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

MedDRA version 11.0 was used for coding.

TEAE = treatment emergent adverse events; IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total, per category).

In the Phase II/III Multiple-dose Double-blind Safety Analysis Set, the percentage of subjects with related TEAEs (that is, TEAEs reported as possibly, probably/likely, or certainly related to the study drug by the investigators) was higher in the "all" tapentadol IR group (82.8%) compared with the placebo group (66.3%) and similar to the "all" oxycodone IR (88.7%) and "all" morphine IR groups (84.3%).

The majority of TEAEs were mild to moderate in intensity across the pooled analysis treatment groups in the Phase II/III Multiple-dose Double-blind Safety Analysis Set.

The TEAEs in the "all" tapentadol IR group were mild in intensity in 35.3% of subjects while at least one event of moderate intensity was observed in 46.2% of subjects and one event of severe intensity in 18.5% of subjects. In particular, in the majority of the subjects, the events nausea, dizziness, somnolence, headache, constipation and pruritus were considered to be mild or moderate in intensity across the pooled analysis treatment groups. Overall, the percentage of subjects with gastrointestinal and nervous system disorder events assessed as mild or moderate was similar for the "all" tapentadol IR and "all" oxycodone IR groups.

Reporting rates of individual adverse events in younger and elderly subjects were similar.

TEAEs with prolonged treatment – KF5503/34

A total of 679 subjects aged ≥18 years with moderate to severe pain from low back pain or osteoarthritis of the knee or hip were treated with a flexible dosing regimen of tapentadol IR (50 mg or 100 mg every 4 to 6 hours, as needed) in the 90-day safety Study KF5503/34 with 318 subjects receiving treatment for at least 90 days. The maximum duration of treatment was 105 days. The percentage of subjects with at least one TEAE was 76.3% in the tapentadol IR (50 mg or 100 mg) and 82.9% in the oxycodone IR (10 mg or 15 mg) groups

(see Table 73). The most common TEAEs (>10% in either group) were nausea, vomiting, constipation, dizziness, headache, somnolence and pruritus. Nausea, vomiting, constipation and pruritus were reported more often for subjects (approximate 1.5-2-fold) in the oxycodone IR group than for subjects in the tapentadol IR group. The overall adverse event profile is thus similar for short-term treatment (up to 10 days of treatment) and prolonged treatment, except withdrawal symptoms. The only cases of drug withdrawal syndrome (PT) and withdrawal syndrome (PT) with tapentadol IR were seen in KF5503/34 and were mostly classified as mild.

Table 74: TEAEs during prolonged treatment in at least 5% of subjects: KF5503/34: Safety Analysis Set

System Organ Class Dictionary Derived Term	Tapentadol IR (N = 679) n (%)	Oxycodone IR (N = 170) n (%)
Total number of subjects with adverse events	518 (76.3)	141 (82.9)
Gastrointestinal Disorders	300 (44.2)	108 (63.5)
Nausea	125 (18.4)	50 (29.4)
Vomiting	115 (16.9)	51 (30.0)
Constipation	87 (12.8)	46 (27.1)
Diarrhoea	45 (6.6)	10 (5.9)
Dry Mouth	36 (5.3)	5 (2.9)
Nervous System Disorders	249 (36.7)	63 (37.1)
Dizziness	123 (18.1)	29 (17.1)
Headache	78 (11.5)	17 (10.0)
Somnolence	69 (10.2)	16 (9.4)
General Disorders and Administration Site Conditions	100 (14.7)	18 (10.6)
Fatigue	38 (5.6)	4 (2.4)
Skin and Subcutaneous Tissue Disorders	58 (8.5)	27 (15.9)
Pruritus	29 (4.3)	20 (11.8)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
All adverse events are coded using MedDRA version 10.0.
IR = immediate release; N, n = number of subjects (total; per category); MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment emergent adverse event.

Phase III Open-label Extension Safety Analysis Set

Treatment emergent adverse events were reported for 34.4% of subjects in the Phase III Open-label Extension Safety Analysis Set. There were no deaths and two serious TEAEs in the Phase III Open-label Extension Safety Analysis Set. There were two subjects with TEAEs leading to discontinuation in the Phase III Open-label Extension Safety Analysis Set. The most commonly reported TEAEs were nausea (6.6%) and headache (5.2%). All other TEAEs were reported in <5% of subjects.

In the Phase III Open-label Extension Safety Analysis Set, related TEAEs (that is, those reported as possibly, probably/likely, or certainly related to the study drug by the investigators) were reported for 60.8% of subjects who experienced a TEAE. The investigators considered most occurrences of nausea, headache, dizziness, somnolence, vomiting and pruritus to be related to the study drug.

The majority of TEAEs were mild to moderate in intensity in the Phase III Open-label Extension Safety Analysis Set. Most of the TEAEs of nausea, headache, dizziness, somnolence, vomiting and pruritus were considered to be mild or moderate in intensity.

Serious adverse events and deaths

No deaths were reported in the Phase I Single-dose Safety Analysis or in the Phase I multiple-dose study. No deaths were reported in the other Phase I studies using tapentadol IR or other formulations. No deaths were reported in the Phase II Single-dose Safety Analysis Set.

No deaths were reported during the treatment period or within 30 days after treatment discontinuation in the "all" tapentadol IR group of the Phase II/III Multiple-dose Double-blind Safety Analysis Set. One subject died of pulmonary embolism in the "all" morphine IR group.

There were no deaths in the Phase III Open-label Extension Safety Analysis Set.

Phase II/III Multiple-dose Double-blind Safety Analysis Set

In the Phase II/III Double-blind Multiple-dose Safety Analysis Set, the percentage of subjects with serious TEAEs was low for subjects in the "all" tapentadol IR and the placebo pooled analysis treatment groups (<1% in each) (see Table 74). A similarly low frequency was observed in the "all" oxycodone IR group and the "all" morphine IR group. Overall, mainly single occurrences of serious TEAEs were observed without a specific pattern.

In KF5503/34, serious TEAEs were reported by five subjects (1.3%) in the tapentadol IR group and 3 subjects (2.4%) in the oxycodone IR group between the start of treatment and two days after the last treatment. The serious TEAEs experienced in subjects in the tapentadol IR group included acute myocardial infarction, myocardial infarction, thalamic infarction, transient ischemic attack and bronchitis viral. All serious events were either unrelated or unlikely related to the study drug, except one drug withdrawal syndrome in the tapentadol IR group that occurred more than two days after the end of treatment.

Table 75: Number (%) of subjects with serious adverse events: Phase II/III Multiple-dose Double-blind Safety Analysis Set

System Organ Class / Preferred Term	Placebo (N = 788)	"All" Tapentadol IR (N = 2694)	"All" Oxycodone IR (N = 675)	"All" Morphine IR (N = 266)
Number (n (%)) of subjects with serious AE	**3 (0.4)**	**18 (0.7)**	**7 (1.0)**	**3 (1.1)**
Cardiac disorders	**1 (0.1)**	**6 (0.2)**	**0**	**0**
Myocardial infarction	0	2 (0.1)	0	0
Acute myocardial infarction	0	1 (0.0)	0	0
Cardiac failure congestive	0	1 (0.0)	0	0
Sinus tachycardia	0	1 (0.0)	0	0
Supraventricular tachycardia	1 (0.1)	1 (0.0)	0	0
Nervous system disorders	**1 (0.1)**	**5 (0.2)**	**0**	**0**
Hypoaesthesia	0	2 (0.1)	0	0
Lethargy	0	1 (0.0)	0	0
Thalamic infarction	0	1 (0.0)	0	0
Transient ischaemic attack	1 (0.1)	1 (0.0)	0	0
Infections and infestations	**1 (0.1)**	**3 (0.1)**	**2 (0.3)**	**1 (0.4)**
Bronchitis viral	0	1 (0.0)	0	0
Osteomyelitis	0	1 (0.0)	0	0
Pneumonia	0	1 (0.0)	0	0
Viral myocarditis	0	1 (0.0)	0	0
Appendicitis	0	0	1 (0.1)	0
Bronchopneumonia	0	0	0	1 (0.4)
Post procedural infection	1 (0.1)	0	0	0
Pyelonephritis	0	0	1 (0.1)	0
Urosepsis	0	0	1 (0.1)	0
Gastrointestinal disorders	0	2 (0.1)	1 (0.1)	0
Ileus	0	1 (0.0)	0	0
Small intestinal obstruction	0	1 (0.0)	0	0
Pancreatitis acute	0	0	1 (0.1)	0
Psychiatric disorders	**0**	**2 (0.1)**	**1 (0.1)**	**0**
Confusional state	0	1 (0.0)	1 (0.1)	0
Depressed mood	0	1 (0.0)	0	0
Respiratory, thoracic and mediastinal disorders	**0**	**2 (0.1)**	**0**	**1 (0.4)**
Chronic obstructive pulmonary disease	0	1 (0.0)	0	0
Pulmonary embolism	0	1 (0.0)	0	1 (0.4)

Table 75 (cont): Number (%) of subjects with serious adverse events: Phase II/III Multiple-dose Double-blind Safety Analysis Set

System Organ Class / Preferred Term	Placebo (N = 788)	"All" Tapentadol IR (N = 2694)	"All" Oxycodone IR (N = 675)	"All" Morphine IR (N = 266)
Blood and lymphatic system disorders	**0**	**1 (0.0)**	**0**	**0**
Anaemia	0	1 (0.0)	0	0
General disorders and administration site conditions	**0**	**1 (0.0)**	**1 (0.1)**	**0**
Drug withdrawal syndrome	0	1 (0.0)	0	0
Pain	0	0	1 (0.1)	0
Injury, poisoning and procedural complications	**0**	**1 (0.0)**	**0**	**1 (0.4)**
Dislocation of joint prosthesis	0	1 (0.0)	0	0
Post procedural haemorrhage	0	0	0	1 (0.4)
Vascular disorders	**0**	**1 (0.0)**	**0**	**0**
Deep vein thrombosis	0	1 (0.0)	0	0
Renal and urinary disorders	**0**	**0**	**1 (0.1)**	**0**
Renal failure acute	0	0	1 (0.1)	0
Surgical and medical procedures	**0**	**0**	**1 (0.1)**	**0**
Spinal fusion surgery	0	0	1 (0.1)	0

Studies included: KF5503/04 (Part 2), KF5503/08 (Part 2), KF5503/21, KF5503/22, KF5503/31, KF5503/32, KF5503/33, KF5503/34, KF5503/35, and KF5503/37.

MedDRA version 11.0 was used for coding.

Includes serious adverse events reported during treatment and up to 30 day after the last dose of the study drug.

AE = adverse event; IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total; per category).

Phase III Open-label Extension Safety Analysis Set

There were three subjects with four serious adverse events in the Phase II/III Open-label Extension Safety Analysis Set (see Table 75 below).

Table 76: Number (%) of subjects with serious adverse events: Phase III Open-label Extension Safety Analysis Set

System Organ Class / Preferred Term	Flex TAP IR (N = 483)
Number (n (%)) of subjects with serious AE	**3 (0.6)**
Injury, poisoning and procedural complications	**2 (0.4)**
Procedural pain	1 (0.2)
Traumatic haematoma	1 (0.2)
Psychiatric disorders	**1 (0.2)**
Anxiety	1 (0.2)
Delirium	1 (0.2)

Studies included: KF5503/31 and KF5503/32.

MedDRA version 11.0 was used for coding.

Includes serious adverse events reported during treatment and up to 30 days after the last dose of study drug.

Flex TAP = Tapentadol IR flexible dose of 50 mg or 100 mg; AE = adverse event; IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total; per category).

Laboratory findings, vital signs, physical findings, ECGs

Phase II/III Multiple-dose Double-blind Safety Analysis Set

There were no clinically relevant changes from baseline to endpoint in mean values for selected laboratory parameters for any pooled analysis treatment group in the Phase II/III Multiple-dose Double-blind Safety Analysis Set. The percentage of subjects with an

abnormal laboratory result at any time during treatment and with a normal baseline value was low (<1% in most laboratory tests) and similar between the placebo and "all" tapentadol IR pooled analysis treatment groups.

The number of subjects reporting liver injuries was low and similar in the "all" tapentadol, the "all" oxycodone and the placebo groups (<2%); the number of subjects reporting liver injuries in the morphine IR group was the highest with 7.1%. No type of liver injury was reported in more than 1% of the subjects across all groups with one exception, the morphine IR group. Similarly, the number of subjects reporting liver abnormality was similar in the "all" tapentadol, the "all" oxycodone and the placebo groups (between 12% and 14.5%). The number of subjects reporting liver abnormalities was the highest in the morphine IR group with 20.9%.

No subjects experienced an elevation greater than 10 times the upper limit of normal in any liver parameter. The overall number of subjects with an elevation in any liver parameters greater than 5 times the upper limit of normal during treatment was low and did not exceed 1% of the subjects in any tapentadol IR or oxycodone IR treatment group and did not exceed 2.5% in any morphine IR group.

There were no clinically relevant changes in mean values for pulse rate, systolic or diastolic blood pressure, respiratory rate, or pulse oxymetry for any of the pooled analysis treatment groups at endpoint in the Phase II/III Multiple-dose Double-blind Safety Analysis Set.

There were no clinically meaningful changes in heart rate or mean ECG values across the pooled analysis treatment groups in the Phase II/III Multiple-dose Double-blind Safety Analysis Set.

Phase III Open-label Extension Safety Analysis Set

There were no clinically relevant changes from baseline to endpoint in mean values for selected laboratory parameters for the tapentadol IR flexible group in the Phase III Open-label Extension Safety Analysis Set. The percentage of subjects with an abnormal value for the selected laboratory parameters at any time during the open-label treatment period and who had a normal baseline value was low (<4%) and there was no apparent pattern.

There were no clinically relevant changes in mean values over time for pulse rate, systolic or diastolic blood pressure, or respiratory rate in the tapentadol IR flexible dose group in the Phase III Open-label Extension Safety Analysis Set. There were no clinically meaningful changes in heart rate or mean ECG values across the pooled analysis treatment groups.

Discontinuation due to adverse events

In the Phase II/III multiple-dose double-blind studies, 2.2% of placebo treated subjects, 10.1% of tapentadol IR treated subjects and 16.7% of oxycodone IR treated subjects discontinued study participation prematurely because of TEAEs. Regarding the comparison with morphine IR, it has to be taken into account that data was collected for up to 90 days for tapentadol whereas for morphine IR data lasting up to 72 hours have only been documented. The comparison between treatments for the two Phase III studies where morphine IR was used as the active comparator revealed similar discontinuation rates in the KF5503/35 (tapentadol IR groups 4.2% to 8.0% and morphine IR 7.1%) and KF5503/37 (tapentadol IR 2.1% and morphine IR 3.1%) studies.

The most frequent treatment emergent adverse events leading to discontinuation amongst tapentadol IR treated subjects were dizziness (2.3%), nausea (2.0%), vomiting (1.3%) and somnolence (1.2%). All other treatment emergent adverse events leading to discontinuation had incidences below 1%. The most frequent treatment emergent adverse events leading to

discontinuations amongst oxycodone IR treated subjects were nausea (6.8%), vomiting (5.2%), dizziness (4.0%), constipation (2.7%), somnolence (2.2%), pruritus (1.6%) and headache (1.2%). Nausea (1.1%) was the most common reason for discontinuation in the morphine IR group.

With prolonged treatment (KF5503/34) discontinuations due to TEAEs occurred less frequently in the tapentadol IR treated group compared with oxycodone IR (21.2% and 31.2%).

Other safety aspects

Respiratory depression was rarely reported following the use of tapentadol IR. The incidence of adverse drug reactions related to the concept of respiratory depression was 0.3%. A long-term safety study over 90 days was performed with tapentadol IR (KF5503/34). There was no tapering of the study drug at the end of the study. In this study adverse events related to withdrawal symptoms were reported in 9 of 679 subjects in the tapentadol IR group, of which one was reported as a serious adverse event and occurred more than two days after the end of treatment and 2 of 170 subjects in the oxycodone group. Adverse events related to withdrawal symptoms were not reported in any other Phase II or Phase III study.

In addition to spontaneous reporting, withdrawal symptoms were specifically investigated at the end of KF5503/34 as part of the safety evaluation in subjects who did not take an opioid medication after stopping study drug. The majority of these subjects had Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) assessments between two and four days after stopping study drug. The percentage of subjects with objective signs of opioid withdrawal in the tapentadol IR group (17.3%) was lower than in the oxycodone IR group (28.8%). Overall, most of the subjects were classified on the COWS as “no withdrawal” by the Investigator. Only five subjects had withdrawal symptoms which were classified as moderate (two subjects in the tapentadol IR [0.3%] group and three subjects in the oxycodone IR group [3%]). In all remaining subjects, withdrawal symptoms were classified as mild; none were classified as severe.

Overdose

Non-clinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol IR. In principle, miosis, vomiting, cardiovascular collapse, loss of consciousness up to coma, convulsions and respiratory depression, even respiratory arrest may occur. Experience with doses of tapentadol IR above the highest protocol defined total daily dose of 700 mg is very limited.

Safety related to drug-drug interactions

Additive central nervous system effects between the concomitant use of tapentadol and other mu-opioid receptor agonist analgesics, general anaesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants (including alcohol and illicit drugs) have not been systematically studied. Even though there is no evidence from the current clinical data, interactive effects could occur due to the pharmacological class of tapentadol, potentially resulting in respiratory depression, hypotension, profound sedation or coma. Therefore, tapentadol IR is contraindicated in subjects with acute intoxication with alcohol, hypnotics, centrally acting analgesics or psychotropic drugs and in subjects who are receiving monoamine oxidase inhibitors, or who have taken them within the last 14 days. When a combination of therapies as outlined above is contemplated, the reduction in dose of one or both agents should be considered.

In the Phase II/III multiple-dose double-blind studies, 182 of 2694 subjects (6.7%) treated with tapentadol IR concomitantly took selective serotonergic reuptake inhibitors (SSRI) or serotonin-noradrenaline reuptake inhibitors (SNRI), which could potentially interact with the mechanism of action of tapentadol IR. Other antidepressants, such as monoamine oxidase inhibitors and tricyclic antidepressants, were prohibited in the clinical studies. The safety profile of subjects taking concomitant serotonergic reuptake inhibitors or serotonin-noradrenaline reuptake inhibitors appeared to be similar to subjects who were not taking one of these medications.

Post marketing experience

No post-marketing data were submitted for evaluation

Evaluator's overall conclusions on clinical safety

The TEAEs observed with tapentadol IR treatment, in the dose range of 50 mg to 100 mg given 4 to 6 hourly, are qualitatively similar to those of a centrally acting analgesic. The most common treatment emergent adverse events were those listed in the System Organ Classes (SOCs) gastrointestinal and nervous system disorders and included nausea, dizziness, vomiting, somnolence and headache. Most treatment emergent adverse events reported with tapentadol IR were of mild or moderate intensity. The prevalence of the most common treatment emergent adverse events decreased with time. Apart from symptoms associated with withdrawal, mostly classified as mild, prolonged use (treatment for up to 90 days) was not associated with a change in the safety profile of tapentadol IR.

The incidence of gastrointestinal treatment emergent adverse events was lower for tapentadol IR than for oxycodone IR. The latter was used as the active comparator in more than two thirds of the subjects in the clinical Phase III program.

For both laboratory parameters and vital signs (including pulse oxymetry), there were no consistent patterns of treatment-related change.

Reporting rates of individual adverse events in young and elderly subjects were similar. Therefore, dose adaptation in elderly subjects is not considered necessary. However, care should be taken with dosing in elderly subjects as they may have impaired renal or hepatic function.

In a thorough QT study, no effect of multiple therapeutic (100 mg) and multiple supratherapeutic (150 mg) doses of tapentadol IR on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (including heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Based on the pharmacology of tapentadol, the potential for abuse with tapentadol IR is consistent with currently marketed drugs such as hydromorphone, oxycodone and morphine. Physicians should be vigilant for symptoms of withdrawal and treat patients accordingly should they occur. No relevant drug-drug interactions were seen.

Based on the data submitted for evaluation, tapentadol IR has a favourable benefit to risk ratio. Overall, tapentadol IR (50 mg to 100 mg) provides analgesia in acute pain similar to the classical mu-opioid receptor agonist analgesic oxycodone IR at doses of 10 mg and 15 mg or morphine IR at doses of 20 mg.

Tapentadol IR demonstrates an improved gastrointestinal tolerability (specifically in the incidence of nausea and/or vomiting and constipation) compared with strong opioids at doses providing similar pain relief. This favourable safety profile represents a clinically significant

benefit to subjects as gastrointestinal adverse events may limit the use of opioids for the relief of moderate to severe pain.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a "list of questions" to the sponsor is generated.

There were no questions for the sponsor.

Clinical Summary and Conclusions

Clinical Pharmacology

Tapentadol IR is rapidly and completely absorbed and demonstrates dose- proportional and time independent pharmacokinetics over the therapeutic dose range. Tapentadol IR can be taken independently of food intake and has a low potential for drug-drug interactions. The results of a study in subjects with mild or moderate hepatic impairment support the administration of tapentadol in patients with mild hepatic impairment without dose adjustment. In patients with moderate hepatic impairment, tapentadol should be used with caution and the dose should be initiated at 50 mg with the interval between doses no less than 8 hours (maximum of 3 doses in 24 hours). Further treatment should aim at maintaining adequate analgesia, with acceptable tolerability, by shortening or lengthening the dosing interval. Subjects with severe hepatic impairment were not studied and it is appropriate that use of tapentadol in this population is not recommended. The results of a study in subjects with mild, moderate or severe renal impairment support the administration of tapentadol to patients with mild or moderate renal impairment without dose-adjustment. Subjects with severe renal impairment were not studied in Phase II/III studies; therefore, the use in this subject population is not recommended.

Efficacy

The efficacy of tapentadol IR for the relief of moderate to severe acute pain compared to placebo was demonstrated in both in-patient and out-patient settings and in both visceral and somatic pain models (bunionectomy, hysterectomy, hip replacement and end-stage degenerative joint disease). All tapentadol IR treatment groups showed a statistically significant improvement in pain on the primary efficacy variable (SPID) compared with placebo in the Phase III efficacy studies. The efficacy results were robust, they were also seen using the more conservative imputation methods of BOCF and WOCF and supported by the analysis of the secondary endpoints.

In the Phase III studies, the proportion of subjects with a clinically meaningful analgesic effect (≥30% improvement in pain intensity from baseline) was clinically and statistically significantly higher in the tapentadol IR groups compared with placebo. These results are likely to be clinically relevant.

There is a dose-dependent analgesic effect over the entire dose range tested in Phase II/III studies. Therefore, as with all analgesics, the prescriber should take into consideration the severity of pain when selecting the dose for initiating therapy. The efficacy of tapentadol IR in the dose range of 50 mg to 100 mg given 4 to 6 hourly appeared similar to that of oxycodone IR in the dose range of 10 mg to 15 mg in studies of pain following bunionectomy (KF5503/21, KF5503/22 and KF5503/32), hip replacement (KF5503/31) and end-stage degenerative joint disease (KF5503/33). Tapentadol IR 75 mg and morphine IR 20 mg had similar efficacy in the study of pain following abdominal hysterectomy (KF5503/35).

Based on the overall evidence of the Phase II/III efficacy studies, the results suggest equianalgesic ratios in the range of 1:5 (KF5503/21) to 1:6.7 (KF5503/32) for

oxycodone:tapentadol and approximately 1:2.15 (KF5503/04 and KF5503/05) to 1:3.75 (KF5503/35) for morphine:tapentadol (based on clinically prescribed doses of oxycodone and morphine, that is, oxycodone hydrochloride and morphine sulfate).

Safety

The most common adverse drug reactions were nausea, dizziness, vomiting, somnolence and headache, observed with tapentadol IR treatment in the dose range of 50 mg to 100 mg. Most adverse drug reactions reported with tapentadol IR were of mild or moderate intensity. Apart from symptoms associated with withdrawal classified as mild in most cases, prolonged use (for up to 90 days) was not associated with a change in the safety profile of tapentadol IR. With prolonged use, the incidence of nausea and vomiting decreased with time, whereas constipation remained at the same level.

The evaluation of adverse events leading to study discontinuation did not reveal a special safety or tolerability issue of tapentadol IR. In addition, the rate of study discontinuation due to adverse events was lower with tapentadol IR than under treatment with oxycodone IR, supporting a positive impact of tapentadol IR on treatment compliance. The rate of reporting of adverse events in young and elderly subjects was similar.

In a thorough QT study with tapentadol IR, no effect of multiple therapeutic (100 mg) and multiple supratherapeutic (150 mg) doses of tapentadol IR on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

The potential for abuse, as measured by drug liking, with tapentadol IR is consistent with currently marketed drugs such as hydromorphone, oxycodone and morphine.

Benefit risk assessment

Overall the data submitted for evaluation support that tapentadol IR has a favourable benefit to risk ratio. Tapentadol IR (50 mg to 100 mg) provides analgesia in acute pain similar to the classical mu-opioid receptor agonist analgesic oxycodone IR, at doses of 10 mg and 15 mg or morphine IR at doses of 20 mg.

The recommended oral dose is 50 mg, 75 mg, or 100 mg tapentadol IR every 4 to 6 hours depending upon the pain intensity and it should be adjusted to maintain adequate analgesia with acceptable tolerability. On the first day of dosing, an additional dose may be taken as soon as one hour after the initial dose if pain control is not achieved. Daily doses greater than 700 mg tapentadol IR on the first day of treatment and maintenance daily doses greater than 600 mg tapentadol IR have not been studied and are therefore not recommended.

Tapentadol IR demonstrates an improved gastrointestinal tolerability (specifically in the incidence of nausea and/or vomiting and constipation) compared with strong opioids at doses providing similar pain relief. This favourable safety profile represents a clinically significant benefit to subjects as gastrointestinal adverse events may limit the use of opioids for the relief of moderate to severe pain.

In summary, the pharmacological profile, the dose- and time-independent pharmacokinetics, the improved gastrointestinal tolerability and the comparable efficacy to opioid standard therapies suggest that tapentadol IR is a beneficial alternative for the treatment of moderate to severe acute pain.

This evaluator considers that the data support registration of tapentadol IR for the proposed indication.

RECOMMENDED CONDITIONS FOR REGISTRATION

The clinical pharmacology, efficacy and safety data submitted for evaluation adequately support that tapentadol IR is a beneficial treatment of moderate to severe acute pain. It is recommended that the application to register tapentadol IR (Palexia IR) ***should be approved.***

V. Pharmacovigilance Findings

Risk Management Plan

Information is provided on the following safety concerns:

- Important identified risks: potential for abuse and convulsion.
- Important potential risks: overdose, off-label use in paediatric patients, potential for medication errors, accidental exposure and diversion.
- Important missing information: use in paediatrics.

For each of these, routine pharmacovigilance (PhV) and risk minimisation activities are proposed.

SUMMARY OF THE RISK MANAGEMENT PLAN

A summary of the Risk Managment Plan (RMP) is presented in Table 77 below.

Table 77: Summary of the Risk Management Plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Potential for abuse Overdose Diversion	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling and the use of legal status of the drug. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date.
Convulsion	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk-minimisation activities are identified as necessary or requested to date.
Potential for medication errors Accidental exposure	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date.
Use in paediatrics Off label use in paediatric patients	Routine Pharmacovigilance Practices are considered to be sufficient.	Appropriate labelling. No further risk-minimisation activities, other than labelling has been conducted to date. No further risk minimisation activities are identified as necessary or requested to date. A development program to address the paediatric population is defined in the agreed PIP.

Upon evaluation of the RMP by the Office of Product Review (OPR), it was considered that the information provided in this RMP was generally acceptable. However, a number of issues were identified. It was considered that information on evaluation of the need for additional risk minimisation activities and justification of the lack of these should have been provided. The sponsor has provided a comprehensive response.

The final OPR recommendations are that:

- More detailed information on use in pregnancy and results from toxicological studies on fertility and development are included in the Australian PI.
- There is reference to the possibility of serotonin syndrome with concomitant use of serotonergic drugs and tapendatol in the Australian PI.
- If approved for marketing in Australia, an agreed RMP for tapendatol should be provided to the TGA prior to its entry onto the ARTG and that this should adhere to the EU RMP template with particular attention to the following:
  - Evaluation of the need for additional risk minimisation activities and justification of the lack of these;
  - Presentation of details of important identified and potential risks in accordance with 1.5.2 of the template and the risk minimisation plan as per section 4 of the template; and
  - Provision of adequate information in the template Annexes.

The amendments requested by OPR were addressed in a subsequently submitted RMP.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

This application was considered at the 132nd meeting of the Pharmaceutical Subcommittee (PSC) of the ACPM on 24 May 2010. The subcommittee had no objections to registration of tapentadol IR on pharmaceutic grounds subject to satisfactory resolution of issues raised by the TGA following the initial evaluation of the application. All of those issues have since been satisfactorily resolved and there are now no objections to registration with respect to Chemistry, Manufacturing and Controls.

The subcommittee raised some additional, pharmacokinetic issues:

1. The PK profile of tapentadol does not appear to follow the expected trend for drug clearance in the elderly. The PSC considered this was odd given that tapentadol has low protein binding and has a clearance approaching liver blood flow.
2. The sponsor's conclusions about body weight in relation to dosing may be flawed given that in the population PK analysis clearance and volume of distribution of tapentadol from the proposed formulation increased as body weight increased; body weight was a statistically significant factor affecting vomiting (the risk of vomiting decreased by 1% when body weight increased by 1 kg); systemic exposure to tapentadol was approximately 20% higher in women than men and this was attributed to the lower body weight and distribution volume in women compared to men.

The sponsor responded to the lack of an expected reduction in clearance with age by agreeing that this is the case. Tapentadol is extensively metabolised primarily by conjugation with glucuronic acid and these reactions tend not to reduce with age (in comparison to P450-mediated reactions which may be affected by age). The sponsor's response to the demonstrated increase in exposure to tapentadol with decreasing body weight was to agree that this occurs however, the inter-subject variability is about 34% and 39% for AUC and C_{max} respectively, and these differences are more significant than differences due to differences in body weight alone. Therefore no dose correction for tapentadol on the basis of body weight variations alone is necessary.

Nonclinical

A revised report was issued following the sponsor's response to the initial evaluation. The non clinical evaluator stated that, provided clinical data adequately address the nonclinical concerns discussed below, there are no nonclinical objections to registration.

Toxicity studies consisted of single dose IV and oral (mice, rats), long-term oral repeat dose (mice, 13 weeks; rats, 26 weeks; dogs, 52 weeks) and more than 20 other repeat dose studies of shorter duration in these species. Excessive toxicity (congestive changes and convulsions/ CNS effects in mice, rats and dogs) constrained dose levels and exposure margins were generally <1. The nonclinical evaluator noted that the primary toxicities observed with tapentadol were CNS effects (including convulsions) and hepatic effects in rodents (including proliferative/ neoplastic changes), possibly consistent with adaptive changes following hepatic enzyme induction (enlarged liver, accentuated lobular pattern, hepatocyte vacuolation, centrilobular hypertrophy) at exposure more than 0.1 - 0.3 times the maximum clinical exposure. Severe convulsions, considered an opioid effect, were observed by various routes with exposure margins: mice 0.5, rats 2.2 – 5.4; dogs 0.1 – 0.2.

A multi-species effect on the cardiovascular system was observed including QT interval prolongation in conscious dogs. Effects on female fertility, embryofetal development/ teratogenicity and postnatal survival were observed, mostly associated with maternotoxicity. Consistent with other opioids, tapentadol exhibited dependence potential, withdrawal effects and tolerance development in animals. Tapentadol dose levels were limited in all nonclinical species due to excessive toxicity, particularly to the CNS. Resulting animal/ human systemic exposure margins were therefore quite low, limiting the ability of the nonclinical studies to assess the safety of tapentadol.

The above toxicity concerns are identified and described in the safety specification in the Risk Management Plan.

Tapentadol was shown to be a slight inhibitor of CYP2D6 activity in human liver microsomes *in vitro* with enzyme activity reduced by 19- 61% in the concentration range 3.08 – 616 µM (compared to estimated clinical C_{max} of 0.8 µM at the MRHD). Tapentadol did not appear to be an inhibitor or a substrate for P-glycoprotein in CACO-2 human colon carcinoma cells *in vitro.* Glucuronidation of tapentadol was inhibited by diclofenac (≤ 90%), meclofenamate (≤ 90%), miconazole (≤ 70%), probenicid (≤ 67%) and naproxen (≤ 65%). The sponsor did not consider the interaction with diclofenac to be clinically relevant as inhibition of tapentadol glucuronidation was predicted to be low (*ca* 6%) at clinical diclofenac concentrations. The most relevant interactions were considered to be with probenicid, meclofenamate and naproxen with 45%, 36% and 27% inhibition of tapentadol glucuronidation predicted at clinical exposure levels respectively.

Placental transfer of tapentadol was confirmed in rats. Low levels of tapentadol and tapentadol-glucuronide were detected in milk from lactating rats following oral dosing. Tapentadol administration during lactation resulted in increased pup mortality between PND1-4 in rats at doses lower than maternotoxic doses (exposure margins of 0.3).

Clinical

Pharmacokinetics

Absorption of tapentadol after oral administration is almost complete. However oral bioavailability is ~32% in fasted subjects, indicating extensive first pass metabolism. Food increases C_{max} by 16% and AUC by 25%. T_{max} was 1 hour in fasted subjects and 1¼ hours in fed subjects. The pharmacokinetics are linear for single doses from 50 to 200 mg. CV was 20% in a post hoc analysis. Approximately 20% of tapentadol is protein bound. Mean (SD)

Vd was 540 (98) L. Metabolic clearance is primarily due to glucuronidation and 3% is excreted unchanged in urine. Mean $t_{½}$ (SD) across studies was 4.3 (0.8) hours with mean (SD) CL/F 4470 (1519) mL/min. Some 96% is eliminated in the urine as tapentadol metabolites. Tapentadol showed a mean accumulation ratio of 1.6 on multiple dosing of 75 to 175 mg every 6 hours. Tapentadol does not have active metabolites.

Hepatic impairment increases AUC by 1.4 fold and 3.5 fold for mild and moderate impairment respectively. The sponsor has proposed that if subjects with moderate hepatic impairment are given tapentadol the initial dose should be 50 mg with a maximum of three doses in 24 hours. Renal function did not significantly alter exposure to tapentadol. However, the concentration of tapentadol-O-glucuronide, the major metabolite, is increased with increasing renal impairment. There is potential for accumulation of this compound in subjects with severe renal impairment and tapentadol is not recommended for this population group.
Probenecid and naproxen were identified as potential candidates for *in vivo* inhibition of glucuronidation. Interaction studies demonstrated a 17% increase in tapentadol AUC with co-administration of naproxen and a 57% increase with co-administration of probenecid.

Pharmacodynamics

In a pain model using carbon dioxide (CO_2)-laser-somatosensory evoked potentials on ultraviolet (UV) B-irradiated skin a dose-response relationship for analgesic effect was seen with single doses of 50 mg, 75 mg and 100 mg of tapentadol IR.

Tapentadol had no relevant effect on ECG parameters (QT interval, heart rate, PR interval, QRS duration, T-wave or U-wave morphology). Multiple doses of tapentadol IR were associated with a dose-related reduction in serum testosterone but most of the testosterone values remained within the normal range. Tapentadol IR showed a similar drug-liking to that of estimated equi-analgesic doses of hydromorphone IR in a study in opioid experienced, non-dependent healthy subjects.

Efficacy

The dose regimen used in the four pivotal efficacy studies was determined from dose-finding studies of single and multiple dose tapentadol in patients following abdominal surgery, third molar tooth surgery and post bunionectomy. Of note, ibuprofen 400 mg provided similar pain relief to tapentadol IR 172 mg and greater relief than morphine IR 60 mg in single dose dose-finding studies in tooth surgery (Study KF5503/03) and post-bunionectomy (Study KF5503/05) though no statistical comparisons between actives were provided.

Four studies provided pivotal efficacy data. These were randomised, double-blind, active and placebo-controlled studies in patients following bunionectomy (Studies KF5503/32 and KF5503/37), abdominal hysterectomy (Study KF5503/35) and end- stage degenerative joint disease of the hip or knee (Study KF5503/33). The active comparators were oxycodone IR (Studies KF5503/32 and KF5503/33) and morphine IR (Studies KF5503/35 and KF5503/37). These studies used a fixed dose of tapentadol with flexible administration of every 4 to 6 hours.

The primary efficacy variable was the Sum of Pain Intensity Difference (SPID). The Pain Intensity Difference (PID) was the difference between baseline pain intensity and current pain intensity. SPID was defined as Σ Wi x PIDi where the sum included all observations of PID collected from baseline to specific fixed time-points and Wi is the time elapsed from the previous observation. Higher SPID indicated greater pain relief. The primary time-point for analysis of efficacy was 48 hours from commencement of study treatment in Studies 32 and 37, 24 hours from commencement in Study 35 and at Day-5 in Study 33.

All these studies showed statistically significant superior efficacy compared with placebo for their primary endpoint. Statistical comparisons between actives were not performed however in each study the actives generally showed similar efficacy to at least one of the tapentadol doses given. Secondary efficacy measures included: time to rescue medication, responder rates (30% and 50% reduction from baseline in pain intensity), time to pain relief and patient global impression of change. These parameters generally showed statistically significant superiority over placebo for the actives.

In Study 35 (abdominal pain) there was little indication of increased pain relief with increasing dose of tapentadol. The mean SPID at 24 hours was 49.0, 52.4 and 52.9 for the 50, 75 and 100 mg doses respectively and 48.8 for 20 mg morphine IR.

Similarly, responder rates (≥ 50% reduction in pain intensity from baseline) at the primary evaluation time-point were between 59.8% and 59.9% for the 3 tapentadol dose groups. Other secondary endpoints did not indicate a clear dose response for tapentadol either.

Dose response at the primary time-point was demonstrated in Study 32 (bunionectomy) with increasing SPID from 127.6 for the 50 mg tapentadol dose to 158.5 for the 100 mg dose, compared with 43.4 for placebo and 170.6 for 15 mg oxycodone.

Secondary efficacy measures in this study also supported increasing efficacy with increased tapentadol dose from 50 to 100 mg every 4 to 6 hours. Although no statistical comparison was performed, in Study 37 (bunionectomy) patients given 75 mg tapentadol had considerably less pain relief than those given 20 mg morphine IR. Both actives were superior to placebo.

Study 33 (degenerative joint disease) examined efficacy of 50 mg and 75 mg tapentadol given every 4 to 6 hours during waking hours compared with oxycodone IR 10 mg and placebo. Some 69% of subjects in this study were considered to have severe pain at baseline. Use of rescue medication during double-blind dosing led to study withdrawal and few patients received it (4% placebo, 3% in each tapentadol group). Patients were permitted to continue taking non-opioid analgesia provided they were taking a stable dose for at least 28 days prior to study entry. Some 82% of study subjects were taking non-opioid analgesia during the study. Mean total daily doses of tapentadol for these dose groups were 186 mg for the 50 mg dose group and 274 mg for 75 mg dose group. While theret was clear evidence of efficacy for both doses of tapentadol and for oxycodone, a dose response for tapentadol was not demonstrated for the primary or key secondary efficacy endpoints. While no statistical comparison between the actives was performed, the mean SPID was higher for oxycodone than for either dose of tapentadol.

Persistence of analgesic effect was demonstrated in Study 34. This study was primarily designed to demonstrate safety of longer term exposure (90 days) to tapentadol. These patients had low back pain or pain due to osteoarthritis of the knee or hip. Of note, the mean daily dose of tapentadol increased by ~10% from Day 15 to Day 71 of this study. The mean daily increase in oxycodone dose was ~ 20%.

Safety

Ten studies were included in the combined analysis of tapentadol IR. This analysis included data from a total of 4498 subjects who were randomised to treatment, 2694 of these received at least one dose of tapentadol IR. Mean duration of exposure to tapentadol IR was 18.6 days. Control groups had less exposure (mean 3.9 days for placebo, 17.8 days for oxycodone and 2.8 days for morphine). The mean daily dose of tapentadol was 281.98 mg (range 50 to 800 mg). There were no deaths in patients given tapentadol nor was there clustering of serious adverse events. Some 71.9% of subjects given tapentadol reported at least one TEAE compared with 47.8% given placebo and 84% given oxycodone.

The overall discontinuation rate due to adverse events was 10.1% for subjects given tapentadol IR compared with 2.2% given placebo and 16.7% given oxycodone.

Gastrointestinal adverse events were a more frequent cause of discontinuation for subjects given oxycodone than for subjects given tapentadol (12.1% compared to 3.8%). Nausea accounted for about half these discontinuations in both the oxycodone and tapentadol groups. Vomiting led to discontinuation of 5.2% of patients given oxycodone compared to 1.3% given tapentadol.

Gastrointestinal and nervous system AEs were the most frequently reported adverse events in both the tapentadol and oxycodone groups; gastrointestinal AEs being more frequent in the oxycodone group (64% compared to 43.3%) and nervous system AEs occurring in 40.9% and 37.2% of oxycodone and tapentadol patients, respectively. Treatment emergent AEs occurring with a frequency of≥ 5% are shown in Table 70. Of note, constipation was considerably less frequent in patients given tapentadol (7.8%) compared with oxycodone (19.7%). Dizziness and somnolence occurred with similar frequency in patients given oxycodone or tapentadol. Pruritus was less frequently reported in patients given tapentadol (4.4% compared to 10.4% for oxycodone).

Longer term safety was examined in Study KF5503/34, a double-blind comparative study with oxycodone. In this study a total of 679 patients received tapentadol IR 50 or 100 mg every 4 to 6 hours for up to 90 days. Some 318 patients received at least 90 days treatment and the maximum duration of treatment was 105 days. Discontinuations due to TEAEs occurred in 21.2% of patients given tapentadol IR and 31.2% given oxycodone. As in the short term studies the most frequently reported TEAEs were: nausea, vomiting, constipation, dizziness, headache, somnolence and pruritus. As in the short term studies nausea, vomiting, constipation and pruritus were more frequently reported with oxycodone than with tapentadol IR. Most patients reported no withdrawal symptoms. Some 17.3% of patients given tapentadol IR had objective signs of opioid withdrawal compared with 26.1% given oxycodone IR when assessed 2 – 5 days after the last dose of study drug. Some 0.3% of patients given tapentadol IR and 3% given oxycodone IR were considered by investigators to have moderate withdrawal effects. No subjects had severe withdrawal symptoms.

Risk Management Plan

The evaluator has noted that routine pharmacovigilance activities are proposed for tapentadol. While generally satisfactory the evaluator has identified areas for greater disclosure of risks in the Product Information. Areas of particular concern were the potential for interactions with other serotonergic medicines and monoamine oxidase inhibitors and the proposed reproductive toxicity statement. An updated Risk Management Plan addressing the concerns raised during evaluations has been provided to the TGA.

Risk-Benefit Analysis

Delegate Considerations

There are no pharmacology issues of concern. Safety issues have been identified that can be adequately managed by the proposed S8 scheduling and by appropriate statements in the product literature and labelling as well as by modifications as requested to the Risk Management Plan. Hepatic enzyme abnormalities do not appear to be of concern though they were highlighted as potential effects in the nonclinical data.

Drug interactions with tapentadol are likely to be fewer than with morphine-based opioids due to the lack of CYP P450 metabolism of tapentadol. Gastrointestinal adverse events were generally less frequent with tapentadol than with oxycodone. The differences in proportion of patients who had withdrawal effects between tapentadol and other opioids may reflect differences in the dose strength rather than factors intrinsic to tapentadol. Use in patients with hepatic or renal impairment has been adequately investigated.

The indications requested for the IR form is consistent with the current indications for oxycodone IR.

Although the efficacy parameter of SPID measured at various time-points across the pivotal efficacy studies was nominated as the primary efficacy parameter, it is difficult to grasp the clinical significance of differences in SPID scores. The 30% and 50% responder rates (that is, % patients with 30% or 50% reductions from baseline in pain intensity) are more easily understood by both patients and clinicians. For tapentadol IR efficacy was well demonstrated, though dose response was inconsistent across studies. The active controls also consistently demonstrated efficacy. The Delegate considered that these studies adequately demonstrate efficacy of the proposed dose regimen of tapentadol IR for the relief of moderate to severe pain.

Conclusion and recommendation

Subject to negotiation of amendments to the Product Information document, the Delegate proposed to approve the registration of Palexia IR for the indication:

For the relief of moderate to severe pain.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from CSL Pty Ltd to register the new chemical entity of tapentadol (Palexia IR) film-coated tablets 50 mg, 75 mg and 100 mg for the indication:

For the relief of moderate to severe pain.

In making this recommendation, the ACPM considered the overall risk benefit profile to be positive. In addition, the ACPM recommended that dosage reduction in view of renal clearance and further clarification of the adverse event profile be included in the PI. The ACPM agreed with the delegate on all other proposed changes to the PI.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Palexia IR instant-release film-coated tablets containing tapentadol 50 mg, 75 mg & 100 mg (as hydrochloride) for the indication:

For the relief of moderate to severe pain.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

PALEXIA® SR PRODUCT INFORMATION
AUST R 165332, 165346, 165347, 165356, 165357

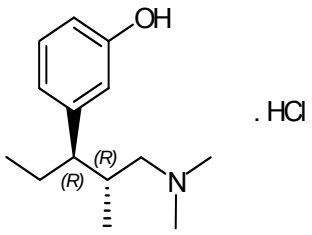
NAME OF THE MEDICINE

PALEXIA® SR 50 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 100 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 150 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 200 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 250 mg (tapentadol as hydrochloride) sustained release tablets

DESCRIPTION

PALEXIA® SR sustained release tablets contain tapentadol hydrochloride (HCl) which is a centrally acting synthetic analgesic combining mu agonist and noradrenaline re-uptake inhibition activity in a single molecule. Tapentadol is a white to off-white powder; freely soluble in water and methanol, and soluble in ethanol. The pKa_1 is 9.36 and pKa_2 is 10.37 determined in 0.15 M KCl solution. The partition coefficient is defined as the ratio of the equilibrium concentrations of a single neutral molecular species in a 1-octanol/aqueous buffered solution 2-phase system. The value of log P for tapentadol hydrochloride in 1-octanol/water is 2.89 ± 0.01. The chemical name for tapentadol HCl is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is $C_{14}H_{23}NO \bullet HCl$.

The structural formula of tapentadol HCl (CAS number: 175591-09-0) is:



PALEXIA® SR tablets contain 50, 100, 150, 200 and 250 mg tapentadol (as hydrochloride). Excipients are: hypromellose 100,000 mPa-s, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate. Excipients in the film coat are: hypromellose 6 mPa-s, lactose monohydrate, talc, macrogol 6000, propylene glycol, titanium dioxide (E171), iron oxide yellow (E172) (100, 150, 200 and 250 mg tablets only), iron oxide red (E172) (150, 200 and 250 mg tablets only), and iron oxide black (E172) (250 mg tablets only).

PHARMACOLOGY

Pharmacodynamics

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. It has 18 times less binding affinity

than morphine to the human mu-opioid receptor but was only 2-3 times less potent in producing analgesia in animal models (on a dose per body weight basis). This low *in-vivo* potency difference is consistent with its two mechanisms of action. Tapentadol has been shown to inhibit noradrenaline reuptake in the brains of rats resulting in increased noradrenaline concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid receptor antagonists (e.g., naloxone), whereas the noradrenaline reuptake inhibition is sensitive to noradrenaline modulators. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

Effects on the cardiovascular system: In ECG studies in conscious dogs, non-persistent QT/QTc interval prolongation was observed at exposures similar to or lower than the clinical plasma C_{max}. These effects were not observed in safety pharmacology studies with repeated ECG measurements. Heart rate was increased in conscious rats and dogs at peak plasma concentrations at least twice the clinical plasma C_{max}, but there was no clear effect on other ECG parameters (PR interval, QRS duration, T-wave or U-wave morphology). In a thorough QT trial in healthy subjects, no effect of multiple therapeutic and supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Pharmacokinetics

The tapentadol PR formulation is a hydrophilic hypromellose-based matrix formulation that provides pH-independent *in-vitro* release of the drug substance over a time period of approximately 12 hours. An initial drug substance release of about 20% occurs over the first 30 minutes with ongoing drug release over the ensuing 12-hour period.

Absorption
Mean absolute bioavailability after single-dose administration (fasting) of PALEXIA® SR is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed at between 3 and 6 hours after administration of PALEXIA® SR tablets.

Dose proportional increases for AUC (the most relevant exposure parameter for sustained-release formulations) have been observed after administration of PALEXIA® SR tablets over the therapeutic dose range.

A multiple dose study with twice daily dosing using 86 mg and 172 mg tapentadol administered as SR tablets showed an accumulation ratio of about 1.5 for the parent drug which is primarily determined by the dosing interval and apparent half-life of tapentadol.

Food Effect
The AUC and C_{max} increased by 8% and 18%, respectively, when PALEXIA® SR tablets were administered after a high-fat, high-calorie breakfast. PALEXIA® SR may be given with or without food.

Distribution
Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The serum protein binding is low and amounts to approximately 20%.

Metabolism and Elimination
In humans, the metabolism of tapentadol is extensive. About 97% of the parent compound is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Elderly patients
The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment
AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment
Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolized by Phase 2 glucuronidation, and only a small amount is metabolized by Phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, any clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. This has been evidenced by clinical pharmacokinetic drug-drug interaction studies with probe drugs naproxen and probenecid with increases in AUC of tapentadol by 17% and 57%, respectively. No changes in the pharmacokinetic parameters of tapentadol were observed when paracetamol and acetylsalicylic acid were given concomitantly. Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro* but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

CLINICAL TRIALS

The efficacy and safety of PALEXIA® SR in the treatment of moderate to severe chronic pain has been investigated in three pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in patients with moderate to severe chronic pain from osteoarthritis of the knee (clinical trials KF5503/11 and KF5503/12) and one in patients with moderate to severe chronic low back pain (clinical trial KF5503/23). These pain conditions were chosen as they usually present with moderate to severe pain that is often treated with opioids.

In all three studies, subjects were initially randomised to receive PALEXIA® SR (50 mg twice daily), placebo or oxycodone CR (10 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 2 weeks (increments of PALEXIA® SR 50 mg, oxycodone CR 10 mg, or placebo twice daily) to achieve a stable optimum dose. Subjects were allowed paracetamol as rescue medication during the titration period. Subjects received the following maximum (minimum) doses: PALEXIA® SR 250 mg (100 mg) twice daily, oxycodone CR 50 mg (20 mg) twice daily, or placebo twice daily. The study drug was taken with or without food.

To enter the 12-week maintenance period, subjects had to be on a stable dose of the study drug for the last 3 days of the titration period without any rescue medication. If needed, subjects could request controlled adjustment of their dose based on their individual analgesia requirements and/or

tolerability experience however adjustments were to be kept to a minimum during the maintenance period.

All three studies had the same primary endpoints - change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point numerical rating scale (NRS), and change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point NRS. Secondary endpoints included 30% and 50% responder rates and Patient Global Impression of Change scale.

The results for these endpoints for all three studies are summarised in Table 1.

Meta-analysis of pivotal studies

A pre-specified meta-analysis of the data generated in the above three clinical trials was undertaken. The two main objectives of the meta-analysis were to assess the superior safety of PALEXIA® SR compared to oxycodone CR with regards to constipation (gastrointestinal tolerability), and to assess the non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

PALEXIA® SR was superior to oxycodone CR with regards to constipation, nausea and vomiting (gastrointestinal tolerability) ($p<0.001$). The non-inferiority of PALEXIA® SR to oxycodone CR in relation to the primary endpoint (change from baseline of the average pain intensity over the 12-week maintenance period or at Week 12) (using LOCF) was also demonstrated (both p-values ≤ 0.001) (Table 1).

Table 1. Meta-analysis of data generated in studies KF5503/11, KF5503/12 and KF5503/23 (ITT, LOCF); non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

	KF5503/11 (n=1023), Osteoarthritis			KF5503/12 (n=987), Osteoarthritis			KF5503/23 (n=958), Lower back pain			Meta-analysis		
	Placebo (n=336)	PALEXIA® SR (n=344)	Oxycodone CR (n=342)	Placebo (n=336)	PALEXIA® SR (n=319)	Oxycodone CR (n=331)	Placebo (n=316)	PALEXIA® SR (n=312)	Oxycodone CR (n=323)	Placebo (n=991)	PALEXIA® SR (n=978)	Oxycodone CR (n=999)
Baseline pain Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)	7.6 (1.32)	7.5 (1.32)	7.5 (1.22)	7.4 (1.25)	7.4 (1.26)	7.3 (1.21)
Wk 12 maintenance Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)	5.5 (2.57)	4.6 (2.66)	4.6 (2.56)	5.1 (2.56)	4.5 (2.54)	4.8 (2.45)
LS Means diff from placebo Baseline vs Wk 12[a]		-0.7 (0.18)	-0.3 (0.18)		-0.3 (0.18)	0.2 (0.18)		-0.8 (0.19)	-0.9 (0.19)		-0.6 (0.11)	-0.3 (0.11)
p-value 95% CI[b]		<0.001 (-1.04, -0.33)	0.069 (-0.68, 0.02)		0.152 (-0.61, 0.09)	0.279 (-0.16, 0.54)		<0.001 (-1.22, -0.47)	<0.001 (-1.24, -0.49)		<0.001 (-0.80, -0.39)	0.002 (-0.53, -0.12)
Overall maintenance Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)	5.5 (2.46)	4.7 (2.52)	4.6 (2.38)	5.2 (2.40)	4.6 (2.40)	4.8 (2.32)
LS Means diff from placebo Baseline vs overall[a]		-0.7 (0.17)	-0.3 (0.17)		-0.2 (0.16)	0.1 (0.16)		-0.7 (0.18)	-0.8 (0.18)		-0.5(0.10)	-0.3(0.10)
p-value 95% CI[b]		<0.001 (-1.00, –0.33)	0.049 (-0.67, -0.00)		0.135 (-0.55, 0.07)	0.421 (-0.18, 0.44)		<0.001 (-1.06, -0.35)	<0.001 (-1.16, -0.46)		<0.001 (-0.73, -0.34)	<0.001 -0.52, -0.14)
30% responder rate	35.9%	43.0%[c]	24.9%[c]	40.9%	41.1%	26.0%[d]	27.1%	39.7%[c]	36.5%	34.8%	41.3%[c]	27.0%[d]
50% responder rate	24.3%	32.0%[c]	17.3%[d]	27.0%	31.0%	22.1%	18.9%	27.0%[c]	17.4%	23.5%	30.1%[c]	20.8%
PGIC assessment of very much improved & much improved	35.5%	58.5%[c]	47.0%[c]	43.2%	56.0%[c]	42.5%	32.7%	55.5%[c]	60.0%[c]	37.4%	56.7%[c]	49.8%[c]

a: Change from baseline in average pain intensity scores based on numerical rating scale (NRS)[a], ITT population; LOCF = last observation carried forward Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).
b: Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled centre and baseline pain intensity as covariate (type III SS) unadjusted p-value.
c:Indicates statistically significant over placebo
d: Indicates statistical significance of placebo over active
LS = least square

Painful diabetic peripheral neuropathy
A randomised withdrawal Phase III clinical trial (KF5503/36 evaluating the efficacy and safety of orally administered PALEXIA® SR (100 to 250 mg twice daily) compared PALEXIA® SR to placebo in subjects with painful diabetic peripheral neuropathy.

The study consisted of two phases: an open label phase (n=588) during which all subjects received PALEXIA® SR and were titrated to an optimal dose, and a double-blind phase (n=389) during which subjects were randomised to receive PALEXIA® SR (n=196) or placebo (n=193).

During the open-label titration phase, subjects initially received PALEXIA® SR (50 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 3 weeks (increments of PALEXIA® SR 50 mg twice daily) to achieve a stable optimum dose. The maximum (minimum) doses administered were: PALEXIA® SR 250 mg (100 mg) twice daily. The study drug was taken with or without food.

Following completion of the open-label titration phase, subjects who had at at least a 1-point improvement on an 11-point NRS in average pain intensity score were randomised into the double-blind maintenance phase to receive their individually determined open-label PALEXIA® SR dose or placebo for 12 weeks.

Subjects were allowed paracetamol as rescue medication during the titration period. Subjects were allowed PALEXIA® SR as supplemental analgesia during the double-blind maintenance phase (25 mg, twice daily for the first 4 days and 25 mg once daily for the remainder of the maintenance phase).

The primary efficacy endpoint was change from baseline at randomisation in average pain intensity over the last week (Week 12) of the double-blind maintenance period, as determined by twice-daily measurements on an 11-point NRS.

For the primary efficacy analysis, PALEXIA® SR showed a statistically significant difference in average pain intensity compared to placebo at Week 12 of the double-blind maintenance period ($p<0.001$, an LS mean difference compared to placebo: –1.3) (Table 2).

Table 2. Change in average pain intensity scores based on numerical rating scale (NRS)[a]- from start of double-blind phase to week 12 of double-blind phase baseline, ITT population

	Placebo	PALEXIA® SR
Start DB		
N	192	193
Mean (SD)	3.4 (1.88)	3.6 (1.90)
Median (Range)	3.3 (0 to 9)	3.8 (0 to 9)
Week 12 of Maintenance		
N	192	196
Mean (SD)	4.7 (2.46)	3.5 (2.13)
Median (Range)	4.8 (0 to 10)	3.2 (0 to 10)
Change from Start DB to Week 12 of		

Maintenance Period		
N	192	193
Mean (SD)	1.3 (2.41)	-0.1 (1.69)
Median (Range)	1.0 (-7 to 9)	-0.1 (-7 to 5)
LS Mean Change	1.4	0.0
LS Mean Difference versus Placebo (SE)		-1.3 (0.20)
95% CI (verses Placebo)		(-1.70, -0.92)
p value (versus Placebo)[b]		<0.001

a: LOCF=last observation carried forward
b: Test for no treatment difference based on the ANCOVA model with treatment, country, dose category and prior opioid use as factors and Start DB pain intensity as a covariate.
Average pain scores are the averages of all scores recorded during the 72-hour period before randomization or during each week.
Daily pain intensity is the average of pain scores over a 24-hour period, starting from time of randomization.
DB=double-blind

INDICATIONS

PALEXIA® SR is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy.

CONTRAINDICATIONS

PALEXIA® SR is contraindicated:
- in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product,
- in situations where drugs with mu-opioid receptor agonist activity are contraindicated, i.e. patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercapnia,
- in any patient who has or is suspected of having paralytic ileus,
- in patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic drugs (see **PRECAUTIONS**, **Interactions with other medicines**),
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see **PRECAUTIONS**, **Interactions with other medicines**).

PRECAUTIONS

Potential for Abuse
As with other drugs that have mu-opioid receptor agonist activity, PALEXIA® SR has a potential for abuse. This should be considered when prescribing or dispensing PALEXIA® SR in situations where there is concern about an increased risk of misuse, abuse, or diversion.

Drugs that have mu-opioid receptor agonist activity may be abused by crushing, chewing, snorting or injecting the product. Such practices pose a significant risk to the abuser and may result in overdose or death.

All patients treated with drugs that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Drug Dependence
Tolerance: Repeated administration of opioids may lead to tolerance. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia, in the absence of disease progression or other external factors.

Withdrawal symptoms: In a study conducted over 12 months, 22.4% of patients given PALEXIA® SR had objective signs of opioid withdrawal compared with 27.3% given oxycodone CR when assessed between 2 - 5 days after the last dose of study drug. Only 4.8% of patients given PALEXIA® SR and 4.5% given oxycodone CR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

Use in patients with pain due to malignancy
There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy; therefore the use of PALEXIA® SR in patients with pain due to malignancy is not recommended.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, PALEXIA® SR may produce dose-related respiratory depression. Therefore, PALEXIA® SR should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and PALEXIA® SR should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid receptor agonist-induced respiratory depression (see **OVERDOSAGE**).

Head Injury and Increased Intracranial Pressure
Like other drugs with mu-opioid receptor agonist activity, PALEXIA® SR should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. PALEXIA® SR should be used with caution in patients with head injury and brain tumors.

Seizures
PALEXIA® SR has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. However, like other analgesics with mu-opioid receptor agonist activity

PALEXIA® SR should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
For patients with mild or moderate renal impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, therefore use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Hepatic Impairment
For patients with mild hepatic impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

A study of PALEXIA® SR in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA® SR should be used with caution in patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Use in Pancreatic/Biliary Tract Disease
Drugs with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. PALEXIA® SR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Effect on fertility
There were no apparent effects on the fertility of male rats at intravenous doses up to 12 mg/kg/day, although histopathology analyses were not conducted. In female rats, the numbers of corpora lutea and implantations were reduced, and pre- and post-implantation losses were increased, at intravenous tapentadol doses associated with maternal toxicity. The clinical relevance of these findings is unknown.

Use in pregnancy (Category C)
There are no adequate and well controlled studies of tapentadol in pregnant women. PALEXIA® SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of tapentadol on labor and delivery in humans is unknown. PALEXIA® SR is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, neonates whose mothers have been taking tapentadol should be monitored for respiratory depression.

Tapentadol crosses the placenta in pregnant rats. Tapentadol was evaluated for teratogenic effects in rats and rabbits following intravenous and subcutaneous administration during organogenesis. Embryofetal toxicity such

as delays in skeletal maturation and cerebral ventricular dilation was observed in rats concomitant with maternal toxicity at subcutaneous doses of 10 mg/kg/day or greater (plasma AUC exposure less than maximum anticipated clinical exposure). Subcutaneous administration of tapentadol to rabbits revealed embryofetal toxicity at doses of 10-24 mg/kg/day (AUC exposure 1 to 2 fold the maximum anticipated human exposure), along with reduced fetal viability, skeletal delays and other variations, and multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia and cleft palate at 10-24 mg/kg/day, and ablepharia, encephalopathy and spina bifida at 24 mg/kg/day. There were no teratogenic effects observed in similar studies conducted in rats and rabbits via the intravenous route (up to 15 mg/kg/day) Embryofetal toxicity, including malformations, may be secondary to maternal toxicity in these species.

Use in lactation
There is limited information on the excretion of tapentadol in breast milk. Tapentadol is excreted into milk in lactating rats following oral dosing. Oral tapentadol administration to rats during lactation resulted in increased postnatal pup mortality, at doses lower than those associated with maternal toxicity (exposure (AUC) less than maximum anticipated clinical exposure). The potential relevance to humans is unknown. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. PALEXIA® SR should not be used during breast feeding.

Paediatric use
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

Use in the elderly (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Carcinogenicity
Tapentadol was administered to rats (diet) and mice (oral gavage) for two years. A significant trend towards increased hepatocellular tumours (adenoma and carcinoma) was observed in mice at oral doses of 100 mg/kg/day or greater. A dose-related increased incidence of hepatocellular hypertrophy (but not tumours) was observed in rats at dietary doses of 125 mg/kg/day or greater. Exposures (plasma AUC) in both species were less than that at the maximum recommended clinical dose. These findings may derive from adaptive changes following hepatic enzyme induction. The potential clinical relevance is unknown.

Genotoxicity
Tapentadol did not induce gene mutations in bacteria, but was clastogenic at cytotoxic concentrations in an *in vitro* chromosomal aberration test with metabolic activation in Chinese hamster V79 cells in 1 of 2 assays. The one

positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis at extrapolated exposures (AUC) similar to the maximum anticipated human exposure. The weight of evidence indicates that tapentadol presents no significant genotoxic potential at clinical doses.

Effects on Ability to Drive and Use Machines
Like drugs with mu-opioid receptor agonist activity, PALEXIA® SR may have major influence on the ability to drive and use machines, due to the fact that it may adversely affect central nervous system functions (see **ADVERSE EFFECTS**). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers (see **Interactions with other medicines**). Patients should be cautioned as to whether driving or use of machines is permitted.

Interactions with other medicines
Tapentadol is mainly metabolised by glucuronidation, a system with a very high capacity which is not easily saturated even in disease. As therapeutic concentrations of drugs that are subject to glucuronidation are generally well below the concentrations needed for potential inhibition of glucuronidation, the risk of clinically relevant interaction between these drugs is generally low. The following substances have been included in a set of interaction studies without any clinically significant finding: paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole and metoclopramide (see **Pharmacokinetics**).

Only a small amount of tapentadol is metabolised by oxidative pathways (see **Pharmacokinetics**). Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity in vitro but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro*, and an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo.* The potential clinical relevance of this finding is unknown.

CNS depressants
Patients receiving other mu-opioid receptor agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA® SR may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with PALEXIA® SR. When such combined therapy is contemplated, the reduction of dose of one or both agents should be considered.

Monoamine oxidase (MAO) inhibitors
PALEXIA® SR is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due

to potential additive effects on noradrenaline levels which may result in adverse cardiovascular events (see **CONTRAINDICATIONS**).

Serotonin Syndrome
PALEXIA® IR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake inhibition activity

A causal relationship between tapentadol and serotonin syndrome has not been established, however there is a theoretical risk of serotonin syndrome when tapentadol is used in combination with serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans. Signs of serotonin syndrome may include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

ADVERSE EFFECTS

Treatment emergent adverse events in the double-blind Phase 2/3 studies
In the pooled all Phase 2/3 PALEXIA® SR studies, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 71.7%. This was higher when compared with the placebo group (54.5%) and lower than the oxycodone CR group (86.3%) (Table 3).

Compared with oxycodone CR there was better gastrointestinal tolerability with PALEXIA® SR. The incidence of nausea (19.5%), vomiting (7.4%) and constipation (13.6%) was lower with PALEXIA® SR than oxycodone CR (36.1%, 19.8% and 31.5%, respectively) (Table 3). PALEXIA® SR also had a beneficial safety profile over that of oxycodone CR for somnolence (11.3% vs 16.3%), dizziness (13.7% vs 19.8%), and pruritus (4.9% vs 12.4%). This suggests that the adverse event profile for PALEXIA® SR is similar to those of other opioid agonists, while at the same time exhibiting a lower incidence of a number of adverse events.
The majority of subjects in all treatment groups in the pooled all Phase 2/3 PALEXIA® SR studies experienced TEAEs that were mild to moderate in intensity. Less subjects in the all PALEXIA® SR group reported severe adverse events compared to those in the oxycodone CR group.

Table 5. TEAEs in at least 5% of subjects in any pooled treatment group (all studies) (PALEXIA® SR formulation Phase 2/3 studies integrated summary of safety: safety analysis set)[a]

System organ class/preferred term	Placebo (n=1498) n (%)	All PALEXIA® SR (n=3613) n (%)	All oxycodone CR (n=1472) n (%)
Number (n (%)) of subjects with TEAE	817 (54.5)	2589 (71.7)	1271 (86.3)
Gastrointestinal disorders	**370 (24.7)**	**1464 (40.5)**	**952 (64.7)**
Nausea	128 (8.5)	704 (19.5)	531 (36.1)
Constipation	85 (5.7)	493 (13.6)	464 (31.5)
Vomiting	44 (2.9)	269 (7.4)	292 (19.8)

Dry mouth	26 (1.7)	217 (6.0)	66 (4.5)
Diarrhoea	78 (5.2)	199 (5.5)	78 (5.3)
Nervous system disorders	**288 (19.2)**	**1308 (36.2)**	**662 (45.0)**
Dizziness	77 (5.1)	495 (13.7)	291 (19.8)
Headache	170 (11.3)	427 (11.8)	174 (11.8)
Somnolence	44 (2.9)	408 (11.3)	240 (16.3)
General disorders and administration site conditions	**138 (9.2)**	**583 (16.1)**	**290 (19.7)**
Fatigue	48 (3.2)	253 (7.0)	139 (9.4)
Skin and subcutaneous tissue disorders	**80 (5.3)**	**481 (13.3)**	**332 (22.6)**
Pruritus	20 (1.3)	176 (4.9)	183 (12.4)
Hyperhidrosis	16 (1.1)	160 (4.4)	75 (5.1)
Musculoskeletal and connective tissue disorders	**167 (11.1)**	**395 (10.9)**	**132 (9.0)**
Myalgia	9 (0.6)	42 (1.2)	10 (0.7)
Bone pain	2 (0.1)	16 (0.4)	1 (0.1)
Ear and labyrinth disorders	**23 (1.5)**	**109 (3.0)**	**49 (3.3)**
Vertigo	12 (0.8)	68 (1.9)	31 (2.1)

a: This summary of clinical safety includes clinical studies that vary in design (controlled dose adjustment, fixed dose, and open label) and subject population (lower back pain, pain due to OA, and pain due to peripheral neuropathy). Studies included: KF5503/09, KF5503/10, KF5503/19, KF5503/20, KF5503/24, KF5503/11, KF5503/12, KF5503/23, KF5503/36
MedDRA version 11.0 was used for coding.
TEAE = treatment emergent adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total, per category).

The following adverse drug reactions (ADRs) were reported from clinical trials performed with PALEXIA® SR:

Very Common (≥ 1/10)

Nervous system disorders:	Dizziness, Somnolence, Headache
Gastrointestinal disorders:	Nausea, Constipation

Common (≥1/100 to <1/10)

Metabolism and nutrition disorders:	Decreased appetite
Psychiatric disorders:	Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness
Nervous system disorders:	Disturbance in attention, Tremor, Muscle contractions involuntary
Vascular disorders:	Flushing
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Gastrointestinal disorders:	Vomiting, Diarrhoea, Dyspepsia
Skin and subcutaneous tissue disorders:	Pruritus, Hyperhidrosis, Rash

General disorders and administration site conditions:	Asthenia, Fatigue, Feeling of body temperature change, Mucosal dryness, Oedema

Uncommon (≥1/1,000 to <1/100)

Immune system disorders:	Drug hypersensitivity
Metabolism and nutrition disorders:	Weight decreased
Psychiatric disorders:	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams, Euphoric mood
Nervous system disorders:	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia
Eye disorders:	Visual disturbance
Cardiac disorders:	Heart rate increased, Heart rate decreased
Vascular disorders:	Blood pressure decreased
Gastrointestinal disorders:	Abdominal discomfort
Skin and subcutaneous tissue disorders:	Urticaria
Renal and urinary disorders:	Urinary hesitation, Pollakiuria
Reproductive system and breast disorders:	Sexual dysfunction
General disorders and administration site conditions:	Drug withdrawal syndrome, Feeling abnormal, Irritability

Rare (≥1/10,000 to <1/1,000)

Psychiatric disorders:	Drug dependence, Thinking abnormal
Nervous system disorders:	Convulsion, Presyncope, Coordination abnormal
Respiratory, thoracic and mediastinal disorders:	Respiratory depression
Gastrointestinal disorders:	Impaired gastric emptying
General disorders and administration site conditions:	Feeling drunk, Feeling of relaxation

Treatment emergent adverse events with prolonged treatment

A total of 894 subjects with moderate to severe pain from low back pain or osteoarthritis of the knee or hip were treated with a flexible dosing regimen of PALEXIA® SR (100 mg to 250 mg twice daily) in a 1 year safety study (KF5503/24). The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The overall incidence of TEAEs was lower in the PALEXIA® SR group (85.7%) compared to oxycodone CR (20 mg to 50 mg) (90.6%).

The most common TEAEs (incidence >10% in either treatment group) were constipation, nausea, vomiting, somnolence, dizziness, headache, fatigue and pruritus. Subjects administered PALEXIA® SR had a lower incidence of constipation, nausea, vomiting, dizziness, fatigue and pruritus compared to oxycodone CR (22.6% vs 38.6%, 18.1% vs 33.2%, 7.0% vs 13.5%, 14.8% vs 19.3%, 9.7% vs 10.3%, and 5.4% vs 10.3% respectively).

Post marketing experience
There have been no adverse reactions identified from spontaneous reports so far for PALEXIA® SR.

DOSAGE AND ADMINISTRATION

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

PALEXIA® SR should be taken twice daily, approximately every 12 hours. PALEXIA® SR may be administered with or without food.

Initiation of therapy
a) Initiation of therapy in patients currently not taking opioid analgesics:
Patients should start treatment with single doses of 50 mg tapentadol administered twice daily.

b) Initiation of therapy in patients currently taking opioid analgesics:
When switching from opioids to PALEXIA® SR and choosing the initial dose, the nature of the previous medication, administration and the mean daily dose should be taken into account.

Titration and maintenance
After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50 mg tapentadol twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Total daily doses of PALEXIA® SR tablets greater than 500 mg tapentadol have not been studied and are therefore not recommended.

Discontinuation of treatment
Tapering of therapy is not required, but patients should be cautioned about the possibility of experiencing withdrawal symptoms (see **ADVERSE EFFECTS**).

Renal Impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment (see **Pharmacokinetics**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, and its use is not recommended. A pharmacokinetic study showed an increased level of an inactive metabolite in subjects with renal impairment (see **PRECAUTIONS** and also **Pharmacokinetics**).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment (see **Pharmacokinetics**).

PALEXIA® SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg tapentadol and not be administered more frequently than once every 24 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see **PRECAUTIONS** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Elderly Patients (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Paediatric Patients
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population (see **PRECAUTIONS**).

OVERDOSAGE

Experience with PALEXIA® SR overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In the clinical setting, these symptoms may include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of overdose should be focused on treating symptoms of mu-opioid receptor agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of PALEXIA® SR is suspected.

Pure opioid antagonists such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute

for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

Contact the Poisons Information Centre on 131 126 for further advice on overdosage management.

PRESENTATION AND STORAGE CONDITIONS

- PALEXIA® SR 50 mg sustained release tablets: white film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H1" engraving on the other side.
- PALEXIA® SR 100 mg sustained release tablets: pale yellow film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H2" engraving on the other side.
- PALEXIA® SR 150 mg sustained release tablets: pale pink film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H3" engraving on the other side.
- PALEXIA® SR 200 mg sustained release tablets: pale orange film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H4" engraving on the other side.
- PALEXIA® SR 250 mg sustained release tablets: brownish red film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H5" engraving on the other side.

Blister Packs of 7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets.

Not all pack sizes may be available.

PALEXIA® SR 50 mg, 100 mg, 150 mg, 200 mg and 250 mg sustained release tablets have a shelf-life of 36 months when stored below 30°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

CSL Limited ABN 99 051 588 348
45 Poplar Road
Parkville 3052
Australia

POISON SCHEDULE OF THE MEDICINE

Controlled Drug, S8

DATE OF TGA APPROVAL 24 December 2010

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PALEXIA® SR PRODUCT INFORMATION
AUST R 165332, 165346, 165347, 165356, 165357

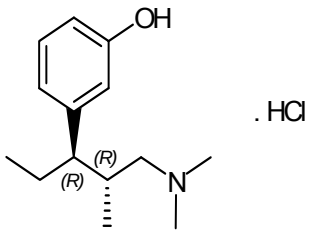
NAME OF THE MEDICINE

PALEXIA® SR 50 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 100 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 150 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 200 mg (tapentadol as hydrochloride) sustained release tablets
PALEXIA® SR 250 mg (tapentadol as hydrochloride) sustained release tablets

DESCRIPTION

PALEXIA® SR sustained release tablets contain tapentadol hydrochloride (HCl) which is a centrally acting synthetic analgesic combining mu agonist and noradrenaline re-uptake inhibition activity in a single molecule. Tapentadol is a white to off-white powder; freely soluble in water and methanol, and soluble in ethanol. The pKa_1 is 9.36 and pKa_2 is 10.37 determined in 0.15 M KCl solution. The partition coefficient is defined as the ratio of the equilibrium concentrations of a single neutral molecular species in a 1-octanol/aqueous buffered solution 2-phase system. The value of log P for tapentadol hydrochloride in 1-octanol/water is 2.89 ± 0.01. The chemical name for tapentadol HCl is 3-[(1*R*,2*R*)-3-(dimethylamino)-1-ethyl-2-methylpropyl]phenol monohydrochloride. The molecular weight of tapentadol HCl is 257.80, and the empirical formula is $C_{14}H_{23}NO \bullet HCl$.

The structural formula of tapentadol HCl (CAS number: 175591-09-0) is:



PALEXIA® SR tablets contain 50, 100, 150, 200 and 250 mg tapentadol (as hydrochloride). Excipients are: hypromellose 100,000 mPa-s, microcrystalline cellulose, colloidal anhydrous silica and magnesium stearate. Excipients in the film coat are: hypromellose 6 mPa-s, lactose monohydrate, talc, macrogol 6000, propylene glycol, titanium dioxide (E171), iron oxide yellow (E172) (100, 150, 200 and 250 mg tablets only), iron oxide red (E172) (150, 200 and 250 mg tablets only), and iron oxide black (E172) (250 mg tablets only).

PHARMACOLOGY

Pharmacodynamics

Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid activity in a single molecule. It has 18 times less binding affinity

than morphine to the human mu-opioid receptor but was only 2-3 times less potent in producing analgesia in animal models (on a dose per body weight basis). This low *in-vivo* potency difference is consistent with its two mechanisms of action. Tapentadol has been shown to inhibit noradrenaline reuptake in the brains of rats resulting in increased noradrenaline concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid receptor antagonists (e.g., naloxone), whereas the noradrenaline reuptake inhibition is sensitive to noradrenaline modulators. Tapentadol exerts its analgesic effects directly without a pharmacologically active metabolite.

Effects on the cardiovascular system: In ECG studies in conscious dogs, non-persistent QT/QTc interval prolongation was observed at exposures similar to or lower than the clinical plasma C_{max}. These effects were not observed in safety pharmacology studies with repeated ECG measurements. Heart rate was increased in conscious rats and dogs at peak plasma concentrations at least twice the clinical plasma C_{max}, but there was no clear effect on other ECG parameters (PR interval, QRS duration, T-wave or U-wave morphology). In a thorough QT trial in healthy subjects, no effect of multiple therapeutic and supratherapeutic doses of tapentadol on the QT interval was shown. Similarly, tapentadol had no relevant effect on other ECG parameters (heart rate, PR interval, QRS duration, T-wave or U-wave morphology).

Pharmacokinetics

The tapentadol PR formulation is a hydrophilic hypromellose-based matrix formulation that provides pH-independent *in-vitro* release of the drug substance over a time period of approximately 12 hours. An initial drug substance release of about 20% occurs over the first 30 minutes with ongoing drug release over the ensuing 12-hour period.

Absorption
Mean absolute bioavailability after single-dose administration (fasting) of PALEXIA® SR is approximately 32% due to extensive first-pass metabolism. Maximum serum concentrations of tapentadol are observed at between 3 and 6 hours after administration of PALEXIA® SR tablets.

Dose proportional increases for AUC (the most relevant exposure parameter for sustained-release formulations) have been observed after administration of PALEXIA® SR tablets over the therapeutic dose range.

A multiple dose study with twice daily dosing using 86 mg and 172 mg tapentadol administered as SR tablets showed an accumulation ratio of about 1.5 for the parent drug which is primarily determined by the dosing interval and apparent half-life of tapentadol.

Food Effect
The AUC and C_{max} increased by 8% and 18%, respectively, when PALEXIA® SR tablets were administered after a high-fat, high-calorie breakfast. PALEXIA® SR may be given with or without food.

Distribution
Tapentadol is widely distributed throughout the body. Following intravenous administration, the volume of distribution (Vz) for tapentadol is 540 +/- 98 L. The serum protein binding is low and amounts to approximately 20%.

Metabolism and Elimination
In humans, the metabolism of tapentadol is extensive. About 97% of the parent compound is metabolized. The major pathway of tapentadol metabolism is conjugation with glucuronic acid to produce glucuronides. After oral administration approximately 70% (55% glucuronide and 15% sulfate of tapentadol) of the dose is excreted in urine in the conjugated form. Uridine diphosphate glucuronyl transferase (UGT) is the primary enzyme involved in the glucuronidation (mainly UGT1A6, UGT1A9 and UGT2B7 isoforms). A total of 3% of drug was excreted in urine as unchanged drug. Tapentadol is additionally metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which are further metabolized by conjugation. Therefore, drug metabolism mediated by cytochrome P450 system is of less importance than phase 2 conjugation.

None of the metabolites contributes to the analgesic activity.

Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys.

The terminal half-life is on average 4 hours after oral administration. The total clearance is 1530 +/- 177 ml/min.

Elderly patients
The mean exposure (AUC) to tapentadol was similar in elderly subjects compared to young adults, with a 16% lower mean C_{max} observed in the elderly subject group compared to young adult subjects.

Renal Impairment
AUC and C_{max} of tapentadol were comparable in subjects with varying degrees of renal function (from normal to severely impaired). In contrast, increasing exposure (AUC) to tapentadol-O-glucuronide was observed with increasing degree of renal impairment. In subjects with mild, moderate, and severe renal impairment, the AUC of tapentadol-O-glucuronide are 1.5-, 2.5-, and 5.5-fold higher compared with normal renal function, respectively.

Hepatic Impairment
Administration of tapentadol resulted in higher exposures and serum levels to tapentadol in subjects with impaired hepatic function compared to subjects with normal hepatic function. The ratio of tapentadol pharmacokinetic parameters for the mild and moderate hepatic impairment groups in comparison to the normal hepatic function group were 1.7 and 4.2, respectively, for AUC; 1.4 and 2.5, respectively, for C_{max}; and 1.2 and 1.4, respectively, for $t_{1/2}$. The rate of formation of tapentadol-O-glucuronide was lower in subjects with increased liver impairment.

Pharmacokinetic Interactions

Tapentadol is mainly metabolized by Phase 2 glucuronidation, and only a small amount is metabolized by Phase 1 oxidative pathways.

As glucuronidation is a high capacity/low affinity system, any clinically relevant interactions caused by Phase 2 metabolism are unlikely to occur. This has been evidenced by clinical pharmacokinetic drug-drug interaction studies with probe drugs naproxen and probenecid with increases in AUC of tapentadol by 17% and 57%, respectively. No changes in the pharmacokinetic parameters of tapentadol were observed when paracetamol and acetylsalicylic acid were given concomitantly. Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro* but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.

The pharmacokinetics of tapentadol were not affected when gastric pH or gastrointestinal motility were increased by omeprazole and metoclopramide, respectively.

Plasma protein binding of tapentadol is low (approximately 20%). Therefore, the likelihood of pharmacokinetic drug-drug interactions by displacement from the protein binding site is low.

CLINICAL TRIALS

The efficacy and safety of PALEXIA® SR in the treatment of moderate to severe chronic pain has been investigated in three pivotal Phase III randomised, double-blind, active- and placebo-controlled, parallel-group, multicentre studies; two in patients with moderate to severe chronic pain from osteoarthritis of the knee (clinical trials KF5503/11 and KF5503/12) and one in patients with moderate to severe chronic low back pain (clinical trial KF5503/23). These pain conditions were chosen as they usually present with moderate to severe pain that is often treated with opioids.

In all three studies, subjects were initially randomised to receive PALEXIA® SR (50 mg twice daily), placebo or oxycodone CR (10 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 2 weeks (increments of PALEXIA® SR 50 mg, oxycodone CR 10 mg, or placebo twice daily) to achieve a stable optimum dose. Subjects were allowed paracetamol as rescue medication during the titration period. Subjects received the following maximum (minimum) doses: PALEXIA® SR 250 mg (100 mg) twice daily, oxycodone CR 50 mg (20 mg) twice daily, or placebo twice daily. The study drug was taken with or without food.

To enter the 12-week maintenance period, subjects had to be on a stable dose of the study drug for the last 3 days of the titration period without any rescue medication. If needed, subjects could request controlled adjustment of their dose based on their individual analgesia requirements and/or

tolerability experience however adjustments were to be kept to a minimum during the maintenance period.

All three studies had the same primary endpoints - change from baseline of the average pain intensity over the 12-week maintenance period of the daily pain intensity on an 11-point numerical rating scale (NRS), and change from baseline of the average pain intensity over the last week of the maintenance period at Week 12 of the daily pain intensity on an 11-point NRS. Secondary endpoints included 30% and 50% responder rates and Patient Global Impression of Change scale.

The results for these endpoints for all three studies are summarised in Table 1.

Meta-analysis of pivotal studies

A pre-specified meta-analysis of the data generated in the above three clinical trials was undertaken. The two main objectives of the meta-analysis were to assess the superior safety of PALEXIA® SR compared to oxycodone CR with regards to constipation (gastrointestinal tolerability), and to assess the non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

PALEXIA® SR was superior to oxycodone CR with regards to constipation, nausea and vomiting (gastrointestinal tolerability) ($p<0.001$). The non-inferiority of PALEXIA® SR to oxycodone CR in relation to the primary endpoint (change from baseline of the average pain intensity over the 12-week maintenance period or at Week 12) (using LOCF) was also demonstrated (both p-values ≤ 0.001) (Table 1).

Table 1. Meta-analysis of data generated in studies KF5503/11, KF5503/12 and KF5503/23 (ITT, LOCF); non-inferior efficacy of PALEXIA® SR compared to oxycodone CR.

	KF5503/11 (n=1023), Osteoarthritis			KF5503/12 (n=987), Osteoarthritis			KF5503/23 (n=958), Lower back pain			Meta-analysis		
	Placebo (n=336)	PALEXIA® SR (n=344)	Oxycodone CR (n=342)	Placebo (n=336)	PALEXIA® SR (n=319)	Oxycodone CR (n=331)	Placebo (n=316)	PALEXIA® SR (n=312)	Oxycodone CR (n=323)	Placebo (n=991)	PALEXIA® SR (n=978)	Oxycodone CR (n=999)
Baseline pain Mean (SD)	7.2 (1.29)	7.4 (1.35)	7.2 (1.29)	7.3 (1.12)	7.3 (1.09)	7.3 (1.10)	7.6 (1.32)	7.5 (1.32)	7.5 (1.22)	7.4 (1.25)	7.4 (1.26)	7.3 (1.21)
Wk 12 maintenance Mean (SD)	5.0 (2.61)	4.4 (2.48)	4.7 (2.35)	4.8 (2.47)	4.5 (2.48)	5.0 (2.44)	5.5 (2.57)	4.6 (2.66)	4.6 (2.56)	5.1 (2.56)	4.5 (2.54)	4.8 (2.45)
LS Means diff from placebo Baseline vs Wk 12[a]		-0.7 (0.18)	-0.3 (0.18)		-0.3 (0.18)	0.2 (0.18)		-0.8 (0.19)	-0.9 (0.19)		-0.6 (0.11)	-0.3 (0.11)
p-value 95% CI[b]		<0.001 (-1.04, -0.33)	0.069 (-0.68, 0.02)		0.152 (-0.61, 0.09)	0.279 (-0.16, 0.54)		<0.001 (-1.22, -0.47)	<0.001 (-1.24, -0.49)		<0.001 (-0.80, -0.39)	0.002 (-0.53, -0.12)
Overall maintenance Mean (SD)	5.1 (2.48)	4.4 (2.40)	4.7 (2.26)	5.0 (2.24)	4.7 (2.28)	5.1 (2.29)	5.5 (2.46)	4.7 (2.52)	4.6 (2.38)	5.2 (2.40)	4.6 (2.40)	4.8 (2.32)
LS Means diff from placebo Baseline vs overall[a]		-0.7 (0.17)	-0.3 (0.17)		-0.2 (0.16)	0.1 (0.16)		-0.7 (0.18)	-0.8 (0.18)		-0.5(0.10)	-0.3(0.10)
p-value 95% CI[b]		<0.001 (-1.00, –0.33)	0.049 (-0.67, -0.00)		0.135 (-0.55, 0.07)	0.421 (-0.18, 0.44)		<0.001 (-1.06, -0.35)	<0.001 (-1.16, -0.46)		<0.001 (-0.73, -0.34)	<0.001 -0.52, -0.14)
30% responder rate	35.9%	43.0%[c]	24.9%[c]	40.9%	41.1%	26.0%[d]	27.1%	39.7%[c]	36.5%	34.8%	41.3%[c]	27.0%[d]
50% responder rate	24.3%	32.0%[c]	17.3%[d]	27.0%	31.0%	22.1%	18.9%	27.0%[c]	17.4%	23.5%	30.1%[c]	20.8%
PGIC assessment of very much improved & much improved	35.5%	58.5%[c]	47.0%[c]	43.2%	56.0%[c]	42.5%	32.7%	55.5%[c]	60.0%[c]	37.4%	56.7%[c]	49.8%[c]

a: Change from baseline in average pain intensity scores based on numerical rating scale (NRS)[a], ITT population; LOCF = last observation carried forward Average pain scores are the averages of all scores recorded during the baseline period or during each time period (Week 12 of maintenance or overall maintenance).
b: Test for no difference between treatment from ANCOVA model with factor(s) treatment, pooled centre and baseline pain intensity as covariate (type III SS) unadjusted p-value.
c:Indicates statistically significant over placebo
d: Indicates statistical significance of placebo over active
LS = least square

Painful diabetic peripheral neuropathy
A randomised withdrawal Phase III clinical trial (KF5503/36 evaluating the efficacy and safety of orally administered PALEXIA® SR (100 to 250 mg twice daily) compared PALEXIA® SR to placebo in subjects with painful diabetic peripheral neuropathy.

The study consisted of two phases: an open label phase (n=588) during which all subjects received PALEXIA® SR and were titrated to an optimal dose, and a double-blind phase (n=389) during which subjects were randomised to receive PALEXIA® SR (n=196) or placebo (n=193).

During the open-label titration phase, subjects initially received PALEXIA® SR (50 mg twice daily) for the first 3 days. Subjects were then titrated upwards over the following 3 weeks (increments of PALEXIA® SR 50 mg twice daily) to achieve a stable optimum dose. The maximum (minimum) doses administered were: PALEXIA® SR 250 mg (100 mg) twice daily. The study drug was taken with or without food.

Following completion of the open-label titration phase, subjects who had at at least a 1-point improvement on an 11-point NRS in average pain intensity score were randomised into the double-blind maintenance phase to receive their individually determined open-label PALEXIA® SR dose or placebo for 12 weeks.

Subjects were allowed paracetamol as rescue medication during the titration period. Subjects were allowed PALEXIA® SR as supplemental analgesia during the double-blind maintenance phase (25 mg, twice daily for the first 4 days and 25 mg once daily for the remainder of the maintenance phase).

The primary efficacy endpoint was change from baseline at randomisation in average pain intensity over the last week (Week 12) of the double-blind maintenance period, as determined by twice-daily measurements on an 11-point NRS.

For the primary efficacy analysis, PALEXIA® SR showed a statistically significant difference in average pain intensity compared to placebo at Week 12 of the double-blind maintenance period ($p<0.001$, an LS mean difference compared to placebo: –1.3) (Table 2).

Table 2. Change in average pain intensity scores based on numerical rating scale (NRS)[a]- from start of double-blind phase to week 12 of double-blind phase baseline, ITT population

	Placebo	PALEXIA® SR
Start DB		
N	192	193
Mean (SD)	3.4 (1.88)	3.6 (1.90)
Median (Range)	3.3 (0 to 9)	3.8 (0 to 9)
Week 12 of Maintenance		
N	192	196
Mean (SD)	4.7 (2.46)	3.5 (2.13)
Median (Range)	4.8 (0 to 10)	3.2 (0 to 10)
Change from Start DB to Week 12 of		

Maintenance Period		
N	192	193
Mean (SD)	1.3 (2.41)	-0.1 (1.69)
Median (Range)	1.0 (-7 to 9)	-0.1 (-7 to 5)
LS Mean Change	1.4	0.0
LS Mean Difference versus Placebo (SE)		-1.3 (0.20)
95% CI (verses Placebo)		(-1.70, -0.92)
p value (versus Placebo)[b]		<0.001

a: LOCF=last observation carried forward
b: Test for no treatment difference based on the ANCOVA model with treatment, country, dose category and prior opioid use as factors and Start DB pain intensity as a covariate.
Average pain scores are the averages of all scores recorded during the 72-hour period before randomization or during each week.
Daily pain intensity is the average of pain scores over a 24-hour period, starting from time of randomization.
DB=double-blind

INDICATIONS

PALEXIA® SR is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy.

CONTRAINDICATIONS

PALEXIA® SR is contraindicated:
- in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product,
- in situations where drugs with mu-opioid receptor agonist activity are contraindicated, i.e. patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma or hypercapnia,
- in any patient who has or is suspected of having paralytic ileus,
- in patients with acute intoxication with alcohol, hypnotics, centrally acting analgesics, or psychotropic drugs (see **PRECAUTIONS**, **Interactions with other medicines**),
- in patients who are receiving MAO inhibitors or who have taken them within the last 14 days (see **PRECAUTIONS**, **Interactions with other medicines**).

PRECAUTIONS

Potential for Abuse
As with other drugs that have mu-opioid receptor agonist activity, PALEXIA® SR has a potential for abuse. This should be considered when prescribing or dispensing PALEXIA® SR in situations where there is concern about an increased risk of misuse, abuse, or diversion.

Drugs that have mu-opioid receptor agonist activity may be abused by crushing, chewing, snorting or injecting the product. Such practices pose a significant risk to the abuser and may result in overdose or death.

All patients treated with drugs that have mu-opioid receptor agonist activity should be carefully monitored for signs of abuse and addiction.

Drug Dependence
Tolerance: Repeated administration of opioids may lead to tolerance. Tolerance is the need for increasing doses of opioids to maintain a defined effect such as analgesia, in the absence of disease progression or other external factors.

Withdrawal symptoms: In a study conducted over 12 months, 22.4% of patients given PALEXIA® SR had objective signs of opioid withdrawal compared with 27.3% given oxycodone CR when assessed between 2 - 5 days after the last dose of study drug. Only 4.8% of patients given PALEXIA® SR and 4.5% given oxycodone CR were considered by investigators to have moderate withdrawal. No subjects had moderately severe or severe withdrawal.

Use in patients with pain due to malignancy
There is currently no clinical trial data available regarding the safety and efficacy of PALEXIA® SR in patients with pain due to malignancy; therefore the use of PALEXIA® SR in patients with pain due to malignancy is not recommended.

Respiratory Depression
At high doses or in mu-opioid receptor agonist sensitive patients, PALEXIA® SR may produce dose-related respiratory depression. Therefore, PALEXIA® SR should be administered with caution to patients with impaired respiratory functions. Alternative non-mu-opioid receptor agonist analgesics should be considered and PALEXIA® SR should be employed only under careful medical supervision at the lowest effective dose in such patients. If respiratory depression occurs, it should be treated as any mu-opioid receptor agonist-induced respiratory depression (see **OVERDOSAGE**).

Head Injury and Increased Intracranial Pressure
Like other drugs with mu-opioid receptor agonist activity, PALEXIA® SR should not be used in patients who may be particularly susceptible to the intracranial effects of carbon dioxide retention such as those with evidence of increased intracranial pressure, impaired consciousness, or coma. Analgesics with mu-opioid receptor agonist activity may obscure the clinical course of patients with head injury. PALEXIA® SR should be used with caution in patients with head injury and brain tumors.

Seizures
PALEXIA® SR has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. However, like other analgesics with mu-opioid receptor agonist activity

PALEXIA® SR should be prescribed with care in patients with a history of a seizure disorder or any condition that would put the patient at risk of seizures.

Renal Impairment
For patients with mild or moderate renal impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, therefore use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Hepatic Impairment
For patients with mild hepatic impairment, no dosage adjustment is recommended (see **DOSAGE AND ADMINISTRATION**).

A study of PALEXIA® SR in subjects with hepatic impairment showed higher serum concentrations than in those with normal hepatic function. PALEXIA® SR should be used with caution in patients with moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Use in Pancreatic/Biliary Tract Disease
Drugs with mu-opioid receptor agonist activity may cause spasm of the sphincter of Oddi. PALEXIA® SR should be used with caution in patients with biliary tract disease, including acute pancreatitis.

Effect on fertility
There were no apparent effects on the fertility of male rats at intravenous doses up to 12 mg/kg/day, although histopathology analyses were not conducted. In female rats, the numbers of corpora lutea and implantations were reduced, and pre- and post-implantation losses were increased, at intravenous tapentadol doses associated with maternal toxicity. The clinical relevance of these findings is unknown.

Use in pregnancy (Category C)
There are no adequate and well controlled studies of tapentadol in pregnant women. PALEXIA® SR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

The effect of tapentadol on labor and delivery in humans is unknown. PALEXIA® SR is not recommended for use in women during and immediately prior to labor and delivery. Due to the mu-opioid receptor agonist activity of tapentadol, neonates whose mothers have been taking tapentadol should be monitored for respiratory depression.

Tapentadol crosses the placenta in pregnant rats. Tapentadol was evaluated for teratogenic effects in rats and rabbits following intravenous and subcutaneous administration during organogenesis. Embryofetal toxicity such

as delays in skeletal maturation and cerebral ventricular dilation was observed in rats concomitant with maternal toxicity at subcutaneous doses of 10 mg/kg/day or greater (plasma AUC exposure less than maximum anticipated clinical exposure). Subcutaneous administration of tapentadol to rabbits revealed embryofetal toxicity at doses of 10-24 mg/kg/day (AUC exposure 1 to 2 fold the maximum anticipated human exposure), along with reduced fetal viability, skeletal delays and other variations, and multiple malformations including gastroschisis/thoracogastroschisis, amelia/phocomelia and cleft palate at 10-24 mg/kg/day, and ablepharia, encephalopathy and spina bifida at 24 mg/kg/day. There were no teratogenic effects observed in similar studies conducted in rats and rabbits via the intravenous route (up to 15 mg/kg/day) Embryofetal toxicity, including malformations, may be secondary to maternal toxicity in these species.

Use in lactation
There is limited information on the excretion of tapentadol in breast milk. Tapentadol is excreted into milk in lactating rats following oral dosing. Oral tapentadol administration to rats during lactation resulted in increased postnatal pup mortality, at doses lower than those associated with maternal toxicity (exposure (AUC) less than maximum anticipated clinical exposure). The potential relevance to humans is unknown. Physicochemical and available pharmacodynamic/toxicological data on tapentadol point to excretion in breast milk and risk to the suckling child cannot be excluded. PALEXIA® SR should not be used during breast feeding.

Paediatric use
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population.

Use in the elderly (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **DOSAGE AND ADMINISTRATION** and also **Pharmacokinetics**).

Carcinogenicity
Tapentadol was administered to rats (diet) and mice (oral gavage) for two years. A significant trend towards increased hepatocellular tumours (adenoma and carcinoma) was observed in mice at oral doses of 100 mg/kg/day or greater. A dose-related increased incidence of hepatocellular hypertrophy (but not tumours) was observed in rats at dietary doses of 125 mg/kg/day or greater. Exposures (plasma AUC) in both species were less than that at the maximum recommended clinical dose. These findings may derive from adaptive changes following hepatic enzyme induction. The potential clinical relevance is unknown.

Genotoxicity
Tapentadol did not induce gene mutations in bacteria, but was clastogenic at cytotoxic concentrations in an *in vitro* chromosomal aberration test with metabolic activation in Chinese hamster V79 cells in 1 of 2 assays. The one

positive result for tapentadol was not confirmed *in vivo* in rats, using the two endpoints of chromosomal aberration and unscheduled DNA synthesis at extrapolated exposures (AUC) similar to the maximum anticipated human exposure. The weight of evidence indicates that tapentadol presents no significant genotoxic potential at clinical doses.

Effects on Ability to Drive and Use Machines
Like drugs with mu-opioid receptor agonist activity, PALEXIA® SR may have major influence on the ability to drive and use machines, due to the fact that it may adversely affect central nervous system functions (see **ADVERSE EFFECTS**). This has to be expected especially at the beginning of treatment, at any change of dosage as well as in connection with alcohol or tranquilizers (see **Interactions with other medicines**). Patients should be cautioned as to whether driving or use of machines is permitted.

Interactions with other medicines
Tapentadol is mainly metabolised by glucuronidation, a system with a very high capacity which is not easily saturated even in disease. As therapeutic concentrations of drugs that are subject to glucuronidation are generally well below the concentrations needed for potential inhibition of glucuronidation, the risk of clinically relevant interaction between these drugs is generally low. The following substances have been included in a set of interaction studies without any clinically significant finding: paracetamol, acetylsalicylic acid, naproxen, probenecid, omeprazole and metoclopramide (see **Pharmacokinetics**).

Only a small amount of tapentadol is metabolised by oxidative pathways (see **Pharmacokinetics**). Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity in vitro but at concentrations 180- to 1400-fold higher than maximum concentrations in humans. *In vitro* induction experiments in human hepatocytes showed that CYP1A2, CYP2C9, and CYP3A4 activities were not markedly induced. Thus *in vitro* studies did not reveal any potential of tapentadol to either inhibit or induce cytochrome P450 enzymes. Tapentadol is an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo*. The potential clinical relevance of this finding is unknown.Tapentadol was shown to be a weak inhibitor of human CYP2D6 activity *in vitro*, and an inducer of CYP1A, CYP2B and CYP2E in rats *in vivo.* The potential clinical relevance of this finding is unknown.

CNS depressants
Patients receiving other mu-opioid receptor agonist analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics or other CNS depressants (including alcohol and illicit drugs) concomitantly with PALEXIA® SR may exhibit an additive CNS depression. Interactive effects resulting in respiratory depression, hypotension, profound sedation, or coma may result if these drugs are taken in combination with PALEXIA® SR. When such combined therapy is contemplated, the reduction of dose of one or both agents should be considered.

Monoamine oxidase (MAO) inhibitors
PALEXIA® SR is contraindicated in patients who are receiving monoamine oxidase (MAO) inhibitors or who have taken them within the last 14 days due

to potential additive effects on noradrenaline levels which may result in adverse cardiovascular events (see **CONTRAINDICATIONS**).

Serotonin Syndrome
PALEXIA® IR is a centrally acting synthetic analgesic combining mu-agonist and noradrenaline re-uptake inhibition activity

A causal relationship between tapentadol and serotonin syndrome has not been established, however there is a theoretical risk of serotonin syndrome when tapentadol is used in combination with serotonergic drugs such as selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), SNRIs, tricyclic antidepressants (TCAs), MAOIs and triptans. Signs of serotonin syndrome may include confusion, agitation, fever, sweating, ataxia, hyperreflexia, myoclonus and diarrhoea. Withdrawal of the serotonergic drugs usually brings about a rapid improvement. Treatment depends on the nature and severity of the symptoms.

ADVERSE EFFECTS

Treatment emergent adverse events in the double-blind Phase 2/3 studies
In the pooled all Phase 2/3 PALEXIA® SR studies, the percentage of subjects administered PALEXIA® SR with at least 1 TEAE was 71.7%. This was higher when compared with the placebo group (54.5%) and lower than the oxycodone CR group (86.3%) (Table 3).

Compared with oxycodone CR there was better gastrointestinal tolerability with PALEXIA® SR. The incidence of nausea (19.5%), vomiting (7.4%) and constipation (13.6%) was lower with PALEXIA® SR than oxycodone CR (36.1%, 19.8% and 31.5%, respectively) (Table 3). PALEXIA® SR also had a beneficial safety profile over that of oxycodone CR for somnolence (11.3% vs 16.3%), dizziness (13.7% vs 19.8%), and pruritus (4.9% vs 12.4%). This suggests that the adverse event profile for PALEXIA® SR is similar to those of other opioid agonists, while at the same time exhibiting a lower incidence of a number of adverse events.
The majority of subjects in all treatment groups in the pooled all Phase 2/3 PALEXIA® SR studies experienced TEAEs that were mild to moderate in intensity. Less subjects in the all PALEXIA® SR group reported severe adverse events compared to those in the oxycodone CR group.

Table 5. TEAEs in at least 5% of subjects in any pooled treatment group (all studies) (PALEXIA® SR formulation Phase 2/3 studies integrated summary of safety: safety analysis set)[a]

System organ class/preferred term	Placebo (n=1498) n (%)	All PALEXIA® SR (n=3613) n (%)	All oxycodone CR (n=1472) n (%)
Number (n (%)) of subjects with TEAE	817 (54.5)	2589 (71.7)	1271 (86.3)
Gastrointestinal disorders	**370 (24.7)**	**1464 (40.5)**	**952 (64.7)**
Nausea	128 (8.5)	704 (19.5)	531 (36.1)
Constipation	85 (5.7)	493 (13.6)	464 (31.5)
Vomiting	44 (2.9)	269 (7.4)	292 (19.8)

Dry mouth	26 (1.7)	217 (6.0)	66 (4.5)
Diarrhoea	78 (5.2)	199 (5.5)	78 (5.3)
Nervous system disorders	**288 (19.2)**	**1308 (36.2)**	**662 (45.0)**
Dizziness	77 (5.1)	495 (13.7)	291 (19.8)
Headache	170 (11.3)	427 (11.8)	174 (11.8)
Somnolence	44 (2.9)	408 (11.3)	240 (16.3)
General disorders and administration site conditions	**138 (9.2)**	**583 (16.1)**	**290 (19.7)**
Fatigue	48 (3.2)	253 (7.0)	139 (9.4)
Skin and subcutaneous tissue disorders	**80 (5.3)**	**481 (13.3)**	**332 (22.6)**
Pruritus	20 (1.3)	176 (4.9)	183 (12.4)
Hyperhidrosis	16 (1.1)	160 (4.4)	75 (5.1)
Musculoskeletal and connective tissue disorders	**167 (11.1)**	**395 (10.9)**	**132 (9.0)**
Myalgia	9 (0.6)	42 (1.2)	10 (0.7)
Bone pain	2 (0.1)	16 (0.4)	1 (0.1)
Ear and labyrinth disorders	**23 (1.5)**	**109 (3.0)**	**49 (3.3)**
Vertigo	12 (0.8)	68 (1.9)	31 (2.1)

a: This summary of clinical safety includes clinical studies that vary in design (controlled dose adjustment, fixed dose, and open label) and subject population (lower back pain, pain due to OA, and pain due to peripheral neuropathy). Studies included: KF5503/09, KF5503/10, KF5503/19, KF5503/20, KF5503/24, KF5503/11, KF5503/12, KF5503/23, KF5503/36
MedDRA version 11.0 was used for coding.
TEAE = treatment emergent adverse events; MedDRA = Medical Dictionary for Regulatory Activities; N, n = number of subjects (total, per category).

The following adverse drug reactions (ADRs) were reported from clinical trials performed with PALEXIA® SR:

Very Common (≥ 1/10)

Nervous system disorders:	Dizziness, Somnolence, Headache
Gastrointestinal disorders:	Nausea, Constipation

Common (≥1/100 to <1/10)

Metabolism and nutrition disorders:	Decreased appetite
Psychiatric disorders:	Anxiety, Depressed mood, Sleep disorder, Nervousness, Restlessness
Nervous system disorders:	Disturbance in attention, Tremor, Muscle contractions involuntary
Vascular disorders:	Flushing
Respiratory, thoracic and mediastinal disorders:	Dyspnoea
Gastrointestinal disorders:	Vomiting, Diarrhoea, Dyspepsia
Skin and subcutaneous tissue disorders:	Pruritus, Hyperhidrosis, Rash

General disorders and administration site conditions:	Asthenia, Fatigue, Feeling of body temperature change, Mucosal dryness, Oedema

Uncommon (≥1/1,000 to <1/100)

Immune system disorders:	Drug hypersensitivity
Metabolism and nutrition disorders:	Weight decreased
Psychiatric disorders:	Disorientation, Confusional state, Agitation, Perception disturbances, Abnormal dreams, Euphoric mood
Nervous system disorders:	Depressed level of consciousness, Memory impairment, Mental impairment, Syncope, Sedation, Balance disorder, Dysarthria, Hypoaesthesia, Paraesthesia
Eye disorders:	Visual disturbance
Cardiac disorders:	Heart rate increased, Heart rate decreased
Vascular disorders:	Blood pressure decreased
Gastrointestinal disorders:	Abdominal discomfort
Skin and subcutaneous tissue disorders:	Urticaria
Renal and urinary disorders:	Urinary hesitation, Pollakiuria
Reproductive system and breast disorders:	Sexual dysfunction
General disorders and administration site conditions:	Drug withdrawal syndrome, Feeling abnormal, Irritability

Rare (≥1/10,000 to <1/1,000)

Psychiatric disorders:	Drug dependence, Thinking abnormal
Nervous system disorders:	Convulsion, Presyncope, Coordination abnormal
Respiratory, thoracic and mediastinal disorders:	Respiratory depression
Gastrointestinal disorders:	Impaired gastric emptying
General disorders and administration site conditions:	Feeling drunk, Feeling of relaxation

Treatment emergent adverse events with prolonged treatment

A total of 894 subjects with moderate to severe pain from low back pain or osteoarthritis of the knee or hip were treated with a flexible dosing regimen of PALEXIA® SR (100 mg to 250 mg twice daily) in a 1 year safety study (KF5503/24). The overall TEAE profile for prolonged treatment did not differ from the profile observed in short-term treatment. The overall incidence of TEAEs was lower in the PALEXIA® SR group (85.7%) compared to oxycodone CR (20 mg to 50 mg) (90.6%).

The most common TEAEs (incidence >10% in either treatment group) were constipation, nausea, vomiting, somnolence, dizziness, headache, fatigue and pruritus. Subjects administered PALEXIA® SR had a lower incidence of constipation, nausea, vomiting, dizziness, fatigue and pruritus compared to oxycodone CR (22.6% vs 38.6%, 18.1% vs 33.2%, 7.0% vs 13.5%, 14.8% vs 19.3%, 9.7% vs 10.3%, and 5.4% vs 10.3% respectively).

Post marketing experience
There have been no adverse reactions identified from spontaneous reports so far for PALEXIA® SR.

DOSAGE AND ADMINISTRATION

As with many centrally acting analgesic medications, the dosing regimen should be individualized according to the severity of pain being treated, the previous treatment experience and the ability to monitor the patient.

PALEXIA® SR should be taken twice daily, approximately every 12 hours. PALEXIA® SR may be administered with or without food.

Initiation of therapy
a) Initiation of therapy in patients currently not taking opioid analgesics:
Patients should start treatment with single doses of 50 mg tapentadol administered twice daily.

b) Initiation of therapy in patients currently taking opioid analgesics:
When switching from opioids to PALEXIA® SR and choosing the initial dose, the nature of the previous medication, administration and the mean daily dose should be taken into account.

Titration and maintenance
After initiation of therapy the dose should be titrated individually to a level that provides adequate analgesia and minimizes side effects under the close supervision of the prescribing physician.

Experience from clinical trials has shown that a titration regimen in increments of 50 mg tapentadol twice daily every 3 days was appropriate to achieve adequate pain control in most of the patients.

Total daily doses of PALEXIA® SR tablets greater than 500 mg tapentadol have not been studied and are therefore not recommended.

Discontinuation of treatment
Tapering of therapy is not required, but patients should be cautioned about the possibility of experiencing withdrawal symptoms (see **ADVERSE EFFECTS**).

Renal Impairment
No dosage adjustment is recommended in patients with mild or moderate renal impairment (see **Pharmacokinetics**).

PALEXIA® SR has not been studied in controlled efficacy studies in patients with severe renal impairment, and its use is not recommended. A pharmacokinetic study showed an increased level of an inactive metabolite in subjects with renal impairment (see **PRECAUTIONS** and also **Pharmacokinetics**).

Hepatic Impairment
No dosage adjustment is recommended in patients with mild hepatic impairment (see **Pharmacokinetics**).

PALEXIA® SR should be used with caution in patients with moderate hepatic impairment. Treatment in these patients should be initiated at 50 mg tapentadol and not be administered more frequently than once every 24 hours. Further treatment should reflect maintenance of analgesia with acceptable tolerability (see **PRECAUTIONS** and also **Pharmacokinetics**).

PALEXIA® SR has not been studied in patients with severe hepatic impairment and, therefore, use in this population is not recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Elderly Patients (persons aged 65 years and over)
In general, recommended dosing for elderly patients with normal renal and hepatic function is the same as for younger adult patients with normal renal and hepatic function. Because elderly patients are more likely to have decreased renal and hepatic function, care should be taken in dose selection as recommended (see **PRECAUTIONS** and also **Pharmacokinetics**).

Paediatric Patients
PALEXIA® SR is not recommended for use in children below 18 years of age due to insufficient data on safety and efficacy in this population (see **PRECAUTIONS**).

OVERDOSAGE

Experience with PALEXIA® SR overdose is very limited. Preclinical data suggest that symptoms similar to those of other centrally acting analgesics with mu-opioid receptor agonist activity are to be expected upon intoxication with tapentadol. In the clinical setting, these symptoms may include miosis, vomiting, cardiovascular collapse, consciousness disorders up to coma, convulsions and respiratory depression up to respiratory arrest.

Management of overdose should be focused on treating symptoms of mu-opioid receptor agonism. Primary attention should be given to re-establishment of a patent airway and institution of assisted or controlled ventilation when overdose of PALEXIA® SR is suspected.

Pure opioid antagonists such as naloxone, are specific antidotes to respiratory depression resulting from opioid overdose. Respiratory depression following an overdose may outlast the duration of action of the opioid antagonist. Administration of an opioid antagonist is not a substitute

for continuous monitoring of airway, breathing, and circulation following an opioid overdose. If the response to opioid antagonists is suboptimal or only brief in nature, an additional antagonist should be administered as directed by the manufacturer of the product.

Gastrointestinal decontamination may be considered in order to eliminate unabsorbed drug. Gastrointestinal decontamination with activated charcoal or by gastric lavage may be considered within 2 hours after intake. Before attempting gastrointestinal decontamination, care should be taken to secure the airway.

Contact the Poisons Information Centre on 131 126 for further advice on overdosage management.

PRESENTATION AND STORAGE CONDITIONS

- PALEXIA® SR 50 mg sustained release tablets: white film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H1" engraving on the other side.
- PALEXIA® SR 100 mg sustained release tablets: pale yellow film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H2" engraving on the other side.
- PALEXIA® SR 150 mg sustained release tablets: pale pink film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H3" engraving on the other side.
- PALEXIA® SR 200 mg sustained release tablets: pale orange film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H4" engraving on the other side.
- PALEXIA® SR 250 mg sustained release tablets: brownish red film-coated oblong shaped tablets with Grünenthal logo engraving on one side and "H5" engraving on the other side.

Blister Packs of 7, 10, 14, 20, 28, 30, 40, 50, 56, 60, 90, 100 tablets.

Not all pack sizes may be available.

PALEXIA® SR 50 mg, 100 mg, 150 mg, 200 mg and 250 mg sustained release tablets have a shelf-life of 36 months when stored below 30°C. Protect from light.

NAME AND ADDRESS OF SPONSOR

CSL Limited ABN 99 051 588 348
45 Poplar Road
Parkville 3052
Australia

POISON SCHEDULE OF THE MEDICINE

Controlled Drug, S8

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Therapeutic Goods Administration

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