Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Buprenorphine/Naloxone

Proprietary Product Name: Suboxone Sublingual Film

Sponsor: Reckitt Benckiser (Australia) Pty Ltd

March 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.
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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 Dose Form
Decision:	Approved
Date of Initial Decision:	18 August 2010
Date of Final Decision:	7 December 2010

Active ingredient(s):	Buprenorphine, naloxone
Product Name(s):	Suboxone Sublingual Film
Sponsor's Name and Address:	Reckitt Benckiser (Australia) Pty Ltd 44 Wharf Road West Ryde 2114
Dose form(s):	Soluble film
Strength(s):	2/0.5 mg and 8/2 mg
Container(s):	Sachets (one soluble film per sachet)
Pack size(s):	28 sachets per carton
Approved Therapeutic use:	Treatment of opiate dependence within a framework of medical, social and psychological treatment.
Route(s) of administration:	Sublingual
Dosage:	Maximum daily dose: 32 mg buprenorphine
ARTG Numbers:	163443, 163444

Product Background

Suboxone contains buprenorphine, a mu opioid receptor partial agonist and kappa opioid receptor antagonist; and naloxone, an antagonist at mu opioid receptors. Because of its almost complete first-pass metabolism, naloxone given orally or sublingually has no detectable pharmacological activity. However, when administered intravenously to opioid-dependent people, the presence of naloxone in Suboxone produces marked opioid antagonist effects and opioid withdrawal, thereby deterring intravenous abuse.

Suboxone 2/0.5 mg and 8/2 mg sublingual tablets were registered in July 2005. That product had initially been rejected for registration following a recommendation from the Australian Drug Evaluation Committee (ADEC) at its 237th meeting in December 2004. The ADEC considered that the sponsor had not made a persuasive case for the central claim that intravenous misuse would be reduced with Suboxone. The ADEC was also concerned about the ethics of supply of a product intended to induce withdrawal symptoms, with the possibility of fatalities. The Delegate rejected the submission but Suboxone was registered after an appeal under section 60. In the current application, the sponsor is now seeking to register the same dosage strengths, for the same indication as the sublingual tablets in a soluble film formulation.

The sponsor has stated that the soluble film formulation is intended to have similar efficacy to the current sublingual tablet and to be associated with the following further safety and compliance features:

- A reduced risk of diversion due to the proposed formulation adhering rapidly to the buccal mucosa and forming a gel which is difficult to remove;
- Faster dissolution in the sublingual cavity which is expected to improve compliance and retention in treatment;
- Improved child-resistant packaging (in individual child-resistant laminate sachets).

The proposed indication is:

Treatment of opiate dependence within a framework of medical, social and psychological treatment.

Doses were proposed to be made up of 2 mg and 8 mg soluble films to be taken all at the same time or in two divided portions, the second portion to be taken directly after the first portion has dissolved. The soluble films are to be placed under the tongue in a manner to minimise overlapping. Suboxone Sublingual Film hydrates to a gel which must be kept under the tongue until completely dissolved. This usually occurs within 4 – 8 minutes. Suboxone Sublingual Film should not be chewed, swallowed or moved from placement.

For patients taking street heroin or other short acting opiates, the first dose should start at least 6 hours after the patient has last used opiates or when early signs of withdrawal appear. The recommended starting dose is 6 – 8 mg on Day 1. Prescribers should aim to achieve 12 – 16 mg daily by Day 3.

For patients on methadone, the methadone dose should be reduced to a maximum of 30 mg daily. The first dose of Suboxone Sublingual Film should be taken at least 24 hours after the patient has last used methadone.

The maximum dose not to exceed 32 mg daily with dose adjusted according to reassessments of the clinical and psychological status of the patient.

Regulatory Status

A registration application for Suboxone Sublingual Film was made to the US FDA in October 2008. Registration was approved in August 2010.

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)

Buprenorphine hydrochloride and naloxone hydrochloride dihydrate are identical to the substances used in the registered sublingual tablets and are obtained from the same sources. One additional source of naloxone hydrochloride dihydrate is also proposed, and satisfactory data have been provided.

Drug Product

Introduction

Suboxone sublingual tablets, containing 2/0.5 mg and 8/2 mg buprenorphine/naloxone as the respective hydrochloride salts, are currently registered in Australia by Reckitt Benckiser.
The present application seeks to register Suboxone Sublingual Film in the same strengths as the sublingual tablets, for the same indication. Although the soluble films were developed for both sublingual and buccal administration, the present application seeks approval for the sublingual route only. The maximum daily dose is 32 mg of buprenorphine.

Suboxone Sublingual Film is placed under the tongue, where it adheres rapidly, forming a gel that is difficult to remove from the mouth. The major advantages claimed for the soluble film over the sublingual tablet are:

- faster disintegration of the soluble film once placed under the tongue; and
- the risk of diversion for illicit use is reduced because of the difficulty of removing the soluble film from the mouth once it is in place.

Naloxone is not an active ingredient as such. It is present in the sublingual tablets and soluble films to deter abuse of the products by injection. Naloxone has very low bioavailability when given orally or sublingually but when injected it produces marked opiate antagonist effects and withdrawal symptoms in opiate dependent patients.

Chemistry, Manufacturing and Controls

Suboxone Sublingual Film is a paper-thin, flexible, orange-coloured, rectangular strip, imprinted with white ink. It is composed primarily of polyethylene oxide with hypromellose and flavouring, sweetening, colouring and buffering agents. The 2/0.5 and 8/2 soluble films are identical in length and width (22.0 ´ 12.8 mm) but the 8/2 soluble film is 25% heavier (50 mg compared to 40 mg). They are distinguishable by the white printing, which includes the product strength. The two strengths do not have directly scaled formulations.

Each soluble film is individually enclosed in a heat-sealed pouch, consisting, from outside to inside, of Polyethylene terephthalate (PET), low density polyethylene (LDPE), aluminium foil and ethylene acrylic acid. Twenty-eight soluble films are packaged in a cardboard carton.

The soluble films are manufactured as follows: a suspension of buprenorphine hydrochloride in an aqueous solution of the excipients and naloxone hydrochloride dihydrate is coated onto a polyester sheet then oven-dried. The resulting soluble film is printed with white ink, then separated from the polyester substrate, cut into the required soluble films and sealed within sachets.

Naloxone is prone to oxidative degradation. In the sublingual tablets, degradation has been minimised by the sponsor, however, the same stabilization approach is not possible for the soluble films. As a consequence, a lower expiry limit for naloxone in the soluble films has been set. The applicant claims that this level of naloxone is sufficient to produce the desired opiate antagonist effects if injected. In addition, the limits proposed for naloxone degradants have been set at much higher levels than in the Australian sublingual tablet specification but are aligned with or more stringent than corresponding limits applied in the USA. In Suboxone Sublingual Film, naloxone degrades rapidly to a large number of and high levels of impurities, whereas naloxone is relatively stable in the sublingual tablet. The sponsor has proposed stricter limits than those of the sublingual tablets. The Medicines Toxicology Evaluation Section of the TGA has advised that the proposed impurity limits have been adequately qualified.[1]

[1] Qualification is the process of acquiring and evaluating data that establishes the biological safety of an

Biopharmaceutics

Five bioavailability studies were submitted. One was a dose proportionality study and the other four involved direct comparisons of various combinations of the soluble films proposed for registration with the corresponding strengths of sublingual tablets. The two most relevant studies were evaluated in detail:

Study 20-250-SA compared single doses of the 2/0.5 mg soluble film with the 2/0.5 mg sublingual tablet. It showed that the bioavailability of buprenorphine from the soluble films is significantly greater than from the sublingual tablets: the area under the plasma concentration time curve (AUC) and the maximal plasma concentration (C_{max}) are increased by 16% (not significant) and 22%, respectively. The bioavailability of naloxone from the soluble films is also significantly greater than from the sublingual tablets: AUC and C_{max} are increased by 2% and 4%, respectively. There is no significant difference between the sublingual tablets and soluble films with regard to plasma levels of naloxone or the essentially inactive, major metabolite of buprenorphine, norbuprenorphine. There is no significant difference between the sublingual tablets and soluble films with regard to plasma levels of naloxone, or of the essentially inactive, major metabolite of buprenorphine, norbuprenorphine.

Study 20-273-SA compared single doses of the 8/2 mg soluble film with the 8/2 mg sublingual tablet. It showed that the bioavailability of buprenorphine from the soluble films is significantly greater than from the sublingual tablets: AUC and C_{max} are increased by 20% and 28%, respectively. The bioavailability of naloxone from the soluble films is also significantly greater than from the sublingual tablets: AUC and C_{max} are increased by 30% and 41%, respectively. There is no significant difference with regard to plasma levels of norbuprenorphine.

The increased bioavailability of buprenorphine and naloxone in the soluble films compared to the sublingual tablets is a matter for clinical consideration.

Consideration by the PSC

This application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC) at its 130th meeting on 27 January 2010. The subcommittee was unable to recommend approval for registration due to the extreme instability of naloxone in the proposed formulation compared to the registered sublingual tablets. The PSC was concerned that compliant patients taking the soluble film would be exposed to unnecessary additional risks with no concomitant benefit as naloxone is present only as an abuse deterrent.

Since that recommendation was made, the limits for naloxone degradants have been tightened significantly. The Medicines Toxicology Evaluation Section has advised that all of the limits now proposed have been adequately qualified.

Quality Summary and Conclusions

There were no objections to registration with regard to chemistry, manufacturing and controls. Storage below 30°C was originally proposed for the soluble films, but a shelf life of 12 months below 25°C has been approved in order to limit the degradation of naloxone.

At this stage, Suboxone Sublingual Films were considered non-approvable because of the extreme instability of naloxone in this dosage form.

The claimed benefits of the soluble film need to be weighed carefully against its clear disadvantages and against the risk/benefit profile of the currently available sublingual tablet. Naloxone is extremely unstable in the soluble film formulation, degrading rapidly to a large

individual impurity or a given impurity profile at the level(s) specified.

number and high levels of impurities, whereas naloxone is relatively stable in the sublingual tablet. As naloxone is present only as an abuse deterrent, compliant patients taking the soluble film would be exposed to unnecessary additional risks with no concomitant benefit.

III. Nonclinical Findings

Introduction

The proposed release and expiry specifications for the Suboxone Sublingual Film are derived from the current US specifications for Suboxone sublingual tablets, which are less stringent than the corresponding Australian specifications for Suboxone sublingual tablets. The US tablets are packed in a high density polyethylene (HDPE) bottle with desiccant and the Australian tablets are packed in aluminium coldform blisters filled under a controlled atmosphere, giving a highly stable product with narrower assay limits than the US tablets. For Suboxone Sublingual Film, packing under those conditions is not possible and, based on the stability performance, the sponsor sought specifications aligned with the US specifications for Suboxone sublingual tablets.

Supporting nonclinical data

The sponsor has submitted qualification toxicology studies conducted on deliberately degraded Suboxone tablets: a 7-day dietary palatability study in rats, a 28-day dietary toxicity study in rats, and 3 genotoxicity studies (bacterial gene mutation assay, *in vitro* cytogenetics assay in human lymphocytes, rat bone marrow micronucleus test). All submitted studies have been provided to and evaluated by the TGA, as part of previous applications.

Qualification of impurities

Impurities not requiring qualification

Norbuprenorphine is the major human metabolite of buprenorphine and is thus qualified[2]. The other buprenorphine-related impurity is specified at the qualification threshold[3] and qualifying studies are not required.

Three naloxone-related impurities VIII, IX, X are also specified at the qualification threshold[4] and qualifying studies are not required.

Impurities requiring qualification

In the repeat dose toxicity studies and the micronucleus test (all in rats), the toxicological profile of the degraded Suboxone preparation did not differ markedly from that of Suboxone. In the 28-day repeat dose study in rats, the oral intakes (on a body surface area (BSA, mg/m^2) basis) of the 3 buprenorphine-related impurities (excluding norbuprenorphine and the other buprenorphine-related impurity) and the 7 naloxone-related impurities (excluding VIII, IX and X) were 2 - 6 fold those anticipated in humans receiving the maximal recommended clinical dose of Suboxone Sublingual Film, if the impurities were present at their proposed specification limits. In the rat micronucleus test, the corresponding single dose intakes of the 10 impurities were 18 - 62 fold the expected human daily intakes.

From a purely technical view, the sensitivity of the *in vivo* studies would have been unlikely to be sufficient to detect any toxicological potential from the presence of small amounts of impurities in the Suboxone preparation. However, the animal exposures in the *in vivo* studies

[2] ICH Q3B(R) *Note for Guidance on Impurities in New Drug Products (Revision)*, CPMP/ICH/2738/.
[3] ICH Q3B(R), CPMP/ICH/2738/99: for maximum daily dose of 10-100 mg, qualification threshold is the lower of 0.5% or 200 µg total daily intake; as 32 mg x 0.5% = 160 µg, the threshold is 0.5%.
[4] ICH Q3B(R), CPMP/ICH/2738/99: for maximum daily dose of < 10 mg, qualification threshold is the lower of 1.0% or 50 µg total daily intake; as 8 mg x 0.625% = 50 µg, the threshold is 50 µg.

were greater than those anticipated clinically at the maximum recommended human dose (MRHD) (assuming comparable bioavailability of these compounds in rats and humans), and this qualification approach of using the product or substance containing the degradants is also endorsed by the relevant European Union (EU) Guideline, adopted by the TGA**Error! Bookmark not defined.** The previous nonclinical evaluation report discussed possible interpretative problems created by using enriched Suboxone tablets to qualify buprenorphine-related impurity levels, since any potential toxicity of a buprenorphine-related impurity mediated through activation of opioid receptors may have been masked by the presence of relatively large amounts of the opioid antagonist naloxone. On the other hand, the presence of all potential impurities in the test article is an appropriate model for the clinical situation, and would test for any potential additive/interactive effects among the impurities. An improved study design could have additionally assessed impurity qualification by separate studies, using a degraded buprenorphine preparation in the absence of an opioid antagonist on one study, and a degraded naloxone preparation in another study.

There was no detectable genotoxic liability in *in vitro* gene mutation and clastogenicity assays, but the validity of these assays is questionable since the achieved exposure to the impurities was very low. This was also discussed in relation to buprenorphine-related impurities in the earlier nonclinical evaluation. The impurity concentrations achieved in the *in vitro* reverse mutation and clastogenicity assays were about 1.5 - 20 µg/plate and 50 - 700 ng/mL, respectively. There is no valid method for comparing these concentrations to those which may occur *in vivo* under clinical conditions.[5] However, the negative result in the *in vivo* micronucleus test can offset this limitation.

7,8-didehydronaloxone

The potential toxicity of 7,8-didehydronaloxone was discussed in an earlier evaluation. The specification limit for this synthesis impurity in Suboxone sublingual tablets is at the same limit proposed for the Suboxone Sublingual Film product. This is acceptable.

Total impurities

The individual impurities in Suboxone Sublingual Film can thus be considered as not requiring qualification or as adequately qualified by the supporting toxicological studies. A further limitation on the individual impurity levels is imposed by the proposed limits for total impurities since the presence of all impurities at their individual limits would exceed the total limits.

It was noted that the proposed limits on total impurities in Suboxone Sublingual Film considerably exceed those in Suboxone sublingual tablets. However, the total potential impurities proposed for the product is within the acceptable threshold.

In view of the qualification of individual impurities, the further limitations on individual impurities imposed by the limits on total impurities, and the existing precedent of the sought impurity limits for Suboxone Sublingual Film being almost identical to those accepted in the USA for Suboxone sublingual tablets, it is considered that the proposed limits for total impurities in Suboxone Sublingual Film are acceptable.

[5] The guideline document EMA/CHMP/SWP/431994/2007 Questions & Answers on the CHMP Guideline on the Limits of Genotoxic Impurities indicates that the estimated detection limit for mutagens in the Ames test is a minimum concentration of 250 µg/plate (based on Kenyon MO, Cheung JR, Kobo KL, Ku WW. An evaluation of the sensitivity of the Ames assay to discern low-level mutagenic impurities. Reg Tox & Pharm 2007; 48: 75-86), suggesting that the achieved concentrations would have been too low.

Nonclinical Summary and Conclusions

The proposed release and expiry specifications for the new formulation are derived from the current US specifications for Suboxone sublingual tablets and soluble films, which are less stringent than the Australian specifications for the sublingual tablets. There are five buprenorphine-related impurities and 10 naloxone-related impurities to be considered.

The sponsor has submitted qualification studies conducted on degraded Suboxone tablets (a 7-day dietary and a 28-day dietary study in rats, and three genotoxicity studies), all of which have been previously evaluated by the TGA.

Two buprenorphine-related impurities and three naloxone-related impurities do not require qualification. With the remaining impurities, the intakes anticipated clinically at the MRHD were exceeded in the 28-day repeat dose rat study (by 2 - 6x) and the rat micronucleus assay (by 18 - 62x). There were no toxicological signals from any of the nonclinical studies.

The naloxone synthesis impurity 7,8-didehydronaloxone, which has a structural alert for genotoxicity, is limited to the same specification currently approved for Suboxone sublingual tablets.

The proposed limits on total impurities exceed the corresponding limits for the sublingual tablets but match those approved for Suboxone sublingual tablets and soluble films in the USA.

In view of the qualification of the individual impurities, the further limitations imposed by the limits on total impurities, and the precedent of the sought limits for Suboxone Sublingual Film being almost identical to those accepted in the USA for Suboxone sublingual tablets, there were no nonclinical objections to the proposed impurity specification limits in Suboxone Sublingual Film.

The sponsor noted that the sought limits for Suboxone Sublingual Film were almost identical to those accepted in the USA for both sublingual tablets and soluble films and that there were no nonclinical objections to the proposed impurity specification limits in the original application for the registration of Suboxone Sublingual Film.

IV. Clinical Findings

Introduction

This is an application to register a new dose form of fixed combination buprenorphine hydrochloride /naloxone hydrochloride. The combination is *currently* registered as:

Suboxone 2/0.5 sublingual tablets containing buprenorphine hydrochloride 2.16 mg (equivalent to buprenorphine 2.0 mg) and naloxone hydrochloride 0.61 mg (equivalent to naloxone 0.5 mg); and

Suboxone 8/2 sublingual tablets containing buprenorphine hydrochloride 8.64 mg (equivalent to buprenorphine 8.0 mg) and naloxone hydrochloride 2.44 mg (equivalent to naloxone 2.0 mg).[6]

The present submission seeks to register the same dosage strengths, for the same indication as the tablets, in a soluble film formulation with the trade name Suboxone Sublingual Film.

[6] For convenience, buprenorphine hydrochloride/naloxone hydrochloride formulations will be hereafter be referred to in this AusPAR as buprenorphine/naloxone formulations, with the strength expressed as the buprenorphine/naloxone dose equivalent.

The clinical development program included a number of pilot studies that investigated the bioavailability of different soluble film formulations and strengths, administered via the sublingual and buccal routes. The pilot studies were followed by definitive studies using the market formulation and strengths via the proposed sublingual route. Six of the seven of these studies were open-label: four studies examined bioequivalence to US-registered Suboxone tablets; one study examined the dose-proportionality of Suboxone soluble films; one study (double-blind) compared induction with Suboxone soluble films and buprenorphine monotherapy soluble films in 38 opioid-dependent subjects; and one study examined safety over a 12-week period in 380 opioid-dependent patients who were transferred from US-registered Suboxone sublingual tablets to Suboxone soluble films administered by the sublingual or buccal routes.

In addition, the sponsor referred to five clinical pharmacology studies from an earlier submission in support of the claim that the proposed expiry limit for naloxone will provide a naloxone dose sufficient to deter intravenous injection of the dissolved soluble films.

Finally, in support of a proposed statement in the product information (PI) that the combination of buprenorphine and naloxone is less frequently abused than buprenorphine alone, the sponsor referred to an interim report of an Australian observational study by Degenhardt et al, provided as a 'publication manuscript' in an appendix to the Risk Management Plan.[7]

The seven fully-reported clinical studies in the current submission were conducted in accordance with Good Clinical Practice (GCP). The five studies from Submission 99/5441/1 that were referred to in the current submission, were conducted after approval by relevant institutional ethics committees. The manuscript describing the observational study by Degenhardt et al stated that ethics approval for the study was obtained from five relevant Human Research Ethics Committees, which were named in the report. There was no statement regarding compliance with other aspects of GCP.

Pharmacokinetics

Introduction

Five open-label, fasting, single dose, randomised crossover studies provided pharmacokinetic (PK) data for the Suboxone Soluble Film market formulation administered by the proposed sublingual route.

Four, three-way crossover, bioequivalence studies used the proposed soluble films administered by the sublingual and buccal routes, and US-registered Suboxone tablets administered sublingually.

- **Study 20-250-SA** compared 1× Suboxone 2/0.5 mg wafer sublingual, 1× Suboxone 2/0.5 mg wafer buccal, and 1× Suboxone 2/0.5 mg tablet sublingual.
- **Study 20-272-SA** compared 2× Suboxone 2/0.5 mg wafer sublingual, 2× Suboxone 2/0.5 mg wafer buccal, and 2× Suboxone 2/0.5 mg tablet sublingual (total dose of each treatment = 4/1 mg).
- **Study 20-273-SA** compared 1× Suboxone 8/2 mg wafer sublingual, 1× Suboxone 8/2 mg wafer buccal, and 1× Suboxone 8/2 mg tablet sublingual.
- **Study 1003395** 2× Suboxone 2/0.5 mg wafer + 1× Suboxone 8/2 mg wafer sublingual, 2× Suboxone 2/0.5 mg wafer + 1× Suboxone 8/2 mg wafer buccal, and 2× Suboxone

[7] Degenhardt et al. Injection of medications used in opioid substitution treatment in Australia after the introduction of a mixed partial agonist-antagonist formulation. Med J Aust 2009; 191: 161-5.

2/0.5 mg tablet + 1× Suboxone 8/2 mg table sublingual (total dose of each treatment = 12/3 mg).

A three-period, five-treatment, three-way crossover study (**20-291-SA**) compared different doses and strengths of the proposed wafer formulation administered sublingually: 1× 2/0.5 mg, 2× 2/0.5 mg, 1× 8/2 mg, 1× 12/3 mg and 1× 16/4 mg (the last two strengths are not proposed for registration in Australia).

Bioequivalence of the Australian-registered sublingual tablets to the US-registered sublingual tablets that were used in the original pivotal trials and the newly-submitted pharmacokinetic studies has been previously demonstrated.

All five pharmacokinetic studies were conducted at the same centre in Texas, USA, and enrolled opioid-naïve or non-opioid-dependent healthy volunteers. Standard inclusion and exclusion criteria, including screening drug tests, were applied. All subjects received naltrexone to block the opioid effects of the study treatments. Demographic information about the study subjects is summarised in Table 1.

Table 1: Pharmacokinetic studies of Suboxone Soluble Films: subject numbers and demographics.

Study ID	Enrolled			Completed
	N	*Sex*	*Age (y)*	N
20-250-SA	45	31M, 14F	18 - 43	39
20-272-SA	48	39M, 9F	19 - 45	37
20-273-SA	47	32M, 15F	18 - 45	44
1003395	48	29M, 19F	18 - 45	43
20-291-SA	60	37M, 23F	18 - 45	50

Fourteen additional pharmacokinetic studies were conducted during the development of Suboxone soluble films and summarised in the submission. Full reports of these studies were not submitted for evaluation, but the studies are not directly relevant, and the summaries did not raise any concerns. Safety information from these studies was included in the sponsor's *Integrated Safety Summary*.

Methods

Statistical analysis

In the four bioequivalence studies, C_{max}, the area under the plasma concentration time curve over a dosing interval (AUC_t) and the area under the plasma concentration time curve from time zero to infinity (AUC_∞) ratios (test: reference) were analysed using log-transformed data and standard statistical methods (analysis of variance [ANOVA] with terms for treatment, sequence, subject within sequence, and period). Ninety percent confidence intervals (CIs) for these ratios were constructed using the log-transformed data and a two-one sided t-tests procedure. In Study 20-291-SA, dose-proportionality was analysed using linear regression and a mixed effects model based on a power function (both using log-transformed data).

Absorption

In vivo disintegration

Each soluble film is 22 mm long, 12.8 mm wide, and sufficiently thin that the physical size of the product would not be expected to hinder sublingual administration, even when more than one soluble film is needed to achieve the required dose. Table 2 summarises comparative data on the time between administration and full disintegration of Suboxone Soluble Films and tablets, both administered sublingually. Similar disintegration times were seen in non-comparative data for Suboxone Soluble Films from Study 20-290-SA. Suboxone Soluble Films disintegrated more rapidly than Suboxone tablets at all doses investigated, but the difference was trivial at the 2/0.5 mg dose.

Table 2: Suboxone Soluble Films and tablets: *in vivo* disintegration time (min:sec) after sublingual administration.

	2/0.5 mg (1 Soluble film or tablet) Study 20-250-SA		**4/1 mg (2 Soluble films or tablets) Study 20-272-SA**		**8/2 mg (1 Soluble film or tablet) Study 20-273-SA**		**12/3 mg (3 Soluble films or tablets) Study 1003395**	
	Film	Tablet	Film	Tablet	Film	Tablet	Film	Tablet
N	43	43	45	42	45	45	44	47
Mean	6:08	7:09	5:26	7:33	6:36	12:23	5:39	8:59
Median	5:50	5:56	4:56	6:49	5:41	12:28	5:12	7:40
Min	1:20	2:08	1:59	2:39	0:50	3:41	2:12	2:03
Max	12:19	22:26	9:29	18:50	17:40	23:49	13:17	26:23
Reduction with soluble film								
- red. in mean	1:01		2:07		5:47		3:20	
- red. in median	0:06		1:53		6:47		2:28	

Bioavailability

Table 3 summarises the main bioavailability results from the five fully-reported PK studies.

Table 3: Bioavailability of buprenorphine, naloxone and norbuprenorphine in plasma after single sublingual doses of Suboxone Soluble Films in healthy volunteers.

Buprenorphine

Study	**Dose (mg)**	**N ***	**T_{max} (h)**	**C_{max} (ng/mL)**	**AUC_{last} (ng.h/mL)**	**AUC_{inf} (ng.h/mL)**
			Median (Range)	*Mean (CV%)*	*Mean (CV%)*	*Mean (CV%)*
20-250-SA	2/0.5	42 (40)	1.53 (0.75 - 4.0)	0.95 (40)	7.82 (35)	8.65 (33)
20-291-SA	2/0.5	31 (28)	1.50 (0.5 - 3.0)	1.07 (49)	7.18 (40)	8.43 (38)
20-272-SA	4/1	40 (39)	1.50 (0.5 - 3.0)	1.40 (49)	12.4 (48)	13.7 (43)
20-291-SA	4/1	31	1.50 (0.75 - 3.0)	1.66 (48)	13.4 (46)	14.6 (44)
20-273-SA	8/2	44	1.25 (0.75 - 4.0)	3.37 (53)	28.7 (45)	30.5 (43)
20-291-SA	8/2	31	1.25 (0.5 - 2.0)	3.55 (35)	28.7 (31)	30.7 (30)
1003395	12/3	44	1.50 (0.5 - 3.0)	4.05 (65)	38.5 (40)	40.5 (39)
20-291-SA	12/3	30	1.25 (0.75 - 3.0)	4.80 (45)	39.9 (37)	41.7 (36)
20-291-SA	16/4	31	1.25 (0.75 - 2.0)	6.05 (40)	50.3 (33)	53.4 (35)

Naloxone

Study	Dose (mg)	N	T_{max} (h)	C_{max} (pg/mL)	AUC_{last} (pg.h/mL)	AUC_{inf} (pg.h/mL)
			Median (Range)	*Mean (CV%)*	*Mean (CV%)*	*Mean (CV%)*
20-250-SA	2/0.5	42 (34)	0.75 (0.5 - 2.0)	54.1 (42)	129 (34)	138 (31)
20-291-SA	2/0.5	30	0.75 (0.25 - 1.0)	48.5 (53)	101 (41)	105 (39)
20-272-SA	4/1	40 (30)	0.75 (0.5 - 1.5)	69.8 (54)	187 (52)	204 (53)
20-291-SA	4/1	30	0.75 (0.25 - 1.0)	72.8 (46)	164 (41)	171 (41)
20-273-SA	8/2	44 (30)	0.75 (0.5 - 1.25)	193 (47)	459 (42)	481 (42)
20-291-SA	8/2	30	0.75 (0.5 - 1.5)	193 (44)	443 (30)	456 (30)
1003395	12/3	44	0.75 (0.5 - 1.02)	207 (69)	561 (58)	583 (56)
20-291-SA	12/3	30	0.72 (0.25 - 1.25)	286 (54)	648 (35)	665 (35)
20-291-SA	16/4	31	0.75 (0.5 - 1.25)	401 (56)	938 (39)	958 (39)

Norbuprenorphine

Study	Dose (mg)	N *	T_{max} (h)	C_{max} (ng/mL)	AUC_{last} (ng.h/mL)	AUC_{inf} (ng.h/mL)
			Median (Range)	*Mean (CV%)*	*Mean (CV%)*	*Mean (CV%)*
20-250-SA	2/0.5	42 (40)	1.38 0.5 - 8.0	0.31 (45)	11.8 37	14.5 (40)
20-291-SA	2/0.5	31	1.00 0.5 - 6.0	0.35 (46)	10.6 41	12.7 (41)
20-272-SA	4/1	40	1.25 0.5 - 48.0	0.62 (51)	20.9 44	23.7 (45)
20-291-SA	4/1	31	1.00 0.5 - 4.0	0.68 (40)	22.7 47	26.0 (48)
20-273-SA	8/2	44 (43)	1.25 0.75 - 12.0	1.40 (78)	48.3 68	54.9 (66)
20-291-SA	8/2	31	1.25 0.5 - 6.0	1.55 (43)	48.1 35	56.2 (40)
1003395	12/3	44	1.01 0.75 - 6.0	2.07 (55)	66.9 49	73.4 (50)
20-291-SA	12/3	29	1.25 0.75 - 6.0	2.19 (73)	69.5 55	77.4 (54)
20-291-SA	16/4	30	1.25 0.75 - 6.0	2.73 (60)	85.5 45	95.9 (46)

*N in parentheses shows the number of subjects in whom λ_z and thus AUC_∞ could be determined.

Bioequivalence

Studies 20-250-SA and 20-273 SA are regarded as the pivotal studies that assessed bioequivalence between a single unit of each of the proposed Suboxone Soluble Film strengths and the corresponding US-registered Suboxone tablets. These studies were evaluated in full in the quality evaluation (see *Section II*). Study 20-272-SA, which used two units of the 2/0.5 mg soluble film and tablet products in each treatment period, provides supporting bioequivalence data. Study 1003395 is not suitable for assessing bioequivalence because the study treatments combined two different product strengths.

The results from Studies 20-250-SA, 20-273 SA and 20-272-SA are summarised in Table 4. The highlighted comparisons are those where the 90% CI falls outside the standard 80-125% range for accepting bioequivalence.

Table 4: Bioavailability comparison of Suboxone soluble films and tablets.

SUBLINGUAL administration of Suboxone soluble film			**Ratio of geometric means (soluble film / tablet)**		
			C_{max}	**AUC_{last}**	**AUC_{inf}**
Study 20-250-SA	Buprenorphine	*estimate*	121.7	116.4	114.2
2/0.5 mg		*90% CI*	112.6 - 131.4	108.7 - 124.6	106.7 - 122.3
sublingual soluble film	Naloxone	*estimate*	104.0	101.8	107.3
vs		*90% CI*	95.8 - 112.9	94.8 - 109.4	97.0 - 118.7
2/0.5 mg	Norbuprenorphine	*estimate*	105.4	99.7	106.0
sublingual tablet		*90% CI*	99.3 - 111.9	93.3 - 106.5	97.9 - 114.7
Study 20-272-SA	Buprenorphine	*estimate*	104.6	108.6	104.6
2×2/0.5 mg		*90% CI*	94.6 - 115.7	99.9 - 118.2	94.6 - 113.4
sublingual soluble film	Naloxone	*estimate*	100.9	99.9	106.5
vs		*90% CI*	91.0 - 111.8	91.3 - 109.4	93.3 - 121.6
2×2/0.5 mg	Norbuprenorphine	*estimate*	104.5	115.7	106.1
sublingual tablet		*90% CI*	93.7 - 116.4	103.8 - 128.9	95.8 - 117.4
Study 20-273-SA	Buprenorphine	*estimate*	127.8	120.2	119.5
8/2 mg		*90% CI*	116.1 - 140.7	110.2 - 131.0	110.3 - 129.5
sublingual soluble film	Naloxone	*estimate*	141.0	130.0	121.2
vs		*90% CI*	126.9 - 156.9	119.5 - 141.5	108.4 - 135.4
8/2 mg	Norbuprenorphine	*estimate*	101.8	101.8	101.1
sublingual tablet		*90% CI*	93.3 - 111.1	94.6 - 109.5	93.9 - 108.8

Highlighted results are outside the standard 80-125% bioequivalence acceptance range.

Elimination

Table 5 summarises the terminal half-life of buprenorphine, naloxone and norbuprenorphine after administration of Suboxone soluble films.

Table 5: Terminal half-life (hours) of buprenorphine, naloxone and norbuprenorphine in plasma after administration of single doses of Suboxone soluble films.

Study	Dose (mg)	Buprenorphine		Naloxone		Norbuprenorphine	
		N	*Mean (CV%)*	*N*	*Mean (CV%)*	*N*	*Mean (CV%)*
20-250-SA	2/0.5	40	33.4 (39)	34	5.0 (110)	40	56.1 (56)
20-291-SA	2/0.5	28	22.7 (57)	30	2.0 (51)	31	44.2 (53)
20-272-SA	4/1	39	24.3 (45)	30	3.9 (86)	40	46.0 (87)
20-291-SA	4/1	31	25.7 (52)	30	2.2 (70)	31	42.5 (46)
20-273-SA	8/2	44	32.8 (30)	30	6.3 (50)	43	42.0 (43)
20-291-SA	8/2	31	36.6 (45)	30	5.2 (71)	31	55.7 (86)
1003395	12/3	44	40.0 (36)	44	7.7 (62)	44	39.3 (43)
20-291-SA	12/3	30	36.1 (29)	29	6.8 (65)	29	45.7 (38)
20-291-SA	16/4	31	40.4 (43)	31	7.0 (49)	30	44.8 (49)

Dose proportionality and time dependency

Dose proportionality

Dose proportionality after administration of Suboxone soluble films was primarily assessed in Study 20-291-SA. Bioavailability data from this study are summarised in Table 3. Dose proportionality was analysed using two methods: linear regression, and a mixed-effects model based on a power function of the form $\ln(PK) = \ln(\beta_0) + \beta_1 \cdot \ln(Dose) + \varepsilon$, where PK is the pharmacokinetic parameter tested, $\ln(\beta_0)$ is the y-intercept, β_1 is the slope, and ε is an error term. Linear regression gave small negative slopes in the regression lines for buprenorphine C_{max} and AUC, indicating a slightly less than dose-proportional increase in exposure. However, in the mixed effects model, the β1 estimates and associated 90% CIs for buprenorphine indicated dose-proportionality. Naloxone exposure was dose-proportional in both models.

Time dependency

The pharmacokinetics of the proposed Suboxone soluble films were only assessed after single doses. No multiple dose pharmacokinetic studies were conducted, and are not normally expected for an immediate-release generic product. All doses were administered in the morning and potential diurnal effects on pharmacokinetics were not assessed.

Intra- and inter-individual variability

As evidenced by the coefficient variations (CVs), the variability of buprenorphine, naloxone and norbuprenorphine pharmacokinetics was high after administration of both the soluble film and tablet formulations. This is consistent with pharmacokinetic data from previous submissions. The studies did not include replicate dosing, and thus were unable to separate intra-subject variability from inter-subject variability.

Pharmacokinetic interactions with other medicinal products or substances

No new clinical data regarding pharmacokinetic interactions was provided in the submission. There was a discussion of the expected interaction between buprenorphine and cytochrome P450 (CYP) 3A4 inhibitors and inducers, noting that buprenorphine is metabolised primarily by CYP3A4. The Suboxone tablet PI contains suitable statements regarding these interactions and these have been duplicated in the draft PI for Suboxone Sublingual Film.

Exposure relevant for safety evaluation

The increased buprenorphine and naloxone AUCs that were seen after a single dose of the 8/2 mg soluble films would be expected to translate into correspondingly higher exposure to buprenorphine and naloxone during chronic administration. In the case of the 2/0.5 mg soluble film, the AUCs of buprenorphine and naloxone did not differ between the soluble film and tablet, and a difference during chronic administration is not expected. The C_{max} of buprenorphine was 22% higher after a single dose of the soluble film, compared to the tablet. At steady state, the percentage difference in C_{max} is expected to be less.

Evaluator's overall conclusions on pharmacokinetics

The 2/0.5 mg sublingual soluble film was bioequivalent to the 2/0.5 mg sublingual tablet in most respects, with the notable exception that the C_{max} of buprenorphine was 22% higher after administration of the soluble film than after the tablet in Study 20-250-SA (but not in Study 20-272-SA). The percentage difference in buprenorphine C_{max} would be less at steady state.

The 8/2 mg sublingual soluble film was more bioavailable than the corresponding sublingual tablet, with higher C_{max}, the area under the plasma concentration time curve from time zero to the last measurable time point (AUC_{last}) and AUC_{∞} of buprenorphine and naloxone. The increased bioavailability of naloxone would be most apparent when the soluble films are fresh and would gradually be offset by the reduction in naloxone content of the soluble films that is seen during storage.

The sponsor submitted a population PK analysis, based on data from the five main PK studies. It concluded that the higher naloxone bioavailability from the 8/2 mg soluble films is unlikely to precipitate withdrawal in patients taking the product in the recommended dose range:

- The *ratio* of naloxone to buprenorphine peak and mean concentrations during simulated chronic use of Suboxone soluble films was similar to or smaller than during simulated chronic use of Suboxone tablets, at doses up to 16/4 mg (the maximum assessed). This finding would also be expected to apply at higher Suboxone doses, as may be used in clinical practice in some individuals.
- The simulated naloxone C_{max} during chronic administration of Suboxone 16/4 mg was compared to the simulated C_{max} associated with administration of 1 mg of naloxone intramuscularly, a dose that had been previously shown not to precipitate withdrawal in opioid-dependent subjects treated with buprenorphine.[8] The estimated mean naloxone C_{max} after administration of 1 mg of naloxone intramuscularly was 1.81 ng/mL. In comparison, the highest estimated naloxone C_{max} during chronic administration of Suboxone 16/4 mg was 0.96 ng/mL in one subject. The maximum

[8] Eissenberg T, Greenwald MK, Johnson RE, Liebson IA, Bigelow GE, Stitzer ML. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. J Pharmacol Exp Ther 1996; 276: 449.

recommended dose in the Suboxone PI is 32/8 mg, and by inference, the peak naloxone concentration at this dose would be about 2 ng/mL. This is approximately the same as the peak concentration after a 1 mg intramuscular dose (which did not produce withdrawal) and about 40% of the peak concentration of 5.4 ng/mL, assuming linear kinetics, expected after a 3 mg intramuscular dose (which did produce withdrawal).

Pharmacodynamics

Introduction

Naloxone is included in Suboxone tablets and the proposed soluble films in an effort to reduce the diversion and intravenous injection of these products. A notable feature of the soluble film formulation is the more rapid degradation of the naloxone component during storage, compared to the tablets. Because of this, the sponsor has proposed a different expiry limit for naloxone. The sponsor has argued that the proposed limit of the labelled content of naloxone is still sufficient to deter intravenous injection of the soluble films, based on data from five previously-submitted studies.

Mechanism of action

No new clinical data were provided in the present submission. As documented in the PI for Suboxone tablets, buprenorphine is a mu opioid receptor partial agonist and a kappa opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the mu receptors in the brain which reduces craving for opiates and opiate withdrawal symptoms. Naloxone is an antagonist at mu opioid receptors. Because of almost complete first-pass metabolism, orally administered naloxone has no detectable pharmacological activity. When administered intravenously to opiate-dependent persons, the presence of naloxone in Suboxone produces acute withdrawal symptoms, thereby deterring intravenous abuse. During sublingual administration, first-pass metabolism is partly avoided and systemic naloxone concentrations are higher than after oral dosing but lower than after intravenous administration.

Relationship between plasma concentration and effect

The sponsor referred to five previously-submitted clinical pharmacology studies in support of the claim that the low proposed expiry limit for naloxone will nevertheless be sufficient to deter intravenous injection of the soluble films.

Two factors are potentially relevant to this issue, namely the amount of naloxone in the product at expiry and the ratio of buprenorphine to naloxone at expiry.

- **Study CR95/001** investigated the bioavailability of Suboxone tablets, administered sublingually, at doses of 4/1 to 16/4 mg, in 7 subjects who had used opiates in the past but were not opiate-dependent according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria. No withdrawal effects were seen. The study did not involve intravenous administration of naloxone and does not address the matter under consideration.
- **Study CR92/111** involved the administration of sublingual buprenorphine solution at a dose of 4 mg then 8 mg daily to opioid-dependent subjects until Day 8. This was followed by "challenges" on Days 9, 10 and 11, in which subjects received, in random order, single doses of buprenorphine 8 mg + placebo, buprenorphine 8 mg + naloxone 4 mg and buprenorphine 8 mg + naloxone 8 mg, each given as a sublingual solution. On Day 12, subjects received a single intravenous dose of buprenorphine 8 mg + naloxone 4 mg. Withdrawal symptoms were assessed using a subject-rated 21-item questionnaire, a subject-rated visual analogue scale (VAS), and an observer-rated

VAS. The investigators found no significant difference between the sublingual treatments and the intravenous challenge for any of the withdrawal measures. In summary, this study does not support the sponsor's claim. On the contrary, it indicates that subjects who regularly take Suboxone will not experience significant withdrawal if they inject their usual dose (suggesting that the presence of naloxone in the product is not a deterrent to patients injecting their own medication). The study provides no information as to whether the naloxone content of Suboxone will produce withdrawal if injected by users who are dependent on other opioids.

- **Study CR93/005** enrolled 13 subjects who used heroin at least once daily and were opiate-dependent according to the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R) criteria. The subjects underwent an initial screening in which they were given a single intravenous dose of naloxone 0.4 mg. Three subjects were excluded from further participation because they had no withdrawal symptoms (VAS rating 0). Five subjects were excluded from further participation in the study because their withdrawal symptoms were too severe (VAS ratings of 60-100). Five subjects continued in the study and received, at intervals of ≥ 5 days, single intravenous doses of buprenorphine 0.4 mg + naloxone 0.4 mg, buprenorphine 0.4 mg, naloxone 0.4 mg, and placebo. In these subjects, the agonist and antagonist effects of buprenorphine 0.4 mg were only minimally different to placebo. Naloxone 0.4 mg produced typical withdrawal effects. The 1:1 combination of buprenorphine 0.4 mg + naloxone 0.4 mg acted predominantly as an antagonist, and was perceived as dysphoric and unpleasant by all 5 subjects. Overall, this study provides only partial support for the sponsor's claim. Naloxone 0.4 mg (less than the 0.425 mg remaining in a Suboxone 2/0.5 mg soluble film at expiry) is clearly capable of producing withdrawal symptoms - and thus acting as a deterrent to abuse - in the majority of opioid-dependent persons when injected alone or in combination with an equal amount of buprenorphine. However, 3/13 subjects (23%) failed to experience withdrawal after injection of 0.4 mg naloxone during the screening period, even though they were daily heroin users who fulfilled DSM-III-R criteria for opiate addiction. The buprenorphine:naloxone 1:1 combination would presumably have also failed to produce withdrawal symptoms in these 3 subjects, had they continued in the study. Furthermore, the study does not provide any information regarding the effect of injecting buprenorphine and naloxone in a ratio of 4:1 (as present in fresh Suboxone soluble films and tablets), or a higher ratio (as present in stored Suboxone soluble films), or at higher doses.
- **Study CR93/004** enrolled 16 subjects who used heroin at least once daily and were opiate-dependent according to DSM-III-R criteria, and used similar methods to CR93/005. However, (a) the screening phase involved an initial naloxone injection of 0.4 mg, plus a second injection of naloxone 2 mg in subjects who did not experience severe withdrawal symptoms at the 0.4 mg dose; and (b) the second phase of Study CR93/004 used higher buprenorphine and naloxone doses than CR93/005 - subjects received intravenous injections of placebo, buprenorphine 2 mg, buprenorphine 2 mg + naloxone 2 mg, and naloxone 2 mg. Six subjects were eliminated during the screening: 1 subject had no withdrawal symptoms after either naloxone dose; 3 subjects had excessive withdrawal symptoms (2 after 0.4 mg naloxone and 1 after 2 mg); 1 subject had hypotension during non-precipitated withdrawal; 1 subject had inaccessible peripheral veins. Ten subjects who experienced moderate withdrawal at the 2 mg naloxone dose continued into the second phase of the study. Intravenous buprenorphine 2 mg exhibited typical opioid agonist effects. The addition of naloxone 2 mg diminished these opioid agonist effects, with a non-significant increase in

withdrawal symptoms that was nevertheless perceived as dysphoric. Naloxone 2 mg, given alone, produced the expected withdrawal effects. However, while the study shows that a 1:1 combination of buprenorphine and naloxone has some potential to deter intravenous abuse, it does not provide any data relating to the buprenorphine:naloxone ratios of 4:1 and higher that are under consideration in this submission.

- **Study CR94/003** enrolled 11 subjects who used heroin at least once daily and were opiate-dependent according to DSM-IV criteria. The subjects were hospitalised and stabilised on intramuscular morphine, 15 mg four times daily (qid). After five days of stabilisation, the subjects were challenged every second day with single intravenous doses of: placebo, buprenorphine 2 mg; buprenorphine 2 mg + naloxone 1 mg (2:1 ratio); buprenorphine 2 mg + naloxone 0.5 mg (4:1 ratio); and buprenorphine 2 mg + naloxone 0.25 mg (8:1 ratio). The challenges were administered in a double-blind, randomised manner. During the challenge phase, subjects continued to receive intramuscular morphine 15 mg qid. The addition of naloxone significantly attenuated the opioid agonist effects of buprenorphine at all ratios studied (2:1, 4:1 and 8:1). A 'Good drug effect' (100 mm VAS) was significantly attenuated for all three combinations, compared to buprenorphine alone. 'Drug liking' (100 mm VAS) was also reduced for all three combinations compared to buprenorphine alone, but the reduction was statistically significant only for the 2:1 ratio. The Global Withdrawal Rating (100 mm VAS) was significantly increased for all three combinations compared to buprenorphine alone. Opiate Withdrawal Scale scores (0-64), 'Bad Drug Effect' (100 mm VAS) and 'Sickness Rating' (100 mm VAS) were increased for all combinations compared to buprenorphine alone, but the effect was statistically significant only for the 2:1 and 4:1 combinations, not for the 8:1 combination. Subjects stated that they would be willing to pay the most for morphine, about one-third less for buprenorphine, and two-thirds less for the 4:1 and 8:1 combinations. Subjects stated that they would not be willing to pay for the 2:1 combination. Overall, these results indicate that the 4:1 ratio of buprenorphine:naloxone that is present in fresh Suboxone soluble films is likely to discourage intravenous abuse, whereas an 8:1 ratio would be somewhat less likely to do so. Interpolating between these results, the ratio of about 4.7:1 that would be expected at expiry of Suboxone soluble films would be less likely to discourage intravenous abuse that the 4:1 ratio present in fresh soluble films, but the difference would be small.

In summary, four of the studies referred to by the sponsor did not provide relevant information. The fifth study, CR94/003, showed that (a) the propensity of buprenorphine:naloxone combinations to produce withdrawal effects decreases as the ratio of buprenorphine to naloxone increases, but (b) the approval of a different limit for naloxone at expiry of Suboxone soluble films is likely to lead to only a small reduction (compared to fresh soluble films) in their propensity to produce withdrawal symptoms after intravenous injection.

Pharmacodynamic interactions with other medicinal products or substances

The sponsor noted that there have been a number of post-marketing reports of coma and death associated with the concomitant use of buprenorphine and benzodiazepines. In many of these cases, buprenorphine was misused by self-injection of crushed buprenorphine tablets. The Precautions - Interactions with Other Drugs section of the Suboxone tablet PI contains a statement regarding this interaction, which has been duplicated in the draft PI for Suboxone soluble films.

Evaluator's overall conclusions on pharmacodynamics

Study CR94/003 showed that (a) the propensity of buprenorphine:naloxone combinations to produce withdrawal effects decreases as the ratio of buprenorphine to naloxone increases, but (b) the approval of a different limit for naloxone at expiry of Suboxone soluble films is likely to lead to only a small reduction (compared to fresh soluble films) in their propensity to produce withdrawal symptoms after intravenous injection.

Efficacy

The requested indication for Suboxone Sublingual Soluble Film is the same as the approved indication for Suboxone tablets, namely:

Treatment of opiate dependence within a framework of medical, social and psychological treatment.

The submission included two Phase II clinical studies of Suboxone soluble films in the proposed indication (RB-US-07-0001 and RB-US-07-0002). Study RB-US-07-0001 was open-label and both lacked a suitable control group (an Australian-registered active comparator or a product that has been shown to be bioequivalent to an Australian-registered active comparator). Accordingly, neither study provides evaluable efficacy data. This is acknowledged by the sponsor which stated: "Efficacy studies were not conducted as part of this application". The sponsor's application letter also stated that these studies were included in the submission "to support safety of the novel dosage form".

Evaluator's overall conclusions on clinical efficacy

The designs of the two clinical studies (RB-US-07-0001 and RB-US-07-0002) mean that neither provides evaluable evidence of efficacy. The submission therefore relies primarily on an extrapolation of efficacy from the sublingual tablet formulation, via the bioequivalence studies:

- Compared to the 2/0.5 mg tablet, a single sublingual dose of the 2/0.5 mg soluble film produced equivalent systemic exposure to buprenorphine and naloxone, and a 22% higher peak concentration of buprenorphine. Accordingly, the efficacy of the 2/0.5 mg soluble film should be at least equivalent to that of the tablet, both after a single dose and during chronic use.
- Compared to the 8/2 mg tablet, a single sublingual dose of the 8/2 mg soluble film produced 20% higher systemic buprenorphine exposure and 28% higher peak buprenorphine concentration. This was accompanied by a 21% increase in naloxone exposure and a 41% increase in naloxone peak concentration. Naloxone concentrations remained about 60% below levels that would be expected to produce frank withdrawal symptoms but it is not clear to what extent the increased naloxone concentrations would offset the increased buprenorphine concentrations, in terms of efficacy. Overall, the PK data do not permit a firm conclusion that the efficacy of Suboxone 8/2 mg soluble films will be equivalent to, or better than, the efficacy of Suboxone 8/2 mg sublingual tablets. This does not necessarily preclude registration, since (a) the increase in naloxone concentrations is similar to the increase in buprenorphine concentrations and the opposing effects of the two differences should approximately cancel each other out, and (b) the standard practice of individual titration to effect would account for any reduced or increased efficacy of the 8/2 mg soluble films. However, the inability to firmly conclude that the tablets and soluble films have equivalent efficacy means that the two formulations should not be regarded as interchangeable.

Safety

Introduction

The submission included two Phase II studies that examined the safety of Suboxone soluble films, RB-US-07-0001 and RB-US-07-0002. The designs of these two clinical studies mean that neither provides confirmatory evidence of safety. Study RB-US-07-0001 provides an assessment of the short-term safety of the proposed formulation (up to 12 weeks), but not medium- to long-term safety. Study RB-US-07-0002 is too small and too short in duration to provide a meaningful assessment of the safety of the study treatments. Dissimilarities between the two studies also mean that it is not appropriate to combine their safety data.

Study RB-US-07-0001

Study RB-US-07-0001 was a Phase II, multicentre, open-label, randomised study that enrolled 382 otherwise healthy, opioid-dependent adult males and females who had been on maintenance therapy with Suboxone sublingual tablets for at least 30 days. Opioid dependence was diagnosed according to DSM-IV-TR criteria. The objective of the study was to assess the safety and tolerability of Suboxone soluble films administered either sublingually or buccally for 12 weeks, with particular emphasis on adverse effects on the oral mucosa. The study consisted of three phases:

- A **Screening phase** of up to 30 days, during which subjects were stabilised on Suboxone sublingual tablets at a dose of 4/1 to 32/8 mg.
- A 12-week **Treatment phase**, in which subjects were randomised to open-label Suboxone soluble films via the sublingual or buccal routes. Study treatments were used as an adjunct to pre-existing counselling and behavioural treatment. Suboxone soluble films were started at the dose that each individual had been taking as Suboxone sublingual tablets. Subsequent dose adjustments were allowed at the discretion of the investigator. Soluble films were available in 2/0.5 mg, 8/2 mg, 12/3 mg, and 16/4 mg strengths. Subjects were told to place no more than two soluble films under the tongue at once. If three soluble films were needed, the third was placed in the mouth at least 5 minutes after the other two to allow time for the first two to disintegrate. The Treatment phase was conducted on an outpatient basis. There were no efficacy assessments. Safety assessments included oral mucosa tolerability (Grade 0 = normal to Grade 3 = ulceration) and recording of treatment-emergent adverse events (TEAEs). A TEAE is an event that was observed or reported after administration of the study drug that was either not present prior to study drug administration or an event that represents the exacerbation of a pre-existing condition. Subjects also completed a "Drug Preference Questionnaire" at the end of the Treatment phase, with a number of questions that related predominantly to the taste of the soluble films, followed by a single question in which subjects were asked whether they preferred the soluble films or tablets. Laboratory tests were not performed.
- A one-week **Discharge phase**, during which subjects were returned to Suboxone sublingual tablets.

The number of patients who failed screening was not stated. A total of 382 subjects were randomised and received at least one dose of Suboxone soluble film (194 sublingual, 188 buccal). Demographic and baseline characteristics were generally well-balanced between the treatment groups. Most subjects were White (99.2%), with a mean age of 36.4 (range 19-71) years. Consistent with the profile of the general opioid-dependent population, there was a greater proportion of male than female subjects (62.8% and 37.2%, respectively). A total of 249 subjects (65.2%) completed the study. As seen in Table 6, discontinuations were more

common in the sublingual group (35.1% compared to 27.7% in the buccal group), with most of the difference accounted for by discontinuations due to “other reasons”.

Table 6: Study RB-US-07-0001: Subject disposition.

	Suboxone soluble film administration route		
	Sublingual N=194	**Buccal** N=188	**Total** N=382
Randomised	194 (100.0)	188 (100.0)	382 (100.0)
Completed *	118 (60.8)	131 (69.7)	249 (65.2)
Discontinued (any reason) †	68 (35.1)	52 (27.7)	120 (31.4)
Adverse event	5 (2.6)	3 (1.6)	8 (2.1)
Subject withdrew consent	12 (6.2)	14 (7.4)	26 (6.8)
Investigator's decision	10 (5.2)	14 (7.4)	24 (6.3)
Sponsor's decision	8 (4.1)	5 (2.7)	13 (3.4)
Protocol violation	2 (1.0)	2 (1.1)	4 (1.0)
Lost to follow-up	17 (8.8)	13 (6.9)	30 (7.9)
Other reason	19 (9.8)	4 (2.1)	23 (6.0)

* Completers were defined as subjects who completed at least 84 days of Suboxone Soluble Film therapy, with a clinic visit not more than 7 days after the last soluble film administration.

† A subject may have been discontinued for more than one reason.

Study RB-US-07-0002

Study RB-US-07-0002 was an inpatient, double-blind, single-site, randomised trial comparing buprenorphine soluble films to Suboxone soluble films for induction of otherwise healthy opioid-dependent subjects. After initial screening, subjects entered a morphine maintenance period during which they received 30 mg of morphine subcutaneously up to 4 times per day for up to 13 days. During this period, each subject underwent two laboratory test sessions, during which they received a challenge of naloxone 0.4 mg or placebo intramuscularly. Subjects who demonstrated significant withdrawal symptoms in response to the naloxone challenge were randomised to receive either buprenorphine soluble films or Suboxone soluble films. Over a 5 day period, the dose was escalated from buprenorphine 12 mg or buprenorphine 12 mg + naloxone 3 mg once daily, to 16 to 24 mg of buprenorphine (with the corresponding proportional dose of naloxone in the second treatment group). During this 5 day period, subjects were evaluated for signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS), pupil diameters, and visual analogue scales (VAS) covering 7 areas ("High", "Drug Effects", "Good Drug Effects", "Bad", "Effects", "Liking" and "Sick"). Subjects who did not complete the study were to be replaced to obtain a total of 34 evaluable subjects (17 per treatment group). This study did not provide evaluable efficacy data relevant to the current submission because it compared two unregistered products. Safety assessments included adverse effects (AEs), oral mucosa exams, vital signs, electrocardiogram (ECG), and laboratory tests (chemistry, haematology and urinalysis).

Seventy-nine subjects were screened, of whom 30 failed screening or withdrew prior to the morphine maintenance phase; 49 subjects participated in the morphine maintenance phase; 39 subjects completed this phase and were randomised; one subject withdrew before starting randomised treatment; 20 subjects received buprenorphine soluble films and 18 received Suboxone soluble films. These subjects were predominantly Caucasian (66%) and male (68%), with a mean age of 40.2 (range 21-56) years. A total of 34 subjects completed at least 2 days of study treatment and were classed as "evaluable" (18 in the buprenorphine group

and 16 in the Suboxone group); 16 subjects (80% of those randomised) completed 5 days of buprenorphine soluble films and 15 subjects (83% of those randomised) completed 5 days of Suboxone soluble films.

Patient exposure

A total of 822 healthy subjects participated in the Phase 1 (PK) crossover studies; 206 subjects were treated with buprenorphine sublingual tablets, 351 with buprenorphine soluble films, 313 with Suboxone sublingual tablets, and 459 with Suboxone soluble films. As these were crossover studies, the number of subjects exposed to each study drug formulation exceeds the total number of subjects in the studies. These numbers include subjects from the 14 pharmacokinetic studies that were not submitted for full evaluation. The PK studies that were submitted for full evaluation enrolled a total of 248 subjects.

A total of 400 opioid-dependent subjects were treated with Suboxone soluble films in the Phase II studies: 382 for up to 12 weeks in RB-US-07-0001 and 18 for up to 5 days in RB-US-07-0002.

Exposure data from Study RB-US-07-0001 are summarised in Table 7.

Table 7: Study RB-US-07-0001: Summary of exposure to Suboxone soluble films.

		Suboxone soluble film administration route		
		Sublingual	**Buccal**	**Total**
		N=194	N=188	N=382
Duration of exposure (days)	*N*	193	187	380
	Mean (SD)	77.0 (25.9)	77.4 (22.8)	77.2 (24.4)
	Median	84.0	84.0	84.0
	Range	7 - 139	9 - 133	7 - 139
Daily dose (mg buprenorphine)	*N*	179	177	356
	Mean (SD)	15.3 (7.7)	15.4 (7.5)	15.3 (7.6)
	Median	16.0	16.0	16.0
	*Range**	2 - 33	2 - 32	2 - 33

The number of subjects is different for exposure (days on treatment) and daily dose due to a different number of missing values for each variable. Daily dose refers to the buprenorphine component. Daily dose is the per subject average and there were several subjects missing all total daily dose data.

* Range of mean (per patient) doses.

In Study RB-US-07-0002, subjects received Suboxone soluble films for a mean of 4.5 (range 1-5) days, at daily doses ranging from 8/2 to 16/4 mg.

Adverse events

Study RB-US-07-0001

Table 8 gives an overall summary of adverse events in Study RB-US-07-0001.

Table 8: Study RB-US-07-0001: Number (%) of subjects with adverse events - Overview.

Event category	Suboxone soluble film administration route		
	Sublingual N=194	Buccal N=188	Total N=382
Any treatment-emergent adverse event (TEAE)	54 (27.8)	62 (33.0)	116 (30.4)
mild	30 (15.5)	34 (18.1)	64 (16.8)
moderate	16 (8.2)	24 (12.8)	40 (10.5)
severe	8 (4.1)	4 (2.1)	12 (3.1)
Treatment-related TEAE *	14 (7.2)	16 (8.5)	30 (7.9)
Discontinuation due to TEAE	5 (2.6)	3 (1.6)	8 (2.1)
Serious adverse event (SAE)	4 (2.1)	2 (1.1)	6 (1.6)
Treatment-related SAE *	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)

* Includes those adverse events considered unknown, possibly, probably, or definitely related to study drug.

Treatment-emergent adverse events

As shown in Table 8, TEAEs were reported in 30.4% of subjects during the use of Suboxone soluble films in Study RB-US-07-0001 (27.8% with sublingual administration; 30.3% with buccal administration). The incidence of TEAEs in Study RB-US-07-0001 according to System Organ Class (SOC) is shown in Table 9.

Table 9: Study RB-US-07-0001: Number (%) of subjects with TEAEs within each SOC.

System Organ Class (SOC)	Suboxone soluble film administration route		
	Sublingual N=194	Buccal N=188	Total N=382
Gastrointestinal disorders	18 (9.3)	22 (11.7)	40 (10.5)
Infections and infestations	21 (10.8)	17 (9.0)	38 (9.9)
Injury, poisoning and procedural complications	6 (3.1)	11 (5.9)	17 (4.5)
Musculoskeletal and connective tissue disorders	9 (4.6)	6 (3.2)	15 (3.9)
General disorders and admin. site conditions	4 (2.1)	7 (3.7)	11 (2.9)
Nervous system disorders	4 (2.1)	7 (3.7)	11 (2.9)
Psychiatric disorders	4 (2.1)	5 (2.7)	9 (2.4)
Metabolism and nutrition disorders	2 (1.0)	2 (1.1)	4 (1.0)
Renal and urinary disorders	2 (1.0)	2 (1.1)	4 (1.0)
Respiratory, thoracic and mediastinal disorders	2 (1.0)	2 (1.1)	4 (1.0)
Skin and subcutaneous tissue disorders	3 (1.5)	0 (0.0)	3 (0.8)
Investigations	0 (0.0)	2 (1.1)	2 (0.5)
Neoplasms benign, malignant and unspecified	1 (0.5)	1 (0.5)	2 (0.5)
Pregnancy, puerperium and perinatal conditions	2 (1.0)	0 (0.0)	2 (0.5)
Blood and lymphatic system disorders	1 (0.5)	0 (0.0)	1 (0.3)
Cardiac disorders	1 (0.5)	0 (0.0)	1 (0.3)
Eye disorders	1 (0.5)	0 (0.0)	1 (0.3)
Reproductive system and breast disorders	1 (0.5)	0 (0.0)	1 (0.3)

The most common TEAEs (incidence≥2% in either study group) in Study RB-US-07-0001 are shown in Table 10.

Table 10: Study RB-US-07-0001: Number (%) of subjects reporting the most common TEAEs (incidence≥2% in either treatment group).

Preferred Term	Suboxone soluble film administration route		
	Sublingual N=194	Buccal N=188	Total N=382
Upper respiratory tract infection	4 (2.1)	2 (1.1)	6 (1.6)
Sinusitis	3 (1.5)	4 (2.1)	7 (1.8)
Oral mucosal erythema	2 (1.0)	6 (3.2)	8 (2.1)
Toothache	2 (1.0)	4 (2.1)	6 (1.6)

Additional TEAEs reported in ≥1% of subjects in the sublingual treatment group were: urinary tract infection, pain (1.5% each); pharyngitis streptococcal, influenza, tooth abscess, skin laceration, arthralgia, musculoskeletal pain, stress, nephrolithiasis, dermatitis contact, pregnancy (1.0% each).

The incidence of TEAEs was much lower than, and the most frequent TEAEs different to, those that were seen in previously-evaluated studies of Suboxone tablets. This difference is accounted for by the fact that the previous studies involved the induction of subjects onto Suboxone therapy (a process that can be associated with a range of opioid withdrawal symptoms), whereas subjects in Study RB-US-07-001 had already undergone that process before the start of adverse event data collection.

TEAEs associated with the oral cavity

Table 11 summarises TEAEs associated with the oral cavity in Study RB-US-07-0001. These TEAEs are of interest because they are potentially related to the specific soluble film formulation.

Table 11: Study RB-US-07-0001: Number (%) of subjects reporting TEAEs associated with the oral cavity.

Preferred Term	Suboxone soluble film administration route		
	Sublingual N=194	Buccal N=188	Total N=382
Oral mucosal erythema	2 (1.0)	6 (3.2)	8 (2.1)
Toothache	2 (1.0)	4 (2.1)	6 (1.6)
Glossodynia	3 (1.5)	1 (0.5)	4 (1.0)
Hypoaesthesia oral	2 (1.0)	1 (0.5)	3 (0.8)
Stomatitis	1 (0.5)	1 (0.5)	2 (0.5)
Oedema mouth	0 (0.0)	1 (0.5)	1 (0.3)
Oral pain	0 (0.0)	1 (0.5)	1 (0.3)
Paraesthesia oral	0 (0.0)	1 (0.5)	1 (0.3)
Tongue coated	1 (0.5)	0 (0.0)	1 (0.3)

Treatment-related TEAEs

Most TEAEs in Study RB-US-07-0001 were considered not related to study drug by the investigator. Treatment-related TEAEs were reported in 30 (7.9%) subjects using Suboxone soluble films: 14 (7.2%) of subjects in the sublingual administration group and 16 (8.5%) of

subjects in the buccal administration group. The most common treatment-related TEAEs (incidence ≥1% in either group) are shown in Table 12. TEAEs reported in <1% of subjects are listed in Table 13.

Table 12: Study RB-US-07-0001: Number (%) of subjects reporting the most common treatment-related TEAEs (incidence 1% in either treatment group).

Preferred Term	**Suboxone soluble film administration route**		
	Sublingual N=194	**Buccal** N=188	**Total** N=382
Oral mucosal erythema	2 (1.0)	5 (2.7)	7 (1.8)
Nausea	2 (1.0)	2 (1.1)	4 (1.0)
Glossodynia	2 (1.0)	1 (0.5)	3 (0.8)
Hypoaesthesia oral	2 (1.0)	1 (0.5)	3 (0.8)
Vomiting	2 (1.0)	1 (0.5)	3 (0.8)
Constipation	1 (0.5)	2 (1.1)	3 (0.8)

Table 13: Study RB-US-07-0001: Treatment-related TEAEs reported in <1% of subjects treated with Suboxone soluble films (sublingual and buccal routes combined).

Gastrointestinal disorders: hypoaesthesia oral, constipation, glossodynia, vomiting, nausea, oedema mouth, oral pain, paraesthesia oral
Injury, poisoning and procedural complications: poisoning
Musculoskeletal and connective tissue disorders: back pain
Nervous system disorders: disturbance in attention, headache, migraine, somnolence
General disorders and administration site conditions: pain
Psychiatric disorders: drug dependence, insomnia, withdrawal syndrome
Skin and subcutaneous tissue disorders: hyperhidrosis
Cardiac disorders: palpitations
Eye disorders: vision blurred

TEAEs according to sex, age and ethnicity

In Study RB-US-07-0001, TEAEs were more common in females than males (35.9% vs 27.1%). The difference was particularly apparent in the sublingual treatment group, in which 37.1% of females and 22.6% of males had TEAEs. In the buccal group, 34.7% of females and 31.9% of males had TEAEs. The basis and clinical relevance of these findings are unclear.

No TEAEs were reported in the 4 subjects aged <21 years. Overall, TEAEs were reported in approximately 30% of subjects treated with Suboxone soluble films in each of the other age groups (21-35, 36-50 and >50 years). However, subjects aged 21-35 years treated sublingually had a higher incidence of TEAEs (31.4%) than older subjects treated sublingually (36-50 years of age, 25.4%; >50 years of age, 23.5%). These differences are not considered to be clinically important.

The number of non-Caucasian subjects was insufficient to provide a meaningful analysis of TEAEs according to ethnicity.

Study RB-US-07-0002

Table 14 provides an overall summary of adverse events reported during treatment with buprenorphine and Suboxone soluble films in Study RB-US-07-0002.

Table 14: Study RB-US-07-0002: Number (%) of subjects with adverse events - overview.

Event category	**Treatment group**	
	Buprenorphine soluble film N=20	**Suboxone soluble film** N=18
Any TEAE	19 (95)	18 (100)
mild	7 (35)	8 (44)
moderate	12 (60)	10 (56)
severe	0 (0)	0 (0)
Treatment-related TEAE *	14 (70)	17 (94)
Discontinuation due to TEAE	2 (10)	2 (11) †
Serious adverse event (SAE)	0 (0)	0 (0)
Treatment-related SAE *	0 (0)	0 (0)
Death	0 (0)	0 (0)

* Includes those adverse events considered unknown, possibly, probably, or definitely related to study drug.
† Includes 1 subject who discontinued due to "subject desires to withdraw" but whose reasons for discontinuation included opioid withdrawal symptoms.

TEAEs were reported in 19 (95%) subjects during induction with buprenorphine soluble films and 18 (100%) subjects during induction with Suboxone soluble films. As seen in Table 15, the most common TEAEs represented opioid withdrawal symptoms. This is consistent with previously-submitted studies of Suboxone tablets. Also, the study design called for the last 2 doses of morphine to be switched to blinded doses of placebo, to induce mild to moderate opioid withdrawal on Day 1 of the induction period.

Table 15: Study RB-US-07-0002: Number (%) of subjects reporting the most common TEAEs (incidence ≥10% in either treatment group).

TEAE	Treatment group	
	Buprenorphine soluble film N=20	Suboxone soluble film N=18
Anxiety	6 (30)	9 (50)
Stomach discomfort	7 (35)	8 (44)
Restlessness	4 (20)	8 (44)
Piloerection	2 (10)	7 (39)
Rhinorrhoea	10 (50)	6 (33)
Headache	6 (30)	6 (33)
Irritability	5 (25)	6 (33)
Cold sweat	6 (30)	5 (28)
Lacrimation increased	4 (20)	5 (28)
Yawning	4 (20)	4 (22)
Arthralgia	3 (15)	4 (22)
Insomnia	3 (15)	4 (22)
Nausea	3 (15)	4 (22)
Tachycardia	6 (30)	3 (17)
Tremor	5 (25)	2 (11)
Abdominal pain	1 (5)	2 (11)
Dyspepsia	1 (5)	2 (11)
Vomiting	1 (5)	2 (11)
Chills	2 (10)	1 (6)
Back pain	2 (10)	1 (6)
Diarrhoea	2 (10)	0 (0)
Pain in extremity	2 (10)	0 (0)

Treatment-related TEAEs during the induction period were reported in 70% of the buprenorphine group and 94% of the Suboxone soluble film group. Information was not presented regarding the nature of the treatment-related TEAEs that occurred during the induction period.

VAS scores for Bad Effects, High, and Sick remained low throughout all scheduled assessments after administration of buprenorphine and Suboxone soluble film products. The sponsor argued that this supports a lack of a precipitated withdrawal during administration of both products. However, two subjects in each treatment group (about 10%) discontinued on Day 1 of the induction period, citing opioid withdrawal symptoms amongst the reasons for discontinuation.

PK studies

Table 16 shows the overall frequency of TEAEs, and individual TEAEs with an incidence ≥2%, in the 19 PK studies in healthy subjects.

Table 16: PK studies: Number (%) of subjects reporting the most common TEAEs (incidence ≥2% in any treatment group).

System Organ Class / Preferred term	Treatment group			
	Buprenorphine tablets	Buprenorphine soluble films	Suboxone tablets	Suboxone soluble films

ANY TEAE	**88**	**(42.7)**	**233**	**(66.4)**	**150**	**(47.9)**	**301**	**(65.6)**
Gastrointestinal disorders	**57**	**(27.7)**	**171**	**(48.7)**	**108**	**(34.5)**	**235**	**(51.2)**
Nausea	40	(19.4)	136	(38.7)	74	(23.6)	184	(40.1)
Vomiting	19	(9.2)	64	(18.2)	19	(6.1)	66	(14.4)
Abdominal pain	14	(6.8)	42	(12.0)	24	(7.7)	62	(13.5)
Constipation	10	(4.9)	27	(7.7)	15	(4.8)	49	(10.7)
Diarrhoea	7	(3.4)	25	(7.1)	5	(1.6)	18	(3.9)
Dyspepsia	3	(1.5)	8	(2.3)	6	(1.9)	12	(2.6)
Dry mouth	1	(0.5)	12	(3.4)	1	(0.3)	7	(1.5)
Paraesthesia oral	1	(0.5)	7	(2.0)	2	(0.6)	6	(1.3)
Nervous system disorders	**56**	**(27.2)**	**150**	**(42.7)**	**63**	**(20.1)**	**188**	**(41.0)**
Headache	27	(13.1)	82	(23.4)	36	(11.5)	103	(22.4)
Dizziness	19	(9.2)	77	(21.9)	24	(7.7)	84	(18.3)
Somnolence	16	(7.8)	52	(14.8)	12	(3.8)	67	(14.6)
General disorders & administrative site conditions	**8**	**(3.9)**	**52**	**(14.8)**	**14**	**(4.5)**	**49**	**(10.7)**
Fatigue	3	(1.5)	23	(6.6)	7	(2.2)	26	(5.7)
Asthenia	4	(1.9)	13	(3.7)	0	(0.0)	7	(1.5)
Psychiatric disorders	**6**	**(2.9)**	**37**	**(10.5)**	**7**	**(2.2)**	**35**	**(7.6)**
Euphoric mood	1	(0.5)	12	(3.4)	4	(1.3)	11	(2.4)
Anxiety	1	(0.5)	10	(2.8)	1	(0.3)	6	(1.3)
Confusional state	2	(1.0)	3	(0.9)	2	(0.6)	9	(2.0)
Infections and infestations	**4**	**(1.9)**	**20**	**(5.7)**	**9**	**(2.9)**	**21**	**(4.6)**
Pharyngitis	1	(0.5)	8	(2.3)	4	(1.3)	6	(1.3)
Upper respiratory tract infection	1	(0.5)	8	(2.3)	3	(1.0)	6	(1.3)
Metabolism and nutrition disorders	**2**	**(1.0)**	**10**	**(2.8)**	**4**	**(1.3)**	**12**	**(2.6)**
Anorexia	2	(1.0)	9	(2.6)	4	(1.3)	12	(2.6)
Reproductive system & breast disorders	**1**	**(0.5)**	**6**	**(1.7)**	**5**	**(1.6)**	**14**	**(3.1)**
Dysmenorrhoea	0	(0.5)	3	(0.9)	1	(0.3)	9	(2.0)

Note: Includes Studies 20-A70-AU, 20-A71-AU, 20-A72-AU, 20-197-SA, 20-A78-AU, 20-250-SA, 20-272-SA, 20-273-SA, 20-277-SA, 20-276-SA, 20-B17-AU, 20-B20-AU, 20-A79-AU, 20-A90-AU, 20-290-SA, 20-291-SA, 20-293-SA, 20-B24-AU, and 1003395. Because these are crossover studies that compared different treatments and routes of administration, the number of subjects exposed to each study drug formulation exceeds the total number of subjects in the studies.

The overall incidence of TEAEs was similar in both soluble film groups (Suboxone soluble film, 65.6%; buprenorphine soluble film, 66.4%) but approximately 20% higher than that in the sublingual tablet groups (Suboxone SL tablets, 47.9%; buprenorphine SL tablets, 42.7%).

The most common TEAEs in any treatment group were in the *Gastrointestinal* and *Nervous System Disorders* SOC, and these occurred more often after treatment with the soluble films than the sublingual tablets. All of the subjects in these studies were pre-treated with naltrexone. Some of the TEAEs may have been related to naltrexone (for example, some

cases of nausea), while the incidence of other TEAEs (for example, somnolence) may have been reduced by naltrexone pre-treatment.

Gastrointestinal and *Nervous System Disorders* were the most common SOCs with TEAEs assessed as related to Suboxone soluble films (45.8% and 34.0% of subjects, respectively). Nausea and vomiting were considered at least possibly related to Suboxone soluble films in 34.2% and 12.6% of subjects, respectively. Headache, dizziness, and somnolence were considered at least possibly related to Suboxone soluble films in 17.2%, 14.8%, and 13.5% of subjects, respectively.

Serious adverse events and deaths

No deaths were reported in the Phase II studies (RB-US-07-0001 and RB-US-07-0002) or the 19 Phase 1 (PK) studies in healthy subjects.

In the 12-week Study RB-US-07-0001, 7 serious adverse events (SAEs) were reported in 6 (1.6%) subjects treated with Suboxone soluble films; 4 in the sublingual group and 2 in the buccal group. The SAEs were skin injury, squamous cell carcinoma of the cervix, anaemia, syncope vasovagal, nephrolithiasis, road traffic accident and oesophageal carcinoma. No SAE was considered related to study drug.

There were no SAEs in the 5-day induction Study RB-US-07-0002.

One SAE was reported in the 19 PK studies: a case of unilateral optic neuritis in a subject with a history of this condition, currently treated with methylprednisone, prednisone ibuprofen and hydrocodone, who received naltrexone, buprenorphine soluble film and Suboxone soluble film in the PK study. The event was considered possibly related to study drug and was ongoing at the last report.

Laboratory findings

Laboratory data in patients taking Suboxone soluble films were available only for the 5-day induction study (RB-US-07-0002) and the PK studies.

RB-US-07-0002

Mean levels of alanine aminotransferase (ALT) at post-test were elevated over those at baseline, with mean changes of 20.7 U/L with buprenorphine soluble films and 18.4 U/L with Suboxone soluble films. Mean levels of aspartate aminotransferase (AST) at post-test were also elevated over those at baseline, with mean changes of 7.7 U/L with buprenorphine soluble films and 7.1 U/L with Suboxone soluble films. No other hepatic function tests, including alkaline phosphatase, total bilirubin, and albumin, exhibited abnormal mean changes during the study.

Total cholesterol and triglycerides were also elevated compared to baseline in both study groups, but the samples were non-fasting, so the results may have been influenced by diet. There were no significant changes in mean haematology parameters.

The majority of subjects in each group had at least one treatment emergent laboratory abnormality: 19/19 subjects in the buprenorphine soluble film group and 14/16 subjects in the Suboxone soluble film group. However, with the exception of total cholesterol and triglycerides (which may have been influenced by diet), the magnitude of the laboratory abnormalities was minimal.

PK studies

Mean changes in clinical chemistry and haematology values in healthy subjects in the 19 PK studies were small, and similar among the treatment groups.

Treatment-emergent abnormal laboratory values were reported for numerous healthy subjects in the PK studies, but the magnitude of the abnormal values was not severe, and the incidence of treatment-emergent laboratory abnormalities was generally similar among the treatment groups, with the following exceptions:

- Treatment-emergent abnormal glucose levels were reported for slightly larger percentages of subjects who received buprenorphine soluble films or Suboxone soluble films (5.7% and 4.6%, respectively) than subjects who received buprenorphine or Suboxone SL tablets (2.4% and 2.2%, respectively).
- Treatment-emergent haemoglobin abnormalities were reported in a larger percentage of the Suboxone soluble film group (8.3%) than the other groups (≤3.4%).

The clinical relevance of these findings is uncertain.

Safety related to drug-drug interactions and other interactions

As previously described, the submission discussed the potential for interactions with CYP3A4 inhibitors and inducers, and discussed post-marketing reports of coma and death associated with the concomitant use of buprenorphine and benzodiazepines. The submission stated that "a review of recently published literature related to buprenorphine or buprenorphine and naloxone and drug-drug interactions was included in the Periodic Safety Update Report (PSUR) for Subutex (buprenorphine monotherapy) and Suboxone sublingual tablets, submitted to the TGA in February 2009". Inspection of the PSUR found only a brief description of a published case series of 19 male buprenorphine injectors in Malaysia, 8 of whom regularly injected buprenorphine with midazolam and reported increased sedation and euphoria with the combination. The Australian PIs for Subutex and Suboxone already include a warning about the interaction between buprenorphine and benzodiazepines. No other new information regarding drug-drug interactions was provided.

Discontinuation due to adverse events

In Study RB-US-07-0001, 8 (2.1%) subjects discontinued due to TEAEs during the administration of Suboxone soluble films: 5 (2.6%) subjects in the buccal group and 3 (1.6%) subjects in the sublingual group. TEAEs leading to discontinuation were considered to be treatment-related in 2 subjects (back pain, migraine, nausea and somnolence in one subject; constipation, disturbance in attention, headache, hyperhidrosis, insomnia, poisoning, vision blurred and withdrawal syndrome in another subject). Other TEAEs that led to discontinuation but were not considered to be treatment-related were road traffic accident, oesophageal carcinoma, skin injury, pregnancy (one with spontaneous abortion), and arthralgia

In Study RB-US-07-0002, two subjects (11%) discontinued Suboxone soluble films due to TEAEs. Two subjects (10%) also discontinued due to TEAEs in the buprenorphine soluble film group. In each case, the responsible TEAE was opioid withdrawal symptoms on the first day of the induction period (family reasons were also cited in one of the Suboxone subjects).

Post marketing experience

Post-marketing adverse event reports

No post-marketing data were available for Suboxone soluble films. The submission included a summary of post-marketing data for Suboxone and Subutex tablets from January 1997 to October 2008. Worldwide exposure, based on sales, was estimated to be 78,500 patient-years for Suboxone and 1.2 million patient-years for Subutex. The most frequently reported post-marketing adverse events are shown in Table 17.

Table 17: Most common* post-marketing adverse events reported with Subutex SL Tablets, Suboxone SL Tablets, or Buprenorphine (Other) by System Organ Class, High Level Group Term, and Preferred Term (January 1, 1997-October 31, 2008).

System Organ Class *High Level Group Term* Preferred Term	Number of reports
Gastrointestinal disorders	
Gastrointestinal motility and defecation conditions	***374***
Constipation	138
Diarrhoea	221
Gastrointestinal signs and symptoms	***1580***
Abdominal pain	95
Abdominal pain upper	94
Nausea	679
Vomiting	580
General disorders and administration site conditions	
Body temperature conditions	***306***
Chills	175
Pyrexia	85
Drug effects (excl toxicity) §	***217***
Drug withdrawal syndrome §	118
Drug withdrawal syndrome neonatal §	72
Fatal outcomes †	***140***
Death	136
General system disorders NEC	***2264***
Asthenia	100
Fatigue	217
Malaise	122
No adverse drug effect	37
No adverse effect	301
No adverse event	425
No adverse reaction	246
Oedema peripheral	181
Pain	155
Therapeutic and non-therapeutic effects (excl toxicity) §	***910***
Drug withdrawal syndrome §	515
Drug withdrawal syndrome neonatal §	162
Hepatobiliary Disorders	
Hepatic and hepatobiliary disorders	***216***
Hepatitis	41
Jaundice	52
Infections and Infestations	
Infections - pathogen class unspecified	***218***
Abscess	43
Endocarditis	25

System Organ Class *High Level Group Term* Preferred Term	Number of reports
Injury, poisoning and procedural complications	
Chemical injury and poisoning	***1090***
Drug exposure during pregnancy §	1055
Poisoning	8
Chemical injury, overdose and poisoning	***628***
Drug exposure during pregnancy §	350
Intentional misuse	191
Medication errors	***809***
Drug exposure during pregnancy §	206
Incorrect route of drug administration	118
Intentional drug misuse §	128
Investigations	
Physical examination topics	***189***
Weight decreased	117
Weight increased	54
Musculoskeletal and connective tissue disorders	
Muscle disorders	***325***
Muscle spasms	143
Myalgia	92
Nervous system disorders	
Headaches	***465***
Headache	428
Migraine	39
Movement disorders (incl Parkinsonism)	***241***
Tremor	174
Neurological disorders NEC	***917***
Dizziness	202
Somnolence	212
Psychiatric disorders	
Anxiety disorders and symptoms	***573***
Agitation	108
Anxiety	319
Depressed mood disorders and disturbances	***166***
Depression	146
Mood disorders and disturbances NEC Total	***192***
Euphoric mood	86
Mood swings	22
Psychiatric and behavioural symptoms NEC	***140***
Abnormal behaviour	13
Drug dependence §	120
Psychiatric disorders NEC	***544***
Drug dependence §	158
Substance abuse §	136
Withdrawal syndrome §	204

System Organ Class *High Level Group Term* Preferred Term	Number of reports
Sleep disorders and disturbances	***384***
Insomnia	324
Sleep disorder	27
Suicidal and self-injurious behaviours NEC	***186***
Suicidal ideation	97
Suicide attempt	59
Respiratory, thoracic and mediastinal disorders	
Respiratory disorders NEC	***453***
Dyspnoea	118
Respiratory depression	61
Skin and subcutaneous tissue disorders	
Epidermal and dermal conditions	***540***
Pruritis	154
Rash	146
Skin appendage conditions	***466***
Alopecia	19
Hyperhidrosis	398

Abbreviations: excl=excluding; HLGT=high level group term; incl=including; NEC=not elsewhere classified; PT=preferred term; SL=sublingual.

* Table includes HLGT categories with at ≥190 events (approximately ≥1% of the total number of reported events).

§ These PTs were recorded under more than one HLGT.

† Includes PTs of death (136 events), sudden death (2 events), drowning (1 event), and brain death (1 event.)

Post-marketing study of intravenous abuse of Suboxone

The sponsor referred to interim results from a post-marketing study by Degenhardt et al, in support of the draft PI claim that "the combination of buprenorphine and naloxone is less commonly and less frequently injected than buprenorphine alone"[7] The data were provided as a study protocol and 'publication manuscript' in an appendix to the Risk Management Plan. The authors obtained national sales data for methadone, buprenorphine and buprenorphine-naloxone between 2003 and 2008. During the same period, regular injecting drug users (IDUs) in Australian capital cities were interviewed (approximately 900 per year) via the previously-established Illicit Drugs Reporting Scheme (IDRS). Current opioid substitution treatment (OST) clients were interviewed in 2007 and 2008. Interview questions related to the diversion, availability, street price and injection of methadone, buprenorphine and buprenorphine-naloxone. Information was also sought regarding adverse effects associated with injection of the three treatments.

The sales data were converted to "factored dose units" based on average daily per-client doses of 70 mg for methadone and 12 mg for buprenorphine (derived from previous Australian research), and the following analyses were conducted:

- Time trends of market share for the three drugs.
- Time trends of the proportion of regular IDUs and OST clients reporting injection of methadone, buprenorphine and buprenorphine-naloxone in the past 6 months, per 100 million factored dose units sold in the same period.

- Multiple logistic regression to ascertain predictors of recent injection of the three drugs amongst IDUs and OST clients.

During 2006-7, the total OST market share of buprenorphine plus buprenorphine-naloxone was about 25%. After its introduction in April 2006, the market share of buprenorphine-naloxone rose steadily to about 14%, with a corresponding decrease in the market share of buprenorphine monotherapy to about 12%.

In 2008, 23% of IDUs had injected methadone in the previous 6 months, whereas 14% had injected buprenorphine and 5% had injected buprenorphine-naloxone. Adjusting for sales, the proportion of IDUs who injected buprenorphine monotherapy any time within the past 6 months rose from about 0.02 per million factored dose units in 2003 to about 0.04 in 2007, then remained stable in 2008. This was initially double, rising to 4 times the corresponding proportions for methadone, which remained stable at 0.01 per million units. When buprenorphine-naloxone was first introduced in 2006, the proportion of IDUs injecting it (0.035 per million units) was initially higher than for buprenorphine monotherapy, but by 2007 and 2008 it had decreased and was about the same as for methadone. Similar trends were seen in the proportion of IDUs injecting the three drugs at least once a week, although the proportions were about halved compared to injection "any time in the last 6 months". These data predominantly represent injection of diverted drugs (that is, drugs that had been dispensed to a different person).

In 2008 the percentages of methadone, buprenorphine and buprenorphine-naloxone OST clients who had injected methadone, buprenorphine or buprenorphine-naloxone, respectively, any time in the past 6 months were 26% (95% CI 19-33%), 33% (25-40%) and 11% (6-16%). Corresponding percentages for injection at least one weekly were reported to be 12% (95% CI 4-12%), 18% (12-24%) and 5% (1-9%). These data generally represent injection by OST clients of their own medication, rather than diversion.

The findings are consistent with a PI claim that the combination of buprenorphine and naloxone is less commonly injected than buprenorphine alone. The sponsor's proposed wording of "less commonly and less frequently" presumably relates to the finding that a difference was seen for "any time" injection and "weekly or more often" injection, but without a comprehensive description of the study (which would not be appropriate), the proposed wording is confusing.

A noteworthy observation is that the inclusion of naloxone does not entirely deter intravenous injection. This is relevant because it means that consideration should be given to the potential consequences of the physical properties of the soluble films (for example, whether the physical properties of the soluble films make them easier or more difficult to disperse/dissolve, and whether they increase or decrease the risk of local thrombosis or distant embolism after injection).

Evaluator's overall conclusions on clinical safety

As noted above, Suboxone soluble films were <u>not</u> bioequivalent on all assessment parameters to Suboxone tablets after sublingual administration.

- The increased buprenorphine C_{max} that was seen with Suboxone 2/0.5 mg soluble film, compared to Suboxone 2/0.5 mg tablets, would be expected to lead to a small increase, on a population basis, in the incidence of adverse effects. The absence of comparative multiple dose safety data for the soluble films versus the tablets means that the exact magnitude of the increase is not known.

- The higher buprenorphine and naloxone bioavailability from Suboxone 8/2 mg soluble film would be expected to lead to a small increase in the incidence of adverse effects. Again, the absence of comparative multiple dose safety data for the soluble films versus the tablets means that the exact magnitude of the increase is not known.

The sponsor argues that although the bioavailability of Suboxone soluble films is higher than that of the tablets, it is nevertheless lower than that of the aqueous ethanolic solution on which a 'significant amount' of the safety and efficacy data in the original Suboxone tablet application was based. The sponsor states data in the original Suboxone tablet submission showed that the relative bioavailability of the solution compared to the 8/2 mg tablet was 1.52, and that this value was confirmed in later population PK analyses performed by the sponsor. Accordingly, the sponsor argues that the safety of Suboxone soluble films should be regarded as acceptable, on the basis of data generated with the ethanolic solution. However, the sponsor did not provide any summary of long term safety (or efficacy) data for the solution, and the TGA evaluation reports for Suboxone did not indicate to what extent the long term safety data were attributable to the solution rather than the tablets. Furthermore, any post-marketing safety data pertain to the tablets and not the solution. Overall, the sponsor has not provided sufficient information to allow acceptance of its assertion that adequate safety has been demonstrated for the solution and hence for the soluble films.

In patients who take *only* the soluble films, the increased bioavailability of the soluble films would be mitigated by the standard clinical practice of individualised dose titration. However, while this means that the soluble films would be potentially registrable (ignoring other objections), they are not interchangeable with the tablets. The difference in bioavailability means that patients who switch from the tablets to the soluble films at the same dose may experience a small increase in adverse effects. In the absence of comparative clinical data, it is unclear whether or not the difference would be clinically meaningful, particularly for the 8/2 mg strength.

In a 12-week open-label study RB-US-07-0001, conducted in subjects who had first been stabilised on Suboxone tablets, the incidence of TEAEs was much lower than, and the most common types of TEAEs different to, those that were seen in previously-submitted studies of Suboxone tablets. This difference is accounted for by the fact that the previous studies included the induction of subjects onto Suboxone therapy (a process that is commonly associated with a range of opioid withdrawal symptoms), whereas subjects in Study RB-US-07-0001 had already undergone that process before the start of adverse event data collection.

In a 5-day double-blind induction study RB-US-07-0002, in which opioid-dependent subjects were transferred from morphine to Suboxone or buprenorphine soluble films, the incidence and types of TEAEs were broadly similar to those seen in previously-submitted studies of Suboxone tablets. However, the study was too small to provide a meaningful comparison.

In an Australian post-marketing study, Suboxone was found to be injected less frequently than Subutex, and at about the same rate as methadone.

An additional safety consideration, relevant to intravenous abuse of the soluble films, is whether the physicochemical properties of soluble films (for example, the fact that the they form an adhesive gel when exposed to small amounts of water) mean that intravenous abuse of the soluble films is more or less practicable (for example, due to ease of dissolution), and more or less dangerous (for example, carrying a higher risk of local vascular damage or distant embolism) than intravenous abuse of the tablets.

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.

Safety

The sponsor should provide a justification for the inclusion of naloxone in the soluble film formulation. The justification should address the objection that the theoretical advantages of the soluble film in relation to diversion and compliance, which derive from the physicochemical properties of the soluble film formulation, are confined to the supervised administration setting and would appear to apply equally well (in that setting) to a buprenorphine-only soluble film formulation. This means that the soluble films do not satisfy one of the 'justification' prerequisites for a fixed-combination product, as set out in Section 1 of the TGA-adopted guideline *Fixed Combination Medicinal Products*.[9] To ensure that current Australian practices are taken into account, the justification should include input from the Australasian Chapter of Addiction Medicine of the Royal Australian College of Physicians.

Given the higher bioavailability of Suboxone soluble films compared to Suboxone tablets (particularly at the 8/2 mg strength), it is anticipated that the soluble films will be associated with a higher incidence of adverse events. The magnitude of the increase and the clinical significance have not been adequately defined due to a lack of studies that directly compare the soluble films and tablets during actual treatment. The sponsor has not provided sufficient information to allow acceptance of its assertion that adequate safety was demonstrated for an oral solution and hence for the less soluble films (which, although more bioavailable than the tablets are stated to be less bioavailable than the solution). To address this deficiency, the sponsor should provide further information regarding the safety data generated with the solution (including the number of patients treated, the treatment duration, and a summary of adverse events and laboratory findings in patients taking the solution). Alternatively, the sponsor could submit a clinical study that directly compares the safety of the two formulations during treatment with the recommended doses, over a sufficient period (for example, 12 weeks) and enrolling a sufficient number of subjects to determine that magnitude of the difference and its clinical significance.

The sponsor should provide information as to whether the physicochemical properties of soluble films (for example, the fact that the they form an adhesive gel when exposed to small amounts of water) mean that intravenous abuse of the soluble films is more or less practicable (for example, due to ease of dissolution), and more or less dangerous (for example, carrying a higher risk of local vascular damage or distant embolism) than intravenous abuse of the tablets.

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

The 2/0.5 mg sublingual soluble film was bioequivalent to the 2/0.5 mg sublingual tablet in most respects, with the notable exception that the C_{max} of buprenorphine was 22% higher after administration of the soluble film than after the tablet in Study 20-250-SA (but not in

[9] EMEA, Committee for Medicinal Products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products. EMEA/CHMP/SWP/258498/2005.

Study 20-272-SA). The percentage difference in buprenorphine C_{max} would be less at steady state.

The 8/2 mg sublingual soluble film was clearly more bioavailable than the corresponding sublingual tablet, with higher C_{max}, AUC_{last} and AUC_{∞} of buprenorphine and naloxone. The increased bioavailability of naloxone would be most apparent when the soluble films are fresh, and would gradually be offset by the reduction in naloxone content of the soluble films that is seen during storage.

The sponsor submitted a population PK analysis based on data from the five main PK studies. It concluded that the higher naloxone bioavailability from the 8/2 mg soluble films is unlikely to precipitate withdrawal in patients taking the product in the recommended dose range.

Pharmacodynamics

A previously-submitted study showed that (a) the propensity of buprenorphine:naloxone combinations to produce withdrawal effects decreases as the ratio of buprenorphine to naloxone increases, but (b) the approval of a different limit for naloxone at expiry of Suboxone soluble films is likely to lead to only a small reduction (compared to fresh soluble films) in their propensity to produce withdrawal symptoms after intravenous injection.

Clinical efficacy

The efficacy of Suboxone soluble films must be extrapolated from that of Suboxone tablets, based on the bioavailability comparison of the two dose forms.

Compared to the 2/0.5 mg tablet, a single sublingual dose of the 2/0.5 mg soluble film produced equivalent systemic exposure to buprenorphine and naloxone, and a 22% higher peak concentration of buprenorphine. Accordingly, the efficacy of the 2/0.5 mg soluble film should be at least equivalent to that of the tablet, both after a single dose and during chronic use.

Compared to the 8/2 mg tablet, a single sublingual dose of the 8/2 mg soluble film produced 20% higher systemic buprenorphine exposure and 28% higher peak buprenorphine concentration. This was accompanied by a 21% increase in naloxone exposure and a 41% increase in naloxone peak concentration. Naloxone concentrations remained about 60% below levels that would be expected to produce frank withdrawal symptoms, but it is not clear to what extent the increased naloxone concentrations would offset the increased buprenorphine concentrations, in terms of efficacy. Overall, the PK data do not permit a firm conclusion that the efficacy of Suboxone 8/2 mg wafers will be equivalent to, or better than, the efficacy of Suboxone 8/2 mg sublingual tablets. This does not necessarily preclude registration, since (a) the increase in naloxone concentrations is similar to the increase in buprenorphine concentrations and the opposing effects of the two differences should approximately cancel each other out, and (b) the standard practice of individual titration to effect would account for any reduced or increased efficacy of the 8/2 mg soluble films. However, the inability to firmly conclude that the tablets and soluble films have equivalent efficacy means that the two formulations should not be regarded as interchangeable.

Clinical safety

In a 12-week open-label study RB-US-07-0001, conducted in subjects who had first been stabilised on Suboxone tablets, the incidence of TEAEs was much lower than, and the most common types of TEAEs different to, those that were seen in previously-submitted studies of Suboxone tablets. This difference is accounted for by the fact that the previous studies included the induction of subjects onto Suboxone therapy (a process that is commonly

associated with a range of opioid withdrawal symptoms), whereas subjects in Study RB-US-07-0001 had already undergone that process before the start of adverse event data collection.

In a 5-day double-blind induction study RB-US-07-0002, in which opioid-dependent subjects were transferred from morphine to Suboxone or buprenorphine soluble films, the incidence and types of TEAEs were broadly similar to those seen in previously-submitted studies of Suboxone tablets. However, the study was too small to provide a meaningful comparison.

Benefit risk assessment

Benefits

The following benefits of Suboxone soluble films were identified in the clinical data:

Efficacy in the treatment of opiate dependence.

Compared to the 2/0.5 mg tablet, a single sublingual dose of the 2/0.5 mg soluble film produced equivalent systemic exposure to buprenorphine and naloxone, and a 22% higher peak concentration of buprenorphine. Accordingly, the efficacy of the 2/0.5 mg soluble film should be at least equivalent to that of the tablet, both after a single dose and during chronic use.

Compared to the 8/2 mg tablet, a single sublingual dose of the 8/2 mg soluble film produced 20% higher systemic buprenorphine exposure and 28% higher peak buprenorphine concentration. This was accompanied by a 21% increase in naloxone exposure and a 41% increase in naloxone peak concentration. Naloxone concentrations remained about 60% below levels that would be expected to produce frank withdrawal symptoms but it is not clear to what extent the increased naloxone concentrations would offset the increased buprenorphine concentrations, in terms of efficacy. Overall, the PK data do not permit a firm conclusion that the efficacy of Suboxone 8/2 mg soluble films will be equivalent to, or better than, the efficacy of Suboxone 8/2 mg sublingual tablets. This does not necessarily preclude registration, since (a) the increase in naloxone concentrations is similar to the increase in buprenorphine concentrations and the opposing effects of the two differences should approximately cancel each other out, and (b) the standard practice of individual titration to effect would account for any reduced or increased efficacy of the 8/2 mg soluble films. However, the inability to firmly conclude that the tablets and soluble films have equivalent efficacy means that the two formulations should not be regarded as interchangeable.

Potential for improved compliance

State and Territory policies regarding opioid substitution therapy require clients to attend for supervised dosing when using Suboxone. Stable clients who satisfy certain criteria are allowed takeaway doses of Suboxone, but unsupervised administration for periods of a week or more is allowed only for low risk clients who have been stable on supervised treatment for many months. The faster disintegration of Suboxone soluble films compared to Suboxone tablets at the 8/2 mg strength means that in the context of supervised administration of that strength, patients may have to remain at the dispensing site for as long, while waiting for the dose to disintegrate. This has the theoretical potential to improve compliance but no studies were performed to confirm this conjecture.

It is worth noting that the sponsor has already registered, but chosen not to market, a rapidly-dissolving buprenorphine monotherapy sublingual tablet (Subutex FDT 8 mg and 16 mg). Subutex FDT would presumably have a similar theoretical compliance advantage in the context of supervised administration but would be unsuitable for takeaway dosing due to the absence of naloxone.

Risks

The following risks associated with Suboxone soluble films were identified in the clinical data:

Adverse events due to the buprenorphine component of the soluble films

The presence of buprenorphine in Suboxone soluble films (and tablets) is clearly associated with a significant incidence of buprenorphine-related adverse events. The increased bioavailability of buprenorphine from Suboxone soluble films compared to Suboxone tablets, most notably for the 8/2 mg strength, means that a small increase in the incidence and/or severity of buprenorphine-related adverse events may be anticipated when patients are switched from the tablets to the soluble films at the same dose. The absence of suitable comparative clinical data means that the magnitude and the clinical relevance of the increase have not been determined. Adverse event data from the PK studies suggest that the increase might be significant after single doses but the clinical relevance of this finding is unclear because the subjects were not opioid-tolerant. The sponsor has argued that the increased bioavailability of buprenorphine from the soluble films does not represent a safety concern, based on data generated with an even more bioavailable oral solution, but did not provide sufficient information to allow acceptance of this assertion.

Adverse events due to the naloxone component of the soluble films

The presence of naloxone in Suboxone soluble films and tablets is expected to be associated with a small incidence of adverse events. The data do not allow quantification of the proportion of adverse events that were due to the naloxone component of the soluble films. No excess of adverse events was evident in the Suboxone soluble film group compared to the buprenorphine monotherapy soluble film group in the PK studies. However, this finding does not negate the possibility of naloxone-related adverse events during chronic use of the soluble films because (a) the subjects received only single doses; (b) their lack of opioid tolerance, combined with the higher bioavailability of buprenorphine from the soluble film formulation, led to a high incidence of buprenorphine-related adverse events that would have swamped any small contribution from naloxone-related adverse events. The sponsor has argued that the increased bioavailability of naloxone from the soluble films does not represent a safety concern, based on data generated with an even more bioavailable oral solution, but did not provide sufficient information to allow acceptance of this assertion.

It is relevant to note that the justification for inclusion of naloxone in these fixed-combination products only applies in the context of unsupervised administration. In the context of supervised administration (the very reason for the soluble film formulation) the naloxone component does not serve any useful purpose.

Diversion and intravenous abuse

As is the case for all opioid-containing products, there is a risk of diversion and intravenous abuse of Suboxone soluble films. The rapid adhesion of the soluble films to the oral mucosa and faster in vivo disintegration compared to Suboxone tablets (at the 8/2 mg strength), mean that in the supervised administration setting, diversion and intravenous abuse of the soluble films should be reduced compared to the tablets.

Safety specification

Comments on the clinical part of the Safety Specification

The clinical part of the Safety Specification of the Risk Management Plan is unsatisfactory. It focuses almost entirely on fatal overdose and diversion, and presents almost no information

on other safety issues. Other adverse events associated with the use of Suboxone are not mentioned at all. Brief mention is made of "possible interactions with known inhibitors and inducers of CYP 3A4", with a cross-reference to the PI, but specific information is not documented in the Safety Specification.

Balance

The evaluator concluded that the sponsor has failed to demonstrate a favourable benefit-risk balance for Suboxone soluble films:

- The naloxone component of Suboxone soluble films is expected to contribute additional adverse events compared to a buprenorphine-only product, and the Sponsor has not provided an adequate justification for its presence in the soluble film formulation.
  - When Suboxone tablets were registered, these additional adverse events were considered to be balanced by the potential benefit to the patient of not having to take each dose under direct supervision. The TGA files show that when registration of Suboxone was first sought, ADEC and the TGA Delegate objected to registration on the grounds that the naloxone component of the tablet provided no benefit to the patient who takes the product, while exposing them to the risk of naloxone-related adverse effects. Suboxone was only approved at appeal on the basis that the naloxone component of the tablet would allow patients to be provided with a takeaway supply of medication without increasing the risk of diversion, thus freeing the patient from daily attendance at a pharmacy or clinic (with its associated stigmatisation and adverse impact on compliance and employment).
  - However, the two main justifications for introducing the soluble film formulation are (a) to further reduce the risk of diversion and (b) to improve compliance by reducing the time that patients have to remain at the dispensary while waiting for the dose to disintegrate. Both of these purported advantages (which have not been empirically demonstrated) apply *only* in the context of *supervised* administration. In this context, a buprenorphine monotherapy soluble film would offer the same advantages and a fixed combination buprenorphine-naloxone soluble film does not provide any additional benefit.
  - Accordingly, one of the two 'justification' prerequisites for a fixed-combination product, as set out in Section 1 of the TGA-adopted guideline *Fixed Combination Medicinal Products*, has not been met.
- The increased bioavailability of buprenorphine from Suboxone soluble films compared to Suboxone tablets, most notably for the 8/2 mg strength, means that a small increase in the incidence and/or severity of buprenorphine-related adverse events may be anticipated when patients are switched from the tablets to the soluble films at the same dose. The absence of suitable comparative clinical data means that the magnitude and the clinical relevance of the increase have not been demonstrated. The sponsor argued that the increased bioavailability of buprenorphine from the soluble films does not represent a safety concern, based on data generated with an even more bioavailable oral solution, but did not provide sufficient information to allow acceptance of this assertion.
- The increased bioavailability of naloxone from Suboxone soluble films compared to Suboxone tablets at the 8/2 mg strength (when the soluble films are fresh), means that a small increase in the incidence and/or severity of naloxone-related adverse events may be anticipated when patients are switched from the tablets to the soluble films at the same dose. The absence of suitable comparative clinical data means that the magnitude and the clinical relevance of the increase have not been demonstrated. The sponsor argued that

the increased bioavailability of naloxone from the soluble films does not represent a safety concern, based on data generated with an even more bioavailable oral solution, but did not provide sufficient information to allow acceptance of this assertion.

- The sponsor has argued that because each soluble film is packaged individually in a child-resistant laminate sachet, this should reduce the risk of unintended exposure in children compared to Suboxone tablets (although only where the patient is allowed to take a supply of the medication home for self-administration). However, if it is truly the case that the child resistance of the current sublingual tablet packaging is inferior to that of the proposed soluble film packaging, then this is an argument for improving the tablet packaging, rather than a valid rationale for registering an entirely new formulation.
- Beyond the clinical data, the instability of naloxone in the soluble film formulation (leading to higher levels of naloxone degradant which have not, as yet, been toxicologically qualified) also contributes to an unfavourable benefit-risk assessment.

Conclusions

Approval of the submission to register Suboxone soluble films containing a fixed combination of buprenorphine 2 mg / naloxone 0.5 mg, or buprenorphine 8 mg / naloxone 2 mg was not recommended, due to failure to demonstrate a favourable benefit-risk balance.

Should the Delegate decide to approve registration, a post-marketing study examining the abuse of Suboxone soluble films in an Australian context would be advisable, corresponding to the study that has been performed for Suboxone sublingual tablets.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The sponsor has noted the following safety concerns and proposed the following activities in the RMP dated June 2010:[10]

[10] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Safety concern	Pharmacovigilance Plan activities	Risk Minimisation Activities
Fatal Overdose	Routine pharmacovigilance	Field force, HCP and patient education
Misuse, Abuse and Diversion	Routine pharmacovigilance Post-marketing study	Field force, HCP and patient education
Hepatitis, Hepatic Adverse Events	Routine pharmacovigilance	HCP and patient education
Drug Withdrawal Syndrome	Routine pharmacovigilance	HCP and patient education
Drug Dependence	Routine pharmacovigilance	Field force, HCP and patient education
CNS Depression (effects on driving ability)	Routine pharmacovigilance	HCP and patient education
Allergic Reactions	Routine pharmacovigilance	HCP and patient education
Use in Pregnancy/Lactation and Drug Withdrawal Syndrome Neonatal	Contraindication in PI and all Labeling	Field force, HCP education

The post-marketing surveillance study referred to in the RMP was a condition of registration for Suboxone sublingual tablets. It was agreed with the TGA that an independent study be conducted into the extent of diversion and misuse of buprenorphine/naloxone. This 3-year study was initiated in 2006 and is now complete and referred to earlier in this document.[7] The sponsor reported that it concludes Suboxone tablets appear to be less frequently injected than methadone or buprenorphine alone.

Based on the theoretical considerations of the product composition and a series of injection safety studies, the sponsor reports that there is no indication that injecting solutions of Suboxone Sublingual Soluble Film carries more risk that injecting the corresponding solution of Suboxone sublingual tablets. The Suboxone Sublingual Soluble Film utilises the same 4 to 1 buprenorphine to naloxone ratio and dosing as the Suboxone sublingual tablet and is anticipated to maintain the trend towards reduced diversion compared to Subutex in Australia. In no way was the Suboxone Sublingual Soluble film was developed to offer a safer, more easily injected product, however, the minimisation of injection harm has not been overlooked in the development, as adverse events related to injection use of buprenorphine products have been noted and are monitored by the sponsor.

The sponsor reported that safety risk management is not new to buprenorphine treatment. A number of measures affecting all areas of the healthcare system involved in their distribution, prescription and dispensing are currently implemented.

Risk minimisation activities already in place for buprenorphine in the treatment of opioid dependence include the following three pronged approach for addressing the identified risks:[11]

1. Pharmacist, physician and patient education

[11] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

2. Targeted and monitored product distribution and sales
3. Active and passive surveillance for diversion, abuse and unintentional paediatric exposure to help target follow up risk mitigation actions

Additionally, in an effort to minimise risks associated with paediatric exposure of these products, the range is enhanced with the unit dose, child-resistant packaging of the Suboxone Sublingual Soluble Film.

The sponsor considered routine pharmacovigilance activities enable the monitoring of the safety concerns of this treatment. However, the OMSM evaluator noted that data from spontaneous adverse drug reactions (ADRs) are unlikely to be sufficient in measuring the effectiveness of these proposed additional risk minimisation activities. This is due to the under-reporting and the lack of reliable exposure (usage) data associated with spontaneous reporting systems, not to mention the information gained from adverse reaction reporting is often incomplete. In relation to Misuse, Abuse and Diversion the sponsor acknowledged that its effectiveness is limited by the undercover nature of the safety concern.

OMSM Recommendations

The sponsor has now provided a justification and submitted data in support of the claim that there is no indication that injecting solutions of Suboxone Sublingual Soluble Film carries more risk that injecting the corresponding solution of Suboxone sublingual tablets. The Suboxone Sublingual Film utilises the same 4 to 1 buprenorphine to naloxone ratio and dosing as the Suboxone sublingual tablet and is anticipated by the sponsor to maintain the trend towards reduced diversion compared to Subutex in Australia.

Consequently it would appear that the introduction of this new dosage form does not adversely affect the risk-benefit or safety profile of this medicine.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The soluble films are manufactured by a process that involves coating a suspension of buprenorphine hydrochloride in an aqueous solution of the excipients and naloxone hydrochloride onto a polyester sheet, drying, printing the resulting soluble film with white ink, separation of the soluble film from the polyester substrate, cutting into the required soluble films, heat-sealing within pouches (sachets) and packaging. The excipients comply with relevant standards.

The initial pharmaceutical chemistry evaluation recommended rejection of this submission because of the extreme instability of naloxone in this dosage form. It was noted that naloxone degrades rapidly to a large number of and high levels of impurities, whereas naloxone is relatively stable in the sublingual tablet.

This submission was discussed at the 130th PSC meeting in January 2010. The committee supported the quality evaluator and issued the following recommendation:

The PSC was unable to recommend approval for registration on pharmaceutic and biopharmaceutic due to the significant deficiencies in the data provided in support of the submission. In particular, the Committee raised concerns about the extreme instability and rapid rate of degradation of naloxone in the proposed formulation compared to the currently registered sublingual tablet formulation.

The PSC endorsed the quality evaluator's conclusion that, in view of the extensive degradation of naloxone in the soluble films compared to the registered sublingual tablets, compliant patients taking the soluble films would be exposed to unnecessary additional risks with no concomitant benefit, as naloxone is only present as an abuse deterrent.

Subsequent to the PSC consideration of Suboxone, the sponsor provided satisfactory responses to questions raised by the quality evaluator. These responses included additional stability data. In response to concerns about the extent of naloxone degradation during storage, the release limit for naloxone assay has been tightened. This now allows a decrease in assay of up to 10% during storage. The shelf-life of 12 months is acceptable provided the storage temperature is reduced from 30ºC to 25ºC. Revised specifications for the finished products have been accepted by the quality evaluator. In addition to a tightening of the release limits for naloxone, release and expiry limits for buprenorphine have been tightened, as have the limits for many of the specified impurities. The revised specifications are satisfactory.

Another issue of concern to the quality evaluator was the effect of food or drink on the pharmacokinetics of buprenorphine and naloxone. Two bioavailability studies were evaluated in detail.

Study 20-250-SA compared single doses of the 2/0.5 mg soluble film with the 2/0.5 mg sublingual tablet. The results showed that:

- The bioavailability of buprenorphine from the soluble films was significantly greater than from the sublingual tablets; AUC and C_{max} increased by 16% (not significant) and 22% respectively.
- The bioavailability of naloxone from the wafers was also significantly greater than from the sublingual tablets; AUC and C_{max} increased by 2% and 4% respectively.
- There was no significant difference between sublingual tablets and films with regard to plasma levels of naloxone, or of norbuprenorphine, the major metabolite of buprenorphine.

Study 20-273-SA compared single doses of the 8/2 mg soluble film with the 8/2 mg sublingual tablet. The results showed that:

- The bioavailability of buprenorphine from the soluble films was significantly greater than from the sublingual tablets; AUC and C_{max} increased by 20% and 28% respectively.
- The bioavailability of naloxone from the soluble films was also significantly greater than from the sublingual tablets; AUC and C_{max} increased by 30% and 41% respectively.
- There was no significant difference with regard to plasma levels of norbuprenorphine.

The PSC endorsed the evaluator's request that the sponsor should provide information on the time period between administration of the soluble films and consumption of the glass of water for the above comparative bioavailability studies. The sponsor responded that in these studies a glass of water was administered upon verification of dissolution of the study medication. Accordingly it proposes to add to the PI the following instruction: *No food or drink should be consumed until the soluble film is completely dissolved.*

Nonclinical

There were no nonclinical objections to registration of this new formulation.

The nonclinical evaluation concerned assessment of the proposed specification limits for impurities for Suboxone Sublingual Film. The nonclinical evaluator noted that the proposed release and expiry specifications for Suboxone Sublingual Film are derived from the current US specifications for Suboxone sublingual tablets and are less stringent than the corresponding Australian specifications for Suboxone sublingual tablets. The sponsor sought to have the specifications for Suboxone Sublingual Film aligned with the US specifications for Suboxone sublingual tablets, with the exception of the naloxone impurity (impurity II) which has a lower specification limit for the tablet in the US but a higher proposed limit for the Suboxone Sublingual Film. This limit has been previously qualified.

The US tablets are packed in an HDPE bottle with desiccant while the Australian tablets are packed in aluminium coldform blisters filled under a controlled atmosphere, giving a highly stable product with narrower assay limits than the US tablets. For Suboxone Sublingual Film, packing under those conditions is not possible, and, based on the stability performance of the sublingual soluble film, the sponsor seeks specifications aligned with those approved in the US for Suboxone sublingual tablets.

The nonclinical studies submitted to qualify the proposed specification limits had been previously evaluated by the TGA.

Clinical

Six open-label and one double-blind clinical studies were submitted, five were bioavailability studies that were also evaluated by the quality evaluator and have been considered by the PSC. As noted previously the wafer is not bioequivalent to the same dose in the sublingual tablet formulation, with higher C_{max} and AUC for both buprenorphine and naloxone from the wafer formulation. Differences were greater with the 8/ 2 mg wafer than with the 2/ 0.5 mg wafer but bioavailability and C_{max} for buprenorphine and naloxone was greater than in the corresponding sublingual tablets for both strengths of the proposed wafer formulation.

The clinical evaluator considered whether the higher C_{max} for naloxone could result in withdrawal symptoms after sublingual administration of Suboxone Sublingual Soluble Film and was satisfied that this would not occur with current maximum recommended doses. It was noted that there was a wide CV, indicative of wide variability in the sublingual absorption of buprenorphine and naloxone. It could not be determined if there would also be wide intra-subject variability as the CV was examined in single dose studies.

The evaluator considered whether the reduction in naloxone content would result in a reduction in the deterrent effect of naloxone and concluded that this is likely to lead to only a small reduction (compared to fresh soluble films) in their propensity to produce withdrawal symptoms after intravenous injection.

No new efficacy studies were submitted with efficacy dependent on acceptance of the previously demonstrated efficacy of the sublingual tablets.

Two safety studies were evaluated and these were discussed by the clinical evaluator. Study -0001 was an open, randomised study of 382 otherwise healthy, opioid-dependent adults who had been on maintenance therapy with Suboxone sublingual tablets for at least 30 days. This study was intended primarily to assess the effect on the oral mucosa of the soluble films after sublingual or buccal administration for 12 weeks.

Study RB-US-07-0002 was a double-blind, randomised trial comparing an unregistered buprenorphine soluble film with Suboxone Sublingual Soluble Film. Only 18 subjects received Suboxone Sublingual Film for a maximum period of 5 days.

There were no new safety issues arising in subjects given Suboxone Sublingual Film. Oral mucosa erythema was reported in 8 (2.1%) of subjects in study -0001. This was the most frequently reported oral cavity TEAE. It was more frequent in subjects taking Suboxone Sublingual Film sublingually, rather than buccally (1% vs 3.2%). Toothache was reported by six (1.2%) subjects and was again more frequent in subjects taking sublingual rather than buccal Suboxone Sublingual Film.

There were no deaths in studies of Suboxone Sublingual Film. Seven serious TEAEs were reported in 6 subjects. None were considered related to study drug.

An interim report of an Australian post-marketing study was discussed by the clinical evaluator.[7] This study considered the self-reported frequency of intravenous injection of methadone, buprenorphine only and buprenorphine/ naloxone among intravenous drug users in Australian capital cities between 2003 and 2008. It was reported that buprenorphine/ naloxone combination product had been injected by both individuals it had been dispensed to (as an oral product) and by individuals to whom it had been diverted. By 2007/2008 the buprenorphine/ naloxone combination product was approximately as likely as methadone to be injected (predominantly after diversion). In 2008 buprenorphine/ naloxone was the least likely of the three products to be injected by individuals to whom it had been dispensed (at least weekly injection was reported by 12%, 18% and 5% of methadone, buprenorphine and buprenorphine/ naloxone opioid substitution treatment clients.

Risk-Benefit Analysis

The soluble film formulation is not bioequivalent to the sublingual tablet. For a product that is dosed according to clinical response over a wide dose range this is not of concern provided individuals are not switched between the sublingual tablet and the soluble film without dose titration. If switching occurs the final dose of buprenorphine/ naloxone from the soluble films should be approximately 16- 20% less than that of the corresponding sublingual tablets, consistent with the differences in AUC for buprenorphine with these products. This should be reflected in the PI. Differences in AUC for naloxone will not influence dosing because the amount of naloxone entering the circulation from both products is not likely to have any clinical effect.

The clinical evaluator raised the issue of whether the proposed combination of buprenorphine and naloxone had been adequately justified according to the EMA requirements which have been adopted by the TGA.[9] Of particular concern was that the justification for inclusion of naloxone in the soluble film formulation was inadequate. The advantages of the combination are confined to the supervised administration setting and would appear to apply equally well (in that setting) to a buprenorphine-only soluble film formulation. The Delegate considered that the advantage of the combination has already been decided when Suboxone sublingual tablets were registered. The issue now is whether there is an advantage in the new dose form. New dose forms are not required to be re-justified according to the criteria of the above Fixed Combination guideline.

While is it likely this new formulation will be more difficult to divert this has not been “field tested”. Accordingly the sponsor should be requested to commit to seeking post-market data on the injection rate of this new formulation relative to the current formulation and other opioid substitution treatments.

The consequences of intravenous injection have not been adequately explored and the Delegate considered this the major unaddressed safety issue with this product. The sponsor was requested to address this issue following receipt of the clinical evaluation report. In

response the sponsor advised of four nonclinical toxicity studies currently underway. Submission of reports of these studies should be a condition of registration.

The Delegate proposed to approve registration of Suboxone Sublingual Soluble Film for the indication:

Treatment of opiate dependence within a framework of medical, social and psychological treatment.

The Delegate also proposed to require, as a condition of registration that the sponsor:

- submit post-market data on the relative injection rate of Suboxone Sublingual Film relative to Suboxone sublingual tablets and other opioid substitution treatments; and
- submit the nonclinical studies currently underway on the toxicity on injection of Suboxone Sublingual Film

The advice of the Advisory Committee on Prescription Medicines (ACPM) was requested particularly concerning:

- the form and desirability of the proposed post-market data on relative injection rates; and
- whether Suboxone Sublingual Film is an acceptable tradename for a product intended to be administered both buccally and sublingually.

The ACPM having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended rejection of the submission.

In making this recommendation, the ACPM advised that the product was not bioequivalent to the current sublingual tablet. Therefore, as efficacy and safety data was only presented for the sublingual tablet; and in the absence of a demonstration of bioequivalence, efficacy and safety data for this new dose form must be presented to support evaluation.

In addition, the ACPM expressed concern that while the new dosage form may have the potential to inhibit diversion in the clinical context of supervised administration, the data were inadequate to inform an appropriate assessment of its safety in the context of anticipated use as an intravenous injection. The ACPM advised that additional pre market studies will be required to determine an adequate risk benefit profile of the new dosage form.

Initial Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Suboxone Sublingual Film.

Final Outcome

Following the initial decision described above, the sponsor appealed under Section 60 of the Therapeutic Goods Act whereby a review of the initial decision was conducted by the Minister.

The Delegate of the Minister examined the data submitted in the submission prepared by the sponsor which accompanied its letter seeking a review of the initial decision. He also noted letters, received separately, directed to the Parliamentary Secretary from the Senior Medical Adviser (Alcohol and Drugs), Victorian Department of Health, dated 9 November 2010, and from an officer in Mental Health, Drug and Alcohol Programs, NSW Health, dated 4 November 2010, seeking to be joined in this appeal with the sponsor as "persons whose interest are affected by an initial decision" within the meeting of Sub-section 60(2) of the *Therapeutic Goods Act 1989*. While supporting the grounds for the appeal in the Statement of Appeal lodged by the sponsor both these correspondents emphasised the constraints

associated with the supervised administration of the Suboxone sublingual tablets and promoted the notion that a reduction of time needed to supervise dosing and, by implication reduce diversion of the treatment product by persons being treated for opioid dependence, will appeal to community pharmacists and might increase pharmacy engagement in service delivery of this pharmacotherapy for opioid dependence. A letter supporting this position from the Pharmacy Guild of Australia (NSW Branch), dated 10 November 2010, directed to the Delegate of Minister of Health was also received.

Before commenting on the sponsor's submission the Delegate of the Minister undertook a review of the Clinical Evaluation Report. In this report, it was noted, the clinical evaluator did not recommend the registration of Suboxone as the justification for inclusion of naloxone in the soluble film formulation was considered inadequate and assessed there was a failure to demonstrate a favourable benefit-risk balance.

The ratified minutes of the ACPM records the Delegate's view that the advantage of the combination had been decided when Suboxone sublingual tablets were registered and new dose forms did not require to be re-justified according to the criteria of the fixed combination guideline. The Delegate's proposed action was to approve Suboxone Sublingual Film for the treatment of opiate dependence within a framework of medical, social and psychological treatment. The recommendation included reference to reports of nonclinical studies then underway on the toxicity on injection of Suboxone Sublingual Film and other opioid substitution treatments which it was considered should be submitted together with various modifications to the Product Information as a condition of registration.

The ACPM did not support this view. The ACPM records that the data provided did not demonstrate bioequivalence of the registered sublingual tablet with the sublingual soluble film forms of Suboxone and that efficacy and safety data for the sublingual form had not been provided. The ACPM also considered there were insufficient data submitted to support the assertion that the sublingual soluble film would reduce diversion to intravenous use that occurs with the sublingual tablets and resolved to recommend rejection of the submission to register the new dose form of Suboxone. In deciding to reject approval for registration the Delegate also took into account the recommendation of the Pharmaceutical Subcommittee to endorse the view of the quality evaluator that the extensive degradation of the soluble films compared to the registered sublingual tablet would expose compliant patients to unnecessary additional risks with no concomitant benefit.

Since the meeting of the ACPM, the sponsor provided notification that, on 30 August 2010, Suboxone Sublingual Film has received initial risk evaluation and mitigation strategy (REMS) approval from the US Food and Drug Administration. The stated indications for use are the maintenance treatment of opioid dependence and should be used as part of a complete treatment plan to include counselling and psychosocial support.

The sponsor's appeal submission provides a section outlining the Public Health Context in which it promotes the advantages of a consistently fast dissolving formulation of Suboxone Sublingual Film and then focuses directly on the Delegate's three reasons for the rejection of the application, namely:

1. The formulation of the soluble film results in increased instability of naloxone compared to the registered sublingual tablets. This has the potential to result in compliant patients taking Suboxone Sublingual Film being exposed to unnecessary additional risks from exposure to naloxone breakdown products with no concomitant benefit, as naloxone is only present as an abuse deterrent.

This issue was not included as a ground for rejection in the ACPM Resolution. The only reference to this matter recorded in the ACPM minutes is the concerns raised by the Pharmaceutic Subcommittee at its 130th meeting. In the Delegate's request for ACPM advice it was noted that subsequent to the PSC consideration of Suboxone Sublingual Film the sponsor had provided satisfactory responses to questions raised by the quality evaluator and, specifically, the Delegate stated that:

"*There are no nonclinical objections to registration of this new formulation"* and,

"The revised specifications are satisfactory".

In the absence of additional evidence to support this change in the Delegate's view and the comprehensive and persuasive information provided in the sponsor's appeal submission to support this position it is not considered reasonable to include the initial concern relating to the stability of the new formulation as a basis for rejection of approval for registration.

2. *The sublingual soluble film is not bioequivalent with the sublingual tablet formulation though it depended on the demonstration of safety and efficacy of the sublingual tablet as evidence of safety and efficacy of the sublingual soluble film. In the absence of a demonstration of bioequivalence, efficacy data for this new dose form are required to support the new product.*

Although the sponsor concedes bioequivalence between Suboxone sublingual tablet and soluble film with regard to buprenorphine exposure was not demonstrated in the studies conducted for all pharmacokinetic parameters, in all cases the exposure parameters were slightly higher for the soluble film compared to the tablet, the sponsor does contend that the relative exposure differences between the soluble film and tablet were not large. This difference, it is proffered in a statement by a clinical expert, can readily be handled within the context of routine clinical practice given an appropriate warning about the difference.

The Delegate of the Minister agreed with the view that efficacy and safety data for Suboxone have been established across a range of doses, and that the safety and efficacy profile for any given dose of Suboxone Soluble Film will be the same as a Suboxone tablet dose 1.2 times higher than the Suboxone Soluble Film dose while the data from study RB-US-07-0001 to indicate that dosage adjustments were generally not required supports the view that this difference in bioequivalence between the two formulations of sublingually administered formulations of Suboxone can be effectively managed in the clinical context.

As the product is intended to be dosed according to clinical response the differences noted in the AUC for both buprenorphine and naloxone is unlikely to be associated with significantly different clinical effects. In the pre-ACPM discussions a practical solution was offered seeking agreement to add a statement in the Dosage and Administration of the Product Information:

"Suboxone Sublingual Film and Suboxone sublingual tablet do not meet all criteria for bioequivalence (see section Pharmacokinetics). Patients being switched between tablets and soluble films may therefore require dosage adjustment."

With this qualification, the Delegate of the Minister agreed there was sufficient relevant efficacy and safety data from Suboxone sublingual tablets to indicate that the differences in bioequivalence and the consequent difference in the likely clinical effect are insufficient to justify the rejection of approval registration of Suboxone Sublingual Film.

3. *While it is acknowledged that the sublingual soluble film may have the potential to inhibit diversion in the clinical context of supervised administration, the data were inadequate to inform an appropriate assessment of its safety in the context of anticipated misuse as an*

intravenous injection. This safety concern requires additional study to determine if the risk benefit profile for this new dose form is acceptable".

The Delegate of the Minister agreed with the sponsor's view that attempts to investigate, in a human population, the potential harmful effects of injection of these products are constrained by the ethics of performing experiments injecting suspensions of solids and medication that are not formulated for intravenous administration even though the non-compliant opioid abuser may themselves take the risk of injecting suspensions or modifications of the products. The possible harmful effects of these aberrant practices, in the view of the Delegate of the Minister, can only be satisfactorily assessed through post market surveillance by the program administering the pharmacotherapy.

Data provided from nonclinical studies in rats demonstrated the absence of any local injection site reaction or lasting effects of systemic toxicity of formulations of sublingual tablets or sublingual soluble film administered by the intravenous route.

The strategy of supervised administration of these products in a comprehensive clinical program does offer the potential outcome of reducing the likelihood of diversion to the non-compliant administration of these products by patients being treated for opioid dependence. A constraint on supervision of the administration of Suboxone sublingual tablets, it has been identified, is the time to dissolution and the possibility of concealment of the tablet which later is diverted to intravenous injection. The theoretical and practical advantages offered by the use of the faster dissolving Suboxone Sublingual Film to assist in a more effectively supervised administration of this pharmacotherapy is supported in the attachment of papers from the professional experts noted above.

The Delegate of the Minister decided to revoke the initial decision. The final decision was:

Suboxone Sublingual Film containing buprenorphine 2 mg plus naloxone 0.5 mg and buprenorphine 8 mg plus naloxone 2 mg may be registered in Australia for:

Treatment of opiate dependence within a framework of medical, social and psychological treatment.

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.

SUBOXONE® SUBLINGUAL FILM

buprenorphine + naloxone 2mg/0.5mg and 8mg/2mg Soluble Film

PRODUCT INFORMATION

NAME OF THE MEDICINE

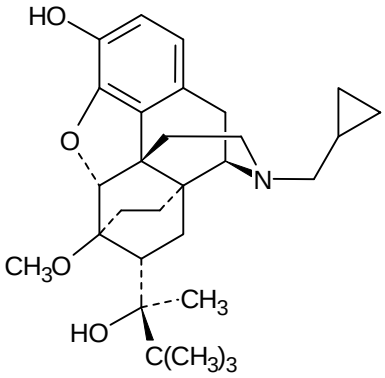
SUBOXONE SUBLINGUAL FILM contains buprenorphine hydrochloride and naloxone hydrochloride at a ratio of 4:1 buprenorphine : naloxone.

DESCRIPTION

SUBOXONE SUBLINGUAL FILM is a soluble film intended for sublingual administration. It is available in two dosage strengths, 2mg buprenorphine + 0.5mg naloxone and 8mg buprenorphine + 2mg naloxone. Each soluble film also contains acesulfame potassium, citric acid anhydrous, maltitol solution, hypromellose, polyethylene oxide, sodium citrate anhydrous, lime flavour, Sunset Yellow FCF and a white printing ink.

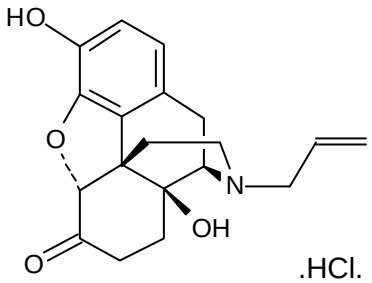
Buprenorphine hydrochloride is a white powder, weakly acidic with limited solubility in water (19.5 mg /mL at 37°C, pH 4.1). Chemically, it is 21- Cyclopropyl-7α-[(S) -1- hydroxy-1, 2, 2 - trimethylpropyl]-6, 14-endo-ethano-6, 7, 8, 14-tetrahydrooripavine hydrochloride. Buprenorphine hydrochloride has the molecular formula $C_{29}H_{41}NO_4$ HCl and the molecular weight is 504.09. The CAS number is 53152-21-9.

Naloxone hydrochloride is a white to slightly off-white powder that exists as the dihydrate and is soluble in water, in dilute acids and in strong alkali. Chemically, it is (-)-17-Allyl-4, 5α-epoxy-3, 14-dihydroxymorphinan-6-one hydrochloride dihydrate. Naloxone hydrochloride has the molecular formula $C_{19}H_{21}NO_4$ HCl .$2H_2O$ and the molecular weight is 399.87. The CAS number of naloxone hydrochloride dihydrate is 51481-60-8. The chemical structures of buprenorphine hydrochloride and naloxone hydrochloride dihydrate are:



.HCl

Buprenorphine hydrochloride



.HCl. $2H_2O$

Naloxone hydrochloride dihydrate

PHARMACOLOGY

Pharmacodynamic properties

Buprenorphine is a μ (mu) opioid receptor partial agonist, κ (kappa) opioid receptor antagonist. Its activity in opioid maintenance treatment is attributed to its slow dissociation from the μ receptors in the brain which reduces craving for opioids and opioid withdrawal symptoms. This minimises the need of the addicted patient for illicit opiate drugs.

During clinical pharmacology studies in opiate-dependent subjects, buprenorphine demonstrated a ceiling effect on a number of parameters, including positive mood, “good effect”, and respiratory depression.

Naloxone is an antagonist at μ (mu) opioid receptors. Because of its almost complete first pass metabolism, naloxone administered orally or sublingually has no detectable pharmacological activity. However, when administered intravenously to opiate dependent persons, the presence of naloxone in SUBOXONE SUBLINGUAL FILM produces marked opiate antagonist effects and opiate withdrawal, thereby deterring intravenous abuse.

Pharmacokinetic properties

Absorption

When taken orally, buprenorphine undergoes first-pass metabolism with N-dealkylation and glucuronidation in the small intestine and the liver. The use of SUBOXONE SUBLINGUAL FILM by the oral route is therefore inappropriate. SUBOXONE SUBLINGUAL FILMS are for sublingual administration.

Table 1 shows the pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after administration of SUBOXONE SUBLINGUAL FILM in randomised, crossover studies. For the 2/0.5 mg soluble film (Study 20-250-SA), the film to tablet ratio of geometric means are ln C_{max} 121.66 % (90% CI 112.62 - 131.43), ln AUC_{last} 116.40% (90% CI 108.70 - 124.63), and ln AUC_{inf} 114.22% (90% CI 106.65 - 122.32). For the 8/2 mg soluble film, (Study 20-273-SA), the film to tablet ratios are ln C_{max} 127.80 (90% CI 116.11 - 140.66), ln AUC_{last} 120.15 (90% CI 110.24 - 130.96), and ln AUC_{inf} 119.51 (90% CI 110.28 - 129.51).. Overall, there was wide variability in the sublingual absorption of buprenorphine and naloxone. Suboxone Sublingual Film and Suboxone Sublingual Tablet do not meet all criteria for bioequivalence. Patients being switched between tablets and soluble films may therefore require dosage adjustment (see Dosage and Administration).

Table 1.	**Pharmacokinetic parameters of buprenorphine, norbuprenorphine, and naloxone after sublingual administration of SUBOXONE SUBLINGUAL FILM**					
Dose	**Analyte**	**Study**	**C_{max} (ng/mL) Mean, (CV%)**	**T_{max} (h) Median, (min-max)**	**AUC_{inf} (h*ng/mL) Mean (CV%)**	**$t_{1/2}$ (h) (Mean, CV%)**
2 mg/ 0.5 mg	Buprenorphine	250-SA	0.947 (40%)	1.53 (0.75 - 1.53)	8.65 (33%)	33.4 (39%)
	Norbuprenorphine	250-SA	0.312 (45%)	1.38 (0.5 - 8.0)	14.5 (40%)	56.1 (56%)
	Naloxone[a]	250-SA	54.1 (42%)	0.75 (0.5 - 2.0)	137 (31%)	5.00 (110%)
8 mg/ 2 mg	Buprenorphine	273-SA	3.37 (53%)	1.25 (0.75 - 4.0)	30.5 (43%)	32.8 (30%)
	Norbuprenorphine	273-SA	1.40 (78%)	1.25 (0.75 - 12.0)	54.9 (66%)	42.0 (43%)
	Naloxone[a]	273-SA	193 (47%)	0.75 (0.5 - 1.25)	481 (42%)	6.25 (50%)

[a] Naloxone C_{max} expressed as pg/mL. Naloxone AUC_{inf} expressed as h*pg/mL

Distribution

The absorption of buprenorphine is followed by a rapid distribution phase (distribution half-life of 2 to 5 hours). Following intravenous administration, naloxone is rapidly distributed (distribution half-life of around 4 minutes).

Buprenorphine is highly lipophilic which leads to rapid penetration of the blood-brain barrier. The drug is around 96% protein bound primarily to alpha and beta globulin. Naloxone is approximately 45% protein bound, primarily to albumin.

Metabolism and elimination

In animals and man buprenorphine is metabolised by Phase 1 (oxidative) and Phase 2 (conjugation) reactions. It is oxidatively metabolised by N-dealkylation to norbuprenorphine by CYP 3A4. In *in vitro* metabolic studies, addition of specific inhibitors of CYP 3A4 (e.g.

ketoconazole, gestodene, nifedipine, norfluoxetine, ritonavir) inhibited formation of norbuprenorphine (see also **PRECAUTIONS** and **Interactions with Other Medicines**). There was no indication of the involvement of CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 in the N-dealkylation of buprenorphine. Buprenorphine was a weak competitive inhibitor of CYP 2D6 and CYP 3A4. Norbuprenorphine is a μ (mu) agonist with weak intrinsic activity and is considered to be an inactive metabolite.

Naloxone undergoes direct glucuroconjugation to naloxone-3-glucuronide as well as N-dealkylation and reduction of the 6-oxo group.

Elimination of buprenorphine is bi- or tri-exponential, with a long terminal elimination phase (mean half-life of 34.6 hours, range 20.4-72.9 hours), due in part to re-absorption of buprenorphine after intestinal hydrolysis of the conjugated metabolite, and in part to the highly lipophilic nature of the molecule. Naloxone has a short elimination half-life (mean 1.1 hours, range 0.63-1.94 hours).

Buprenorphine is essentially eliminated in the faeces by biliary excretion of the glucuroconjugated metabolites (70%), the rest being eliminated in the urine. Naloxone is excreted in the urine.

Elderly: No pharmacokinetic data in elderly patients are available.

CLINICAL TRIALS
Efficacy of buprenorphine in combination with naloxone was demonstrated with SUBOXONE Tablets. No clinical efficacy studies have been conducted with SUBOXONE SUBLINGUAL FILM.

All trials used buprenorphine in conjunction with psychosocial counselling as part of a comprehensive addiction treatment program. There have been no clinical studies conducted to assess the efficacy of buprenorphine as the only component of treatment.

Clinical pharmacology studies on SUBOXONE tablets demonstrate an aversive effect if SUBOXONE tablets are misused by the injection route by opioid dependent patients.

INDICATIONS
Treatment of opiate dependence within a framework of medical, social and psychological treatment.

CONTRAINDICATIONS
Hypersensitivity to buprenorphine or naloxone or any other component of the soluble film.
Children less than 16 years of age.
Severe respiratory or hepatic insufficiency (Child-Pugh B or C).
Acute intoxication with alcohol or other CNS depressant.
Pregnancy.
Breastfeeding.

PRECAUTIONS
General: SUBOXONE SUBLINGUAL FILM should be administered with caution in elderly or debilitated patients and those with impairment of hepatic, pulmonary, or renal function; myxoedema or hypothyroidism, adrenal cortical insufficiency (eg Addison's disease); CNS depression or coma; toxic psychoses; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; or kyphoscoliosis.

Buprenorphine increases intracholedochal pressure as do other opiates. Therefore, caution should be exercised when SUBOXONE SUBLINGUAL FILM is to be administered to patients with dysfunction of the biliary tract.

As with other opioids, caution is advised in patients using buprenorphine and having:
- hypotension,

- prostatic hypertrophy and urethral stenosis.

As with other mu-opiate receptor agonists, the administration of SUBOXONE SUBLINGUAL FILM may obscure the diagnosis or clinical course of patients with acute abdominal conditions.

Respiratory Depression: SUBOXONE SUBLINGUAL FILM is intended for sublingual use only. Significant respiratory depression has been associated with buprenorphine, particularly by the intravenous route. A number of deaths have occurred when individuals have intravenously misused buprenorphine, usually with benzodiazepines concomitantly. Deaths have also been reported in association with concomitant administration of buprenorphine with other depressants such as alcohol or other opioids. Patients should be warned of the potential danger of the self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE SUBLINGUAL FILM.

In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

SUBOXONE SUBLINGUAL FILM should be used with caution in patients with compromised respiratory function (e.g., chronic obstructive pulmonary disease, cor pulmonale, decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression).

CNS Depression: Patients receiving SUBOXONE SUBLINGUAL FILM in the presence of other narcotic analgesics, general anaesthetics, benzodiazepines, phenothiazines, other tranquillisers, sedative/hypnotics, or other CNS depressants (including alcohol) may exhibit increased CNS depression. When such combined therapy is contemplated, reduction of the dose of one or both agents should be considered. SUBOXONE SUBLINGUAL FILM should be used cautiously with MAOIs, based on experience with morphine.

Hepatitis, Hepatic Events: Hepatic necrosis and hepatitis with jaundice have been reported with buprenorphine use. The spectrum of abnormalities ranges from transient asymptomatic elevations in hepatic transaminases to case reports of hepatic failure, hepatic necrosis, hepatorenal syndrome, and hepatic encephalopathy. Serious cases of acute hepatic injury have also been reported in a context of misuse, especially by the intravenous route. These hepatic injuries were dose-related, and could be due to mitochondrial toxicity. Pre-existing or acquired mitochondrial impairment (genetic diseases, viral infections particularly chronic hepatitis C, alcohol abuse, anorexia, associated mitochondrial toxins, e.g. aspirin, isoniazid, valproate, amiodarone, antiviral nucleoside analogues) could promote the occurrence of such hepatic injuries. These co-factors must be taken into account before prescribing SUBOXONE SUBLINGUAL FILM and during treatment monitoring. Measurement of liver function prior to initiation of treatment is recommended to establish a baseline. Periodic monitoring of liver function tests during treatment is also recommended. A biological and etiological evaluation is recommended when a hepatic event is suspected. Depending upon the findings, the medicinal product may be discontinued cautiously so as to prevent withdrawal syndrome and to prevent a return to drug addiction. If the drug treatment is continued, hepatic function should be monitored closely.

Hepatic Disease: Because buprenorphine is metabolised by the liver, its activity may be increased and/or extended in those individuals with impaired hepatic function. Naloxone metabolism may also be impaired in hepatic failure patients. Because hepatic elimination plays a relatively large role (~70%) in the overall clearance of SUBOXONE SUBLINGUAL FILM, lower initial doses and cautious titration of dosage may be required in patients with hepatic dysfunction.

CYP3A4 Inhibitors: Because CYP3A4 inhibitors may increase concentrations of buprenorphine, patients already treated with CYP3A4 inhibitors should have their dose of SUBOXONE

SUBLINGUAL FILM titrated carefully since a reduced dose may be required in these patients (see **Interactions with Other Medicines**).

Renal Disease: Renal elimination plays a relatively small role (~30%) in the overall clearance of buprenorphine. Therefore no dose modification based on renal function is required. Metabolites of buprenorphine accumulate in patients with renal failure. Caution is recommended when dosing patients with severe renal impairment (CL_{cr} <30 mL/min).

Use in Ambulatory Patients: SUBOXONE SUBLINGUAL FILM may impair the mental or physical abilities required for the performance of potentially dangerous tasks such as driving a car or operating machinery. Patients should be cautioned accordingly. Like other opiates, SUBOXONE SUBLINGUAL FILM may produce orthostatic hypotension in ambulatory patients.

Head Injury and Increased Intracranial Pressure: SUBOXONE SUBLINGUAL FILM, like other potent opiates may itself elevate cerebrospinal fluid pressure and should be used with caution in patients with head injury, intracranial lesions and other circumstances where cerebrospinal pressure may be increased. SUBOXONE SUBLINGUAL FILM can produce miosis and changes in the level of consciousness that may interfere with patient evaluation.

Opiate Withdrawal Effects: Because SUBOXONE SUBLINGUAL FILM contains naloxone, it is highly likely to produce marked and intense opiate withdrawal symptoms if injected.

SUBOXONE SUBLINGUAL FILM may produce withdrawal symptoms in opiate dependent subjects if it is administered too soon after another opiate. Discontinuation of treatment may result in a withdrawal syndrome that may be delayed. Studies in animals, as well as clinical experience, have showed that buprenorphine may produce dependence but at a lower level than morphine. Consequently, it is important to follow the **DOSAGE AND ADMINISTRATION** recommendations.

Neonatal Abstinence Syndrome: Neonatal withdrawal has been reported in the infants of women treated with buprenorphine during pregnancy. Time to onset of withdrawal symptoms ranged from Day 1 to Day 8 of life with most (69%) occurring on Day 1. Adverse events associated with neonatal withdrawal syndrome included hypertonia, neonatal tremor, neonatal agitation, and myoclonus. There have been rare reports of convulsions and in one case, apnoea and bradycardia were also reported. In many cases the withdrawal was serious and required treatment (See **Use in Pregnancy**).

Allergic Reactions: Cases of acute and chronic hypersensitivity to buprenorphine have been reported both in clinical trials and in the post-marketing experience. The most common signs and symptoms include rashes, hives, and pruritus. Cases of bronchospasm, angioneurotic oedema, and anaphylactic shock have been reported. A history of hypersensitivity to buprenorphine or naloxone is a contraindication to SUBOXONE SUBLINGUAL FILM use.

Effects on Fertility

There were no effects on mating performance or fertility in rats following buprenorphine treatment at oral doses ca 20 times the maximum clinical dose of 32mg/day (based on mg/m^2). Dietary administration of SUBOXONE tablets to rats at doses of 47mg/kg/day or greater (estimated respective buprenorphine and naloxone exposures 14 and 24 times the anticipated clinical exposure, based on plasma AUC) resulted in reduced female conception rates. A dietary dose of 9.4mg/kg/day (twice the anticipated clinical exposure for both buprenorphine (based on AUC) and naloxone (based on mg/m^2) had no adverse effect on fertility.

Use in Pregnancy (Category C)

In rats, oral administration of buprenorphine at doses up to 20 times the maximum clinical dose of 32mg/day (based on mg/m^2) prior to and during gestation and lactation resulted in reduced implantation, fewer live births, and reduced pup weight gain and survival. There was no evidence of teratogenicity in rats and rabbits following parenteral administration of buprenorphine during the

period of organogenesis, although there was embryofoetal toxicity, and reduced pup viability and developmental delays in rats. There was no evidence of teratogenicity in rats and rabbits following oral or intramuscular administration of maternally toxic doses of combinations of buprenorphine + naloxone during the period of organogenesis, although post-implantation losses were increased. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response).

There are no adequate or well controlled studies of SUBOXONE SUBLINGUAL FILM in pregnant women. Buprenorphine readily crosses the placental barrier, and may cause respiratory depression in neonates. During the last three months of pregnancy, chronic use of buprenorphine may be responsible for a withdrawal syndrome in neonates. SUBOXONE SUBLINGUAL FILM is contraindicated in pregnancy (see **CONTRAINDICATIONS**). Continued use of heroin during pregnancy is associated with significant risk to the mother and the foetus and neonate.

Use in Lactation
Animal studies indicate buprenorphine has the potential to inhibit lactation or milk production. In rats, oral (20 times maximum clinical dose, based on mg/m^2) or intramuscular administration of buprenorphine from late gestation to weaning was associated with increased stillbirths, reduced postnatal survival, and delayed postnatal development including weight gain and some neurological functions (surface righting reflex and startle response). The no effect level for developmental effects was twice the maximum clinical dose, based on mg/m^2. Because buprenorphine is excreted into human milk, SUBOXONE SUBLINGUAL FILM should not be used by breastfeeding women.

Paediatric Use
SUBOXONE SUBLINGUAL FILM is not recommended for use in children. The safety and effectiveness of SUBOXONE SUBLINGUAL FILM in subjects below the age of 16 has not been established.

Carcinogenicity
In mice, no evidence for carcinogenicity due to buprenorphine was noted in life-time studies at dietary doses of up to 100mg/kg/day, which equates to *ca* 14-fold human exposure at the maximum recommended clinical dose of 32mg based on body surface area.

In rats, statistically significant (trend test adjusted for survival) dose-related increases in testicular interstitial (Leydig) cell tumours occurred at a dietary buprenorphine dose of 55mg/kg/day (16 fold the maximal recommended human sublingual dose of 32mg, on a mg/m^2 basis); the no-effect dose was 5.4mg/kg/day (twice the maximal human dose, on a mg/m^2 basis).

The carcinogenic potential of naloxone alone has not been investigated in long term animal studies.

In a 2 year dietary study with SUBOXONE tablets in rats, Leydig cell adenomas were found at doses of 6-115mg/kg/day, associated with respective exposures (plasma AUC) to buprenorphine and naloxone of 2-21 fold, and up to 58 fold, anticipated human exposure. A NOEL was not established in the study.

Genotoxicity
In genotoxicity studies using buprenorphine and naloxone (9:2), assays for bacterial gene mutations and chromosomal damage (human lymphocytes *in vitro* and rat micronucleus test *in vivo*) were negative.

Interactions with Other Medicines
Benzodiazepines: A number of deaths and cases of coma have occurred when individuals have

intravenously misused buprenorphine and benzodiazepines concomitantly. Patients should be warned of the potential danger of the intravenous self-administration of benzodiazepines or other CNS depressants at the same time as receiving SUBOXONE SUBLINGUAL FILM (see **PRECAUTIONS**).

CYP3A4 inhibitors: An interaction study of buprenorphine with ketoconazole (a potent inhibitor of CYP3A4) resulted in increased Cmax and AUC of buprenorphine (approximately 50% and 70% respectively) and, to a lesser extent, of norbuprenorphine. Patients receiving SUBOXONE SUBLINGUAL FILM should be closely monitored, and may require dose-reduction if combined with potent CYP3A4 inhibitors e.g. protease inhibitors like ritonavir, nelfinavir or indinavir, azole antifungals like ketoconazole or itraconazole, calcium channel antagonists, and macrolide antibiotics (see **PRECAUTIONS**).

CYP3A4 inducers: The interaction of buprenorphine with CYP3A4 inducers has not been investigated; therefore it is recommended that patients receiving SUBOXONE SUBLINGUAL FILM should be closely monitored if inducers (e.g. phenobarbital, carbamazepine, phenytoin, rifampicin) are co-administered.

Effects on Laboratory Tests
Athletes should be aware that this medicine may cause a positive reaction to “anti-doping” tests.

ADVERSE EFFECTS
Safety Study of SUBOXONE SUBLINGUAL FILM
The clinical safety of SUBOXONE SUBLINGUAL FILM was evaluated in a trial (RB-US-07-0001) of 382 patients stabilised on Suboxone sublingual tablets for at least 30 days and then switched to SUBOXONE SUBLINGUAL FILM for maintenance treatment. Two hundred and forty-nine (249) patients completed at least 12 weeks of dosing with the SUBOXONE SUBLINGUAL FILM. Patients received SUBOXONE SUBLINGUAL FILM sublingually or buccally in a 1:1 ratio (N=194 sublingually, N=188 buccally). Adjunctive treatment was treatment as usual with varying levels of counselling and behavioural treatment. Treatment was conducted on an outpatient basis. Among all patients who received SUBOXONE SUBLINGUAL FILM either sublingually or buccally, the most common treatment emergent adverse events were oral mucosal erythema, sinusitis, toothache, and upper respiratory infection. The most common treatment emergent adverse event for the patients administered SUBOXONE SUBLINGUAL FILM sublingually were vomiting (4 patients, 2.1%) and upper respiratory tract infection (4 patients, 2.1%). All other adverse events were reported in 3 (1.5%) or fewer patients.

Adverse events reported to occur to at least 1% of patients being treated with SUBOXONE SUBLINGUAL FILM in this trial are shown in Table 2.

Table 2 Adverse Events (≥1%) by Body System and Treatment Group in Study RB-US-07-0001, Sublingual Administration

System Organ Class Preferred term	Sublingual N=194
Infections and Infestations	
Sinusitis	3 (1.5%)
Upper respiratory tract infection	4 (2.1%)
Pharyngitis streptococcal	3 (1.5%)
Urinary tract infection	3 (1.5%)
Influenza	2 (1.0%)
Tooth abscess	3 (1.5%)
Gastrointestinal Disorders	
Glossodynia	3 (1.5%)
Hypoaesthesia oral	2 (1.0%)
Nausea	3 (1.5%)
Oral mucosal erythema	2 (1.0%)
Toothache	3 (1.5%)
Vomiting	4 (2.1%)
Musculoskeletal and Connective Tissues Disorders	
Back pain	3 (1.5%)
Arthralgia	3 (1.5%)
Musculoskeletal pain	2 (1.0%)
Psychiatric Disorders	
Insomnia	2 (1.0%)
Stress	2 (1.0%)
Injury, Poisoning and Procedural Complications	
Skin laceration	2 (1.0%)
General Disorders and Administration Site Conditions	
Pain	3 (1.5%)
Nervous System Disorders	
Headache	2 (1.0%)
Renal and Urinary Disorders	
Nephrolithiasis	2 (1.0%)
Skin and Subcutaneous Tissue Disorders	
Dermatitis contact	2 (1.0%)
Pregnancy, Puerperium and Perinatal Conditions	
Pregnancy	2 (1.0%)

* AEs are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 terminology.

Clinical trials of SUBOXONE Tablets

Adverse events reported to occur to at least 5% of patients being treated in clinical trials of SUBOXONE tablets (CR96/013 + CR96/014) are shown in Tables 3 and 4.

Table 3. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/013

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) sublingual tablets 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Body as a Whole				
Abscess	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Asthenia	7 (6.5%)	5 (4.9%)	7 (6.5%)	19 (6.0%)
Chills	8 (7.5%)	8 (7.8%)	8 (7.5%)	24 (7.6%)
Fever	3 (2.8%)	3 (2.9%)	4 (3.7%)	10 (3.2%)
Headache	39 (36.4%)	30 (29.1%)	24 (22.4%)	93 (29.3%)
Infection	6 (5.6%)	12 (11.7%)	7 (6.5%)	25 (7.9%)
Accidental Injury	2 (1.9%)	5 (4.9%)	5 (4.7%)	12 (3.8%)

Body System/ Adverse Event (COSTART Terminology)	SUBOXONE (buprenorphine/naloxone) sublingual tablets 16/4 mg/day N=107 n (%)	SUBUTEX (buprenorphine) sublingual tablets 16 mg/day N=103 n (%)	Placebo N=107 n (%)	All Subjects (N = 317) n (%)
Pain	24 (22.4%)	19 (18.4%)	20 (18.7%)	63 (19.9%)
Pain abdomen	12 (11.2%)	12 (11.7%)	7 (6.5%)	31 (9.8%)
Pain back	4 (3.7%)	8 (7.8%)	12 (11.2%)	24 (7.6%)
Withdrawal syndrome	27 (25.2%)	19 (18.4%)	40 (37.4%)	86 (27.1%)
Cardiovascular System				
Vasodilation	10 (9.3%)	4 (3.9%)	7 (6.5%)	21 (6.6%)
Digestive System				
Constipation	13 (12.1%)	8 (7.8%)	3 (2.8%)	24 (7.6%)
Diarrhea	4 (3.7%)	5 (4.9%)	16 (15.0%)	25 (7.9%)
Dyspepsia	4 (3.7%)	5 (4.9%)	5 (4.7%)	14 (4.4%)
Nausea	16 (15.0%)	14 (13.6%)	12 (11.2%)	42 (13.2%)
Vomiting	8 (7.5%)	8 (7.8%)	5 (4.7%)	21 (6.6%)
Metabolic/Nutritional Disorders				
Peripheral Edema	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)
Musculoskeletal System				
Myalgia	4 (3.7%)	1 (1.0%)	1 (0.9%)	6 (1.9%)
Nervous System				
Agitation	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Anxiety	3 (2.8%)	5 (4.9%)	4 (3.7%)	12 (3.8%)
Dizziness	5 (4.7%)	3 (2.9%)	4 (3.7%)	12 (3.8%)
Hyperkinesia	3 (2.8%)	2 (1.9%)	0	5 (1.6%)
Hypertonia	2 (1.9%)	0	2 (1.9%)	4 (1.3%)
Insomnia	15 (14.0%)	22 (21.4%)	17 (15.9%)	54 (17.0%)
Nervousness	5 (4.7%)	6 (5.8%)	4 (3.7%)	15 (4.7%)
Paresthesia	3 (2.8%)	3 (2.9%)	0	6 (1.9%)
Somnolence	8 (7.5%)	4 (3.9%)	2 (1.9%)	14 (4.4%)
Thinking Abnormal	2 (1.9%)	1 (1.0%)	1 (0.9%)	4 (1.3%)
Tremor	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Respiratory System				
Cough Increased	1 (0.9%)	2 (1.9%)	2 (1.9%)	5 (1.6%)
Pharyngitis	2 (1.9%)	4 (3.9%)	1 (0.9%)	7 (2.2%)
Rhinitis	5 (4.7%)	10 (9.7%)	14 (13.1%)	29 (9.1%)
Skin And Appendages				
Sweating	15 (14.0%)	13 (12.6%)	11 (10.3%)	39 (12.3%)

Special Senses				
Amblyopia	3 (2.8%)	1 (1.0%)	0	4 (1.3%)
Lacrimation Disorder	0	4 (3.9%)	6 (5.6%)	10 (3.2%)
Urogenital System				
Dysmenorrhea	2 (1.9%)	1 (1.0%)	2 (1.9%)	5 (1.6%)
Urinary Tract Infection	1 (0.9%)	1 (1.0%)	2 (1.9%)	4 (1.3%)

Abbreviations: COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms.

Table 4. Adverse Events (≥1%) by Body System and Treatment Group in Study CR96/014

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE sublingual tablet Subjects N=472 n (%)
Body as a Whole	
Abscess	17 (3.6%)
Allergic Reaction	8 (1.7%)
Asthenia	48 (10.2%)
Chills	44 (9.3%)
Cyst	7 (1.5%)
Edema, Face	8 (1.7%)
Fever	36 (7.6%)
Flu Syndrome	89 (18.9%)
Headache	202 (42.8%)
Infection	5 (1.1%)
Infection, Viral	5 (1.1%)
Accidental Injury	72 (15.3%)
Malaise	9 (1.9%)
Neck Rigid	5 (1.1%)
Pain	197 (41.7%)
Pain, Abdomen	77 (16.3%)
Pain, Back	132 (28.0%)
Pain, Chest	23 (4.9%)
Pain, Neck	12 (2.5%)
Withdrawal Syndrome	194 (41.1%)
Cardiovascular System	
Hypertension	17 (3.6%)
Migraine	13 (2.8%)
Vasodilation	29 (6.1%)
Digestive System	
Abscess, Periodontal	10 (2.1%)
Anorexia	16 (3.4%)
Constipation	115 (24.4%)
Diarrhea	50 (10.6%)
Dyspepsia	45 (9.5%)
Flatulence	11 (2.3%)
Gastrointestinal Disorder	
Liver Function Abnormal	18 (3.8%)
Nausea	76 (16.1%)
Stomatitis	5 (1.1%)
Tooth Disorder	37 (7.8%)
Ulcer, Mouth	6 (1.3%)
Vomiting	61 (12.9%)
Hemic/Lympatic System	
Anemia	7 (1.5%)
Ecchymosis	6 (1.3%)
Lymphadenopathy	5 (1.1%)
Metabolic/Nutritional Disorders	
Peripheral Edema	24 (5.1%)
Hyperglycemia	5 (1.1%)
Weight Decreased	15 (3.2%)
Musculoskeletal System	
Arthralgia	20 (4.2%)
Arthritis	5 (1.1%)
Leg Cramps	13 (2.8%)
Joint Disorder	9 (1.9%)
Myalgia	31 (6.6%)
Nervous System	
Agitation	10 (2.1%)
Anxiety	65 (13.8%)
Depression	70 (14.8%)
Dizziness	33 (7.0%)
Dream Abnormalities	9 (1.9%)
Drug Dependence	9 (1.9%)
Hypertonia	9 (1.9%)
Insomnia	138 (29.2%)
Libido Decreased	9 (1.9%)
Nervousness	42 (8.9%)
Paresthesia	28 (5.9%)
Somnolence	40 (8.5%)
Thinking Abnormal	6 (1.3%)
Tremor	7 (1.5%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE sublingual tablet Subjects N=472 n (%)
Respiratory System	
Asthma	21 (4.4%)
Bronchitis	9 (1.9%)
Cough Increased	36 (7.6%)
Dyspnea	9 (1.9%)
Lung Disorder	10 (2.1%)
Pharyngitis	64 (13.6%)
Pneumonia	12 (2.5%)
Respiratory Disorder	7 (1.5%)
Rhinitis	75 (15.9%)
Sinusitis	7 (1.5%)
Sputum Increased	5 (1.1%)
Yawn	6 (1.3%)
Skin and Appendages	
Acne	5 (1.1%)
Dermatological Contact	5 (1.1%)
Herpes Simplex	6 (1.3%)
Nodule, Skin	6 (1.3%)

Body System/ Adverse Event (COSTART Terminology)	All SUBOXONE sublingual tablet Subjects N=472 n (%)
Pruritus	11 (2.3%)
Skin Dry	6 (1.3%)
Sweat	74 (15.7%)
Urticaria	6 (1.3%)
Special Senses	
Amblyopia	5 (1.1%)
Conjunctivitis	14 (3.0%)
Eye Disorder	8 (1.7%)
Lacrimation Disorder	14 (3.0%)
Pain, Ear	8 (1.7%)
Urogenital System	
Dysmenorrhea	19 (4.0%)
Dysuria	9 (1.9%)
Hematuria	8 (1.7%)
Impotence	11 (2.3%)
Urinary Tract Infection	19 (4.0%)
Urine Abnormality	12 (2.5%)
Vaginitis	11(2.3%)

The most common adverse events reported were those related to withdrawal symptoms (e.g. abdominal pain, diarrhoea, muscle aches, anxiety, sweating). In patients with marked drug dependence, initial administration of buprenorphine can produce a withdrawal effect similar to that associated with naloxone.

Note - Patients enrolled in study RB-US-07-0001 on the soluble film were on a stable buprenorphine treatment prior to study initiation, while patients enrolled in studies CR96/013 and CR96/014 were buprenorphine-naïve individuals. As a result, the number of AEs observed in study RB-US-07-0001 are likely to be fewer than those observed in studies CR96/013 and CR96/014.

As with other opiates, orthostatic hypotension can occur (see **PRECAUTIONS**).

Post-marketing experience with buprenorphine alone

Post-marketing experience with buprenorphine alone for treatment of opiate dependence has been associated with the following rare side effects: respiratory depression and coma, hallucinations, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, foetal disorders, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, and deaths.

Very rare (<0.01%) side effects: loss of consciousness, cognitive disorders, psychosis, hallucinations, suicidal ideation, disorders of pregnancy (such as miscarriage and termination of pregnancy, premature birth, placental abruption, prolonged labour), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, decreased oxygen saturation, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, cleft palate, Klinefelter's Syndrome, intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, infant respiratory distress syndrome and subarachnoid bleeding), heart murmur, convulsions, confusion, miosis, weight decrease, asphyxia, hypoventilation, pruritus, angioedema, heart rate and rhythm disorders, pulmonary oedema, septic shock, infections (including sepsis, septic arthritis and septic embolus, staphylococcal sacroileitis, brain abscess, pneumonia and endocarditis and amniotic fluid infection) events associated with intravenous misuse (such as cutaneous ulceration,

eschar, lividoid and necrotic lesions and penile and scrotal lesion), aphasia, aphonia, slurred speech, diplopia, facial palsy, ascites and lympodoema, pulmonary oedema, pulmonary artery thrombosis, pericardial effusion, shock, cerebrovascular accident, Popeye syndrome, intracranial haemorrhage, nephropathy, colic, denutrition splenic infarction, electrolyte imbalance (such as hyperkalaemia, hyponatraemia and hypoglycaemia), deaths (including death from suicide and sudden infant death syndrome) and unusual reactions. The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit drug use of the population under treatment.

Post-marketing experience with SUBOXONE TABLETS
A post-marketing study looking at injecting practices in Australia suggested that the combination of buprenorphine and naloxone is less commonly injected than buprenorphine alone.

Additionally, post-marketing experience with SUBOXONE tablets for treatment of opiate dependence has been associated rarely with the following side effects: insomnia, reduced feeling, anorexia (see also Tables 3 and 4 above), amnesia, convulsions, blood in vomit, fatigue, jaundice, swollen joints, miscarriage, shortness of breath, and suicide ideation.

Cases of hepatitis with jaundice, hepatic failure, hepatic necrosis, hepatorenal syndrome, hepatic encephalopathy, and asymptomatic elevations in hepatic transaminases have been reported with buprenorphine use (see **PRECAUTIONS**).

In cases of intravenous misuse of buprenorphine, local reactions, sometimes septic, and potentially serious acute hepatitis have been reported.

Cases of acute or chronic hypersensitivity have been reported with buprenorphine with symptoms including rashes, hives, pruritus and reported cases of bronchospasm, angioneurotic oedema, and anaphylactic shock. (see **PRECAUTIONS** and **CONTRAINDICATIONS**).

Additionally, post-marketing experience with SUBOXONE tablets for treatment of opiate dependence has been associated very rarely (<0.01%) with the following side effects: attempted suicide, disorders of pregnancy (such as premature birth), foetal and neonatal complications (such as foetal disorders, foetal malformation, foetal growth retardation, foetal cystic hygroma, micrognathia, macrocephaly, meconium staining and aspiration, decreased oxygen saturation, neonatal aspiration, asphyxia, developmental speech disorder, foetal dwarfism, foetal asphyxia, foetal cardiac rhythm disorder, low birth weight, Klinefelter's Syndrome, mitochondrial disease, abnormal behaviour, developmental delay, developmental speech disorder intersexual genitalia, neonatal withdrawal syndrome, neonatal tremor, neonatal feeding disorder, subarachnoid bleeding and sudden infant death syndrome), pancreatitis, loss of consciousness, depression of consciousness, coordination disturbance, hallucinations, psychosis, mental disturbance and altered mental state, cerebral oedema, heart rate and rhythm disorders, septic shock, infections (including sepsis, pneumonia, chorioamniotitis and amniotic fluid infection) events associated with intravenous misuse (such as cellulitis), blurred vision, papilloedema, ascites and peripheral oedema, renal failure, adrenal insufficiency, electrolyte imbalance (such as hyperkalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypoglycaemia) and deaths (including death from suicide and sudden infant death syndrome). The actual incidence of all cases is extremely low and must be taken in consideration with the co-morbidities, life-style, environmental factors, and concomitant illicit and licit drug use of the population under treatment.

DOSAGE AND ADMINISTRATION
Treatment with SUBOXONE SUBLINGUAL FILM is intended for adults and children aged 16 years or over who have agreed to be treated for addiction. When initiating buprenorphine treatment, the physician should be aware that it can precipitate withdrawal in opioid-dependent patients if given too soon after the administration of heroin, methadone or another opiate.

Suboxone Sublingual Film and Suboxone Sublingual Tablet do not meet all criteria for

bioequivalence (see section ***Pharmacokinetics***). Patients being switched between tablets and soluble films may therefore require dosage adjustment.

The route of administration of SUBOXONE SUBLINGUAL FILM is sublingual. SUBOXONE SUBLINGUAL FILMS should not be swallowed whole as this reduces the bioavailability of the medicine. Physicians must advise patients that the sublingual route is the only effective and safe route of administration for this medicine.

Please note: The following instructions refer to the buprenorphine content of each dose. SUBOXONE SUBLINGUAL FILM 8mg/2mg (buprenorphine/naloxone) is referred to as the "8mg" dose and SUBOXONE SUBLINGUAL FILM 2mg/0.5mg (buprenorphine/naloxone) is referred to as the "2mg" dose.

Method of Administration
Place SUBOXONE SUBLINGUAL FILM under the tongue. If an additional SUBOXONE SUBLINGUAL FILM is necessary to achieve the prescribed dose, place it sublingually on the opposite side from the first film, and in a manner to minimise overlapping as much as possible. If more than two films are required, place the next film or films after the first two have dissolved. The soluble film must be kept under the tongue until it is completely dissolved, which takes on average between 4 and 8 minutes. No food or drink should be consumed until the film is completely dissolved. SUBOXONE SUBLINGUAL FILMS should NOT be chewed, swallowed, or moved from placement.

Starting SUBOXONE SUBLINGUAL FILM
An adequate maintenance dose, titrated to clinical effectiveness, should be achieved as rapidly as possible to prevent undue opiate withdrawal symptoms due to inadequate dosage.

Prior to induction, consideration should be given to the type of opiate dependence (i.e., long- or short-acting opiate), the time since last opiate use and the degree or level of opiate dependence.

Induction onto SUBUTEX (buprenorphine tablets) is recommended when there is doubt about the level of dependence or previous drug use, to avoid precipitating opiate withdrawal. Patients can be switched to SUBOXONE SUBLINGUAL FILM on the third day.

Patients taking Street Heroin (or Other Short-acting Opiates): When treatment starts the dose of SUBOXONE SUBLINGUAL FILM should be taken at least 6 hours after the patient last used opiates or when the early signs of withdrawal appear. The recommended starting dose is 4 mg SUBOXONE SUBLINGUAL FILM on Day One, with a possible additional 4 mg depending on the individual patient's requirement.

Patients on Methadone: Before starting treatment with SUBOXONE SUBLINGUAL FILM, the maintenance dose of methadone should be reduced to a maximum of 30mg per day. The first dose of SUBOXONE SUBLINGUAL FILM should be taken at least 24 hours after the patient last used methadone. The initial 4mg SUBOXONE SUBLINGUAL FILM induction dose should ideally be administered when early signs of withdrawal are evident.

Dosage Adjustment and Maintenance
The dose of SUBOXONE SUBLINGUAL FILM should be adjusted progressively according to the clinical effect in the individual patient and should not exceed a maximum daily dose of 32 mg. The dosage is adjusted according to reassessments of the clinical and psychological status of the patient.

Less than Daily Dosing of SUBOXONE SUBLINGUAL FILM
After a satisfactory period of stabilisation has been achieved the frequency of dosing may be decreased to dosing every other day at twice the individually titrated daily dose. For example, a patient stabilised to receive a daily dose of 8mg may be given 16mg on alternate days, with no

medication on the intervening days. However, the dose given on any one day should not exceed 32mg.

In some patients, after a satisfactory period of stabilisation has been achieved, the frequency of dosing may be decreased to 3 times a week (for example on Monday, Wednesday and Friday). The dose on Monday and Wednesday should be twice the individually titrated daily dose, and the dose on Friday should be three times the individually titrated daily dose, with no medication on the intervening days. However, the dose given on any one day should not exceed 32mg.

Reducing Dosage and Stopping Treatment
The decision to discontinue therapy with SUBOXONE SUBLINGUAL FILM should be made as part of a comprehensive treatment plan. A gradual dose taper over a period of 21 days is shown in Table 3.

Table 3.	**Gradual dose taper schedule**		
Week	**20mg Maintenance dose**	**16mg Maintenance dose**	**8mg Maintenance dose**
1	16mg	12mg	8mg
2	8mg	8mg	4mg
3	4mg	4mg	4mg

OVERDOSAGE
Manifestations of acute overdose include pinpoint pupils, sedation, hypotension, respiratory depression and death.

In the event of accidental overdose, general supportive measures should be instituted including close monitoring of respiratory and cardiac status of the patient. The major symptom requiring intervention is respiratory depression, which could lead to respiratory arrest and death. If the patient vomits, care must be taken to prevent aspiration of the vomitus.

Treatment
In the event of depression of respiratory or cardiac function, primary attention should be given to the re-establishment of adequate respiratory exchange through provision of a patent airway and institution of assisted or controlled ventilation. Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. High doses of naloxone hydrochloride 10-35 mg/70 kg may be of limited value in the management of buprenorphine overdose.

The long duration of action of SUBOXONE SUBLINGUAL FILM should be taken into consideration when determining the length of treatment needed to reverse the effects of an overdose.

PRESENTATION AND STORAGE CONDITIONS
SUBOXONE SUBLINGUAL FILM is supplied as an orange rectangular soluble film with a white printed logo in two dosage strengths:

- 2/0.5 mg buprenorphine/naloxone and
- 8/2 mg buprenorphine/naloxone

Each soluble film is packed in an individual child resistant polyethylene terephthalate (PET)/low density polyethylene (LDPE)/aluminium/ethylene acrylic acid (EAA) sachet. There are 28 sachets in a pack.

Store below 25^{o}C.

NAME AND ADDRESS OF SPONSOR
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POISON SCHEDULE OF THE MEDICINE
Schedule 8

DATE OF TGA APPROVAL: 11 Jan 2011

Therapeutic Goods Administration

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