Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Buprenorphine

Proprietary Product Name: Transtec

Sponsor: Mundipharma Pty Ltd

December 2016

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

- An Australian Public Assessment Report (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; it provides 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

Common abbreviations

Abbreviation	Meaning
ACPM	Advisory Committee on Prescription Medicines
ADRs	Adverse drug reactions
AE	Adverse event
ASA	Australian specific annexe (to the RMP)
AUC	Area under the concentration time curve
AUC_{0-24h}	Area under the concentration time curve from 0 to 24 hours
AUC_{t1-t2}	Area under the curve from time t1 to time t2
BUP	buprenorphine
CCDS	Company core data sheet
CI	confidence interval
CMI	Consumer medicines information
C_{max}	Maximum observed concentration
CNS	central nervous system
CYP3A4	Cytochrome P450 3A4
EMA	European Medicines Agency
EU	European Union
h, hrs	hour(s)
HERG	Human Ether-a-Go-Go-Related Gene
ITT	intention-to-treat
IV	intravenous(ly)
kg	kilogram
MAH	Market authorisation holder
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MR	Mutual recognition procedure (EU)
µg	micrograms

Abbreviation	Meaning
µg/hr	micrograms per hour
mEq	milli-equivalents
mg	milligram
mg/h	milligrams per h
MRHD	maximum recommended human dose
NRS	Numeric Rating Scale (11 point NRS for pain) 0 = no pain, 11 = pain as bad as you can imagine
NSAID	Non-Steroidal Anti-Inflammatory Drug
PD	Pharmacodynamics
PI	Product information
PK	Pharmacokinetic
PP	Per protocol
pg	picogram
pg/mL	picogram per millilitre
PSURs	Periodic safety update reports
QT	QT interval for heart rate
QTc	QT interval corrected for heart rate
QTci	QT interval individually corrected
RR	relative risk
SADR	serious adverse drug reaction
SAE	serious adverse event
SD	standard error of the mean
SL	Sublingual
SmPC	Summary of product characteristics
SR	Slow release
T_{max}	time of occurrence of maximum observed concentration (time to reach C_{max})

Abbreviation	Meaning
t½,z	half-life, (apparent) terminal phase half-life
TD	Transdermal
TDP	Transdermal patch
TDS	Transdermal delivery system
TdP	Torsade de Pointes
TTS	Transdermal therapeutic system
TTS50	20mg transdermal patch = BUP-TDP35 µg/hr
TTS75	30mg transdermal patch = BUP-TDP 52.5 µg/hr
TTS100	40mg transdermal patch = BUP-TDP 70 µg/hr
UGT	uridine diphosphate glucuronosyltransferase
UK	United Kingdom
ULQ	upper limit of quantification
VRS	Verbal rating scale
WHO	World Health Organisation

I. Introduction to product submission

Submission details

Type of submission:	major variation (new indication, dose form and dose regimen)
Decision:	Rejected
Date of initial TGA decision:	14 December 2015
Date of final TGA decision	28 April 2016
AAT outcome*	Appeal was withdrawn[1]
Date of entry onto ARTG	Not applicable
Active ingredient:	buprenorphine
Product names:	Transtec and additional trade names
Sponsor's name and address:	Mundipharma Pty Ltd GPO Box 5214 Sydney NSW 2001
Dose form:	Transdermal drug delivery system
Strength(s):	35 µg/h, 52.5 µg/h and 70 µg/h
Container(s):	Sachet
Pack size(s):	4 and 8
Approved therapeutic use:	Not applicable
Route of administration:	transdermal
Dosage:	A dosing interval of 72 to 96 hours has been proposed with dose to be adjusted according to clinical response. 3 patch strengths with the following release rates: • 20 mg buprenorphine patch delivering 35 µg/h over a period of 96 hours • 30 mg buprenorphine patch delivering 52.5 µg/h over a period of 96 hours • 40 mg buprenorphine patch delivering 70 µg/h over a period of 96 hours. The patch size is proportional to the total buprenorphine content with patch sizes of 25 cm^2, 37.5 cm^2 and 50 cm^2.
ARTG number (s):	Not applicable

*AAT= Administrative Appeals Tribunal

[1] The sponsor appealed to the AAT for a review of the TGA's decision not to register Transtec.

Product background

This AusPAR describes the application by Mundipharma Pty Ltd (the sponsor) to register Transtec and additional trade names [2] 35 µg/h, 52.5 µg/h and 70 µg/h transdermal drug delivery system for the indication:

> *Management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.*[3]

Buprenorphine is a potent opioid analgesic. It was first registered in Australia in 1991 in a parenteral formulation (Temgesic) indicated:

> *for short term use (not more than 1 week)in patients suffering from acute pain of moderate to severe pain intensity. It is not recommended for use in children.*

Sublingual (SL) tablets (Temgesic) were subsequently registered in 1992 for the indication:

> *Strong analgesic for the short-term (not more than one week) relief of moderate to severe pain, including post-operative and terminal pain. Temgesic injection should be employed when sublingual administration is not practical e.g. pre or peri-operatively. It is not recommended for use in children.*

Other versions of SL tablets or film of buprenorphine as a single active (Bupradex, Subutex, Subutex FTD), or together in a fixed dose combination with naloxone (Bupradone, Suboxone Sublingual Film) have been registered for the management of opiate dependence.

Registration of buprenorphine in a transdermal drug delivery system was first approved in Australia in 2005 as Norspan indicated for:

> *Management of moderate to severe pain.*

The proposed Transtec patch is almost identical to Norspan patches; buprenorphine transdermal drug delivery system 5, 10, 15, 20, 25, 30 and 40 µg/h in that it contains the same amount of buprenorphine however the dose regimen is different. Transtec is proposed to be applied every 3 to 4 days rather than every 7 days as is recommended for Norspan. This results in a substantially higher average release rate of buprenorphine. The Transtec range of transdermal patches have mean buprenorphine release rates of 35 µg/h to 70 µg/h compared to 5 to 40 µg/h for the Norspan range. The indication proposed for Transtec is slightly different from that of Norspan.

Norspan and Transtec share the same Australian sponsor (Mundipharma Pty Limited) and same manufacturer but had separate developments.

Regulatory status

At the time the TGA considered this application, Transtec with the same delivery rates of buprenorphine as are proposed in this submission was first approved in Switzerland in 2000. Subsequently it was approved with varying indications in Europe (as shown in Table 1), in South American countries and in Turkey. Transtec has not been submitted to USA, Canada, New Zealand or Singapore. The indication proposed by the sponsor is the same as the approved indication in the EU.

[2] The sponsor proposed additional names; further references in this document will use only the trade name Transtec.

[3] The indication in the proposed PI was '*management of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics*' and was amended in the pre ACPM response to '*Use in patients with moderate to severe cancer pain not adequately treated by previous opioids'.*

Table 1. Registration status in the EU

Country	Submission date	Approval date	Approved indications
European Union: initial registration			
Germany	28/07/1999	24/07/2001	Moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics. Transtec is not suitable for the treatment of acute pain
European Union: mutual recognition process[4] (reference member state was Germany)			
Austria	4/09/2001	11/03/2002	As above
Belgium	4/09/2001	02/04/2002	
Ireland	4/09/2001	03/05/2002	
Italy	4/09/2001	18/04/2003	
Luxembourg	4/09/2001	17/04/2002	
Portugal	3/09/2001	19/02/2002	
Spain	3/09/2001	08/04/2002	
United Kingdom	3/09/2001	27/02/2002	
Denmark	8/07/2002	14/01/2003	
Slovenia	6/10/2005	7/03/2006	
Italy	27/03/2015	Not yet approved	
Portugal	27/03/2015	11/09/2015	
European Union: Other national approvals not via mutual recognition procedure			
Netherlands	04/07/2005	05/01/2007	Severe chronic pain which does not respond to a treatment of non opioid analgesics. Transtec is not suitable for the treatment of acute pain

[4] Since 1 January 1998, the mutual recognition procedure is compulsory for all medicinal products to be marketed in a Member State other than that in which they were first authorised. Any national marketing authorisation granted by an EU Member State's national authority can be used to support an application for its mutual recognition by other Member States.

Country	Submission date	Approval date	Approved indications
Spain Duplicate generic application under Tradename Buprenorfina Grünenthal	30/09/2014	28/07/2015	As for initial registration in Germany
Sweden			Not yet registered
European Union: Not members of the EU at the time of submission (national registration)			
Croatia	6/12/2004	13/10/2005	As for initial registration in Germany
Czech Republic	10/12/2001	28/08/2002	
Hungary	18/12/2001	25/06/2003	
Poland	10/12/2001	5/12/2002	
Slovakia	9/07/2002	20/12/2002	

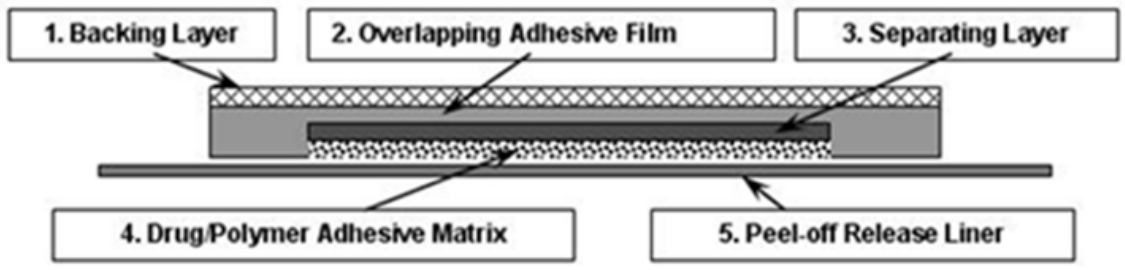
II. Quality findings

Introduction

This submission is to register three transdermal drug delivery systems (transdermal patches) containing buprenorphine which are stated to release the drug substance at an average of 35 µg/h, 52.5µg/h and 70 µg/h.

It is important to note that the design of the Transtec and Norspan products are identical as detailed in the diagram below.

Figure 1: Description of the Norspan/ Butrans[5] patch



NORSPAN patches are either a rectangular, or square, beige-coloured, matrix patch with rounded corners, marked with the trade name and consisting of a protective liner and functional layers. Proceeding from the outer surface towards the surface adhering to the skin, the layers are (1) a beige-coloured web backing layer of polyester material; (2) an adhesive matrix rim without buprenorphine; (3) a separating layer ("foil") consisting of polyethylene terephthalate over the adhesive matrix; (4) the

[5] In some countries (for example USA) the trade name Butrans is used instead of Norspan.

buprenorphine-containing adhesive matrix; and (5) a release liner. Before use the release liner covering the adhesive layer is removed and discarded.

For each series of products, the same buprenorphine adhesive matrix is used with the amount of this matrix increasing proportionally with strength. The surface area of the matrix is also increased proportionally. These two things combine to result in the average release rate increasing proportionally with the strengths. One excipient imparts the modified release and adhesive properties.

Table 2: Overview of strengths of Norspan products

Norspan Products							
Buprenorphine (mg/patch)	5	10	15	20	25	30	40
Surface area (cm^2)	6.25	12.5	18.75	25	31.25	37.5	50
Average release rate (µg/h)	5	10	15	20	25	30	40

Table 3: Overview of strengths of Transtec products

Transtec Products			
Buprenorphine (mg/patch)	20	30	40
Surface area (cm^2)	25	37.5	50
Average release rate (µg/h)	35	52.5	70

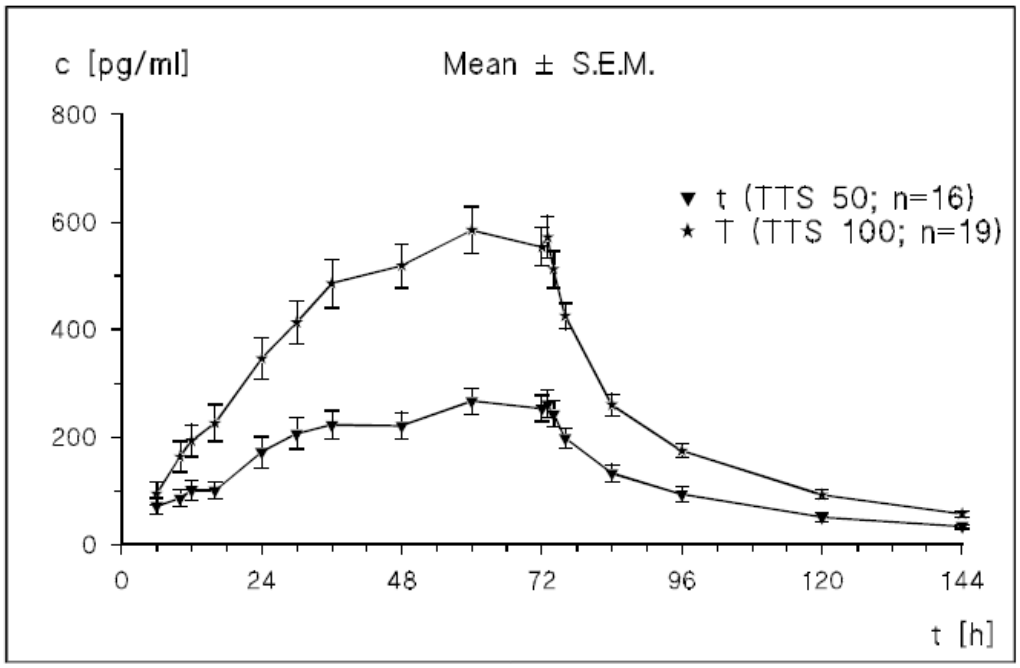
When comparing the Norspan and Transtec patches with the same buprenorphine content:

- There is only a very slight difference in the formulations in that the amount of the excipient for modified release and adhesive is slightly different and that the amounts of the other excipients and the surface areas are the same.
- However there is a very large difference in the average release rate.

This is not due to any fundamental change in the release profiles, in fact the pharmacokinetics (PK) profiles are very similar to 4 days (as can be seen by the following PK profiles), but to the way the average release rate is calculated.

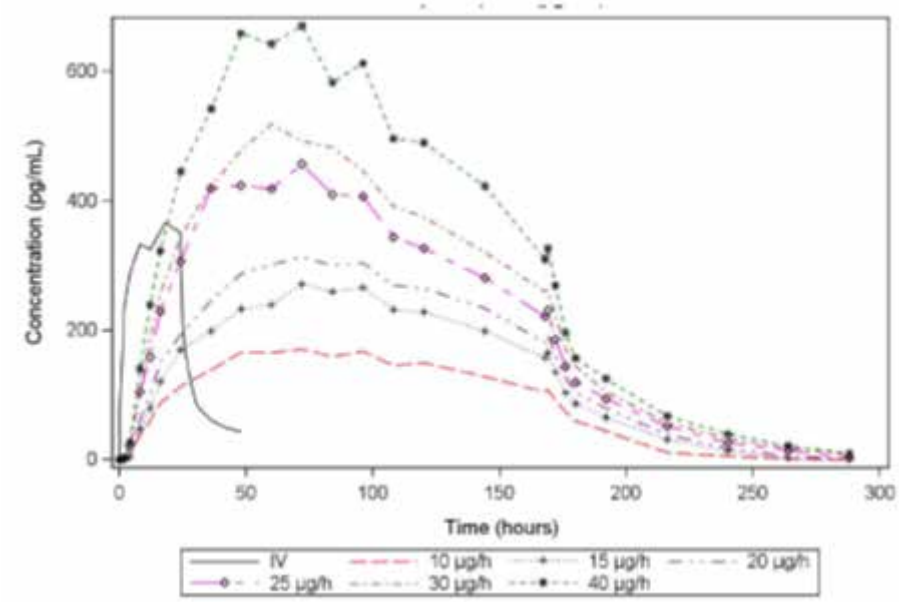
- For Transtec it is calculated as the average over 3 days to which time the levels increase continually.
- For Norspan it is calculated as the average over 7 days, where levels decline after reaching a peak at about 72 hours.
- The number of days used in the calculations reflects the time each patch will be in place.

Figure 2: PK profiles for 20 mg and 40 mg Transtec products worn to Day 3 (72 hours)



(TTS 50 = 20 mg, 35 µg/h and TTS 100 = 40 mg, 70 µg/h) taken from Study HP5303/01.

Figure 3: PK profiles for 10 mg, 15 mg, 20 mg, 25 mg, 30 mg and 40 mg Norspan products worn to Day 7 (168 hours)



Here strength in µg/h equates to strength in mg content.

One result of the decrease in the time each patch is left in place (that is, when two patches are used per week rather than one patch) will be that the steady state concentration will be higher using Transtec than using Norspan.

Finally, the amount of buprenorphine remaining in the discarded patches will be slightly higher with Transtec than Norspan. For example, with the 40 mg patch this will be

approximately 35 mg if the Transtec patch is discarded at 3 days[6] and approximately 33.3 mg when the Norspan patch is discarded at 7 days.

Drug product

The active ingredient material is compliant with the British Pharmacopeia monograph for Buprenorphine and is covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability (R1-CEP 2007-190-Rev 02).

The Transtec products are manufactured in the same way as the Norspan products. The buprenorphine is dissolved during manufacture and remains dissolved in the finished product matrix.

The specifications of the Transtec products are similar to those for Norspan. The only difference is that the expiry limit for the degradant norbuprenorphine. Given that norbuprenorphine is a metabolite, this is acceptable.

The stability data support a shelf life of 36 months when stored below 25°C.

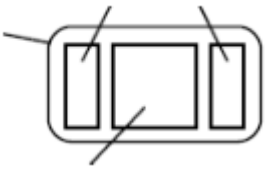
Biopharmaceutics

Bioavailability and Pharmacokinetics

Three studies were evaluated.

The products used in the clinical efficacy studies were either the proposed products, or a 3 chamber product that allowed blinding: the 20 mg 3 chamber product had active in the middle 20 mg section and placebo in the outer two 10 mg sections; the 30 mg 3 chamber product had active in the middle section and one of the outer sections; and the 40 mg 3 chamber product had active in all three sections. The area of active material in contact with the skin for each 3 chamber product was the same as for the proposed 20 mg, 30 mg and 40 mg, 1 chamber products. Study HP5303-01 demonstrated that the amount of buprenorphine absorbed is proportional to this area. So each strength of the 3 chamber product can be considered equivalent to the corresponding strength of the 1 chamber commercial product.

Figure 4: Structure of the 3 chamber patch used for blinding in studies



Study HP5303/01

Study HP5303/01 compared the proposed 20 mg (35 µg/h) and 40 mg (70 µg/h) products to an intravenous infusion in an attempt to determine the absolute bioavailability and examine dose proportionality. The infusion was for 30 mins and the patches were in place for 72 hours.

Due to a procedural error, the absolute bioavailability could not be determined. From the data provided this could be estimated to be about 6% after a 3 day period, which is probably a low estimate given the absolute bioavailability for Norspan is approximately15% after a 7 day period. The results of the two patches were dose

[6] The maximum time recommended for application of the patch in the proposed PI is 96 hours. (4 days).

proportional for both area under the concentration time curve (AUC) and maximum observed concentration (C_{max}) with a time to reach C_{max} (T_{max}) for both of approximately 60 hours.

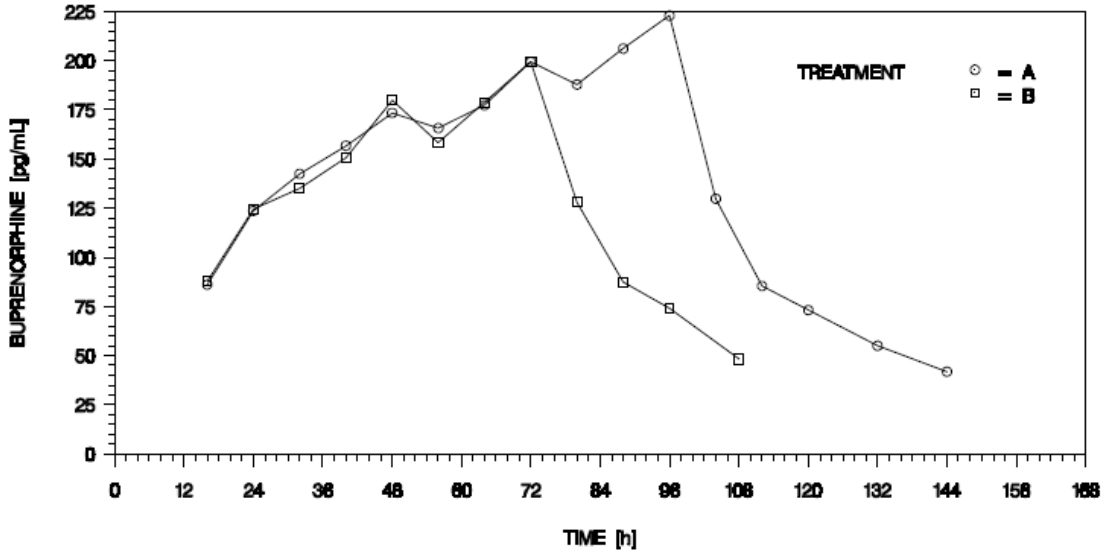
PK profiles are shown in Figure 2 above.

Study HP5303/04

Study HP5303/04 compared the bioavailability of the 20 mg (35 µg/h) product after being in place for 72 and 96 hours (3 and 4 days).

- Absorption of buprenorphine continued to 96 hours with no decrease in the plasma levels between 72 and 96 hours.
- After 96 hours the normalised AUC (5.85 pg.h/mL/mg) was similar to that at 72 hours (5.64 pg.h/mL/mg).

Figure 5: Concentration time profiles of buprenorphine following application of the two transdermal treatments; A (application of patch for 96 hours) and B (application for 72 hours)



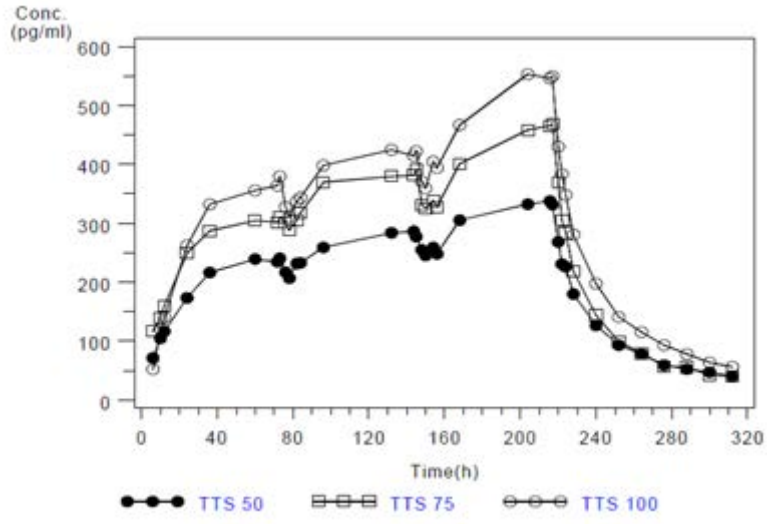
Study HP5303/02

Study HP5303/02 compared the proposed 20 mg (35 µg/h), 30 mg (52.5 µg/h) and 40 mg (70 µg/h) products on multiple administration. The patches were in place for 3 x 72 hours (216 hours in total).

- The AUC of each strength increased from patch 1 to patch 2 to patch 3, but the increase from patch 2 to patch 3 was less than the increase from patch 1 to patch 2. It was calculated that steady state was reached at approximately200 hours (16 hours before removal of the third patch). The accumulation ratio from patch 1 to patch 2 was 1.49 and from patch 2 to patch 3 was 1.18.
- The levels of buprenorphine drop slightly when changing from one patch to the next, but this does not lead to significantly low levels of buprenorphine (claimed to be below 100 pg/mL).
- The increase in AUC and C_{max} when comparing the 20 mg and 30 mg products was by a factor of 1.35 which is less than the expected increase by a factor of 1.5 based on the strength and surface area.

- The increase in AUC and C_{max} when comparing the 30 mg and 40 mg products was by a factor of 1.11 which is less than the expected increase by a factor of 1.33 based on the strength and surface area.
- The increase in AUC and C_{max} when comparing the 20 mg and 40 mg products was by a factor of 1.50 which is less than the expected increase by a factor of 2 based on the strength and surface area.
- It might be concluded from the above that results do not show dose proportionality. However, the 90% confidence intervals for the above comparisons did include 1 and this was a parallel group study and as such the results are less predictive of dose proportionality than study HP5303/01 which was a crossover study.

Figure 6: Mean concentration-time profiles for buprenorphine



Note TTS 50 = 20 mg 35 µg/h, TTS 75 = 30 mg 52.5 µg/h and TTS 100 = 40 mg 70 µg/h

- No dose dumping was observed in any of these bioavailability studies.
- The test methods used to detect buprenorphine in subject plasma samples were acceptable. However the levels of the metabolite norbuprenorphine (that may decrease respiratory rate) were not determined. The sponsor has provided clinical arguments to support this approach which were brought to the attention of the clinical evaluator.

Quality summary and conclusions

Approval of the products is recommended with respect to chemistry, manufacturing and control.

From a pharmaceutical chemistry point of view the bioavailability data are acceptable, but this might not be the case from a clinical perspective.

III. Nonclinical findings

Pharmacology

Primary pharmacology

The pharmacology of buprenorphine is well established, and more recently better understood in relation to ceiling effects and dose response curves for analgesia and respiratory depression. Several previously unevaluated pharmacology studies were included in this submission which expands the general information known about the pharmacology of buprenorphine.

Toxicology

Toxicity

Carcinogenicity

Some carcinogenicity studies have previously been evaluated by the TGA for Norspan, including two using the dermal route in rodents (BUP-P-012, BUP-N-004). The current submission also referenced the German summary of product characteristics (SmPC) for Temgesic.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0–24h}$, using the maximum recommended human dose (MRHD). In the draft PI document, the MRHD of Transtec is not clearly stated, but the wording under dosage and administration, '*At the same time no more than two transdermal patches regardless of the strength should be applied*', appears to indicate the MRHD as two of the highest strength patches (70 µg/h). There are no human exposure data for this dose; however, clinical Study PK402 provides plasma AUC data for three consecutive 3 day application periods (Days 0 to 3, 3 to 6, and 6 to 9), showing increasing exposure with each application (the AUC for Days 6 to 9 was almost twice the AUC for Days 0 to 3). Clinical Study WIS-BUP02PK (using five consecutive 3 day applications) found that plasma concentrations reached steady state with the third and subsequent patches. Therefore, the plasma $AUC_{6\text{-}9days}$ value of 34.723 ng.h/mL, (70 µg/h patch; Study PK402) has been selected for relative exposure comparisons; for two simultaneously applied 70 µg/h patches, this equates to an $AUC_{6\text{-}9days}$ value of 69.446 ng.h/mL and an estimated steady state $AUC_{0\text{-}24h}$ value of 23.149 ng.h/mL.

Table 4: Relative exposure to buprenorphine in carcinogenicity studies, for Transtec and Norspan

Species	Dose (mg/kg/day)	Buprenorphine		
		$AUC_{0-24\,h}$ (ng·h/mL) M/F	Exposure ratio (Transtec)[b] M/F	Exposure ratio (Norspan)[c] M/F
Mouse (Tg.AC) [Study BUP-P-012]	18.75	540/549	23/24	45/46
	37.5	798/713	34/31	67/59
	150	1,565/909	68/39	130/76
	600	3,391/1,968	146/85	283/164
Rat (SD) [Study BUP-N-004]	20	1,153/900	50/39	96/75
	60	1,768/1,706	76/73	147/142
	200	2,648/2,794	114/120	221/233
Human (healthy subjects)	[70 µg/h BUP-TDP] 2 x 70 µg/h Transtec [a]	23.15	–	

[a] MRHD from Transtec PI is 2 x 70 µg/h patches (see text); [b] at Transtec MRHD; [c] results for Norspan 40 mg (40 µg/h) patch with AUC_{0-24h} of 12.0 ng.h/mL. M = male; F = female

Exposure ratios for Transtec are about half those for Norspan but are still high and considered adequate. As such, the large safety margins allow similar conclusions to be drawn in that it is unlikely that the drug related testicular tumours observed in male rats at ≥ 60 mg/kg/day are of clinical significance. Furthermore, no drug related tumours were observed in female rats.

The Norspan evaluation also considered relative exposure to the metabolite norbuprenorphine in the carcinogenicity studies. For simplicity, these ratios are not tabulated above but remain adequate for the Transtec evaluation.

Reproductive toxicity

As no new reproductive toxicity data were submitted, reference was made to previously evaluated studies and published literature. The tabulated exposure ratios for Transtec (below) have been derived by comparing the plasma $AUC_{6\text{-}9days}$ value of 34.723 ng.h/mL (70 µg/h patch; clinical Study PK402) x 2 for two simultaneously applied 70 µg/h patches, giving a 3 day AUC value of 69.446 ng.h/mL, with the animal $AUC_{0\text{-}72h}$ values. For comparison, exposure ratios previously derived for Norspan are reproduced also.

Table 5: Exposure ratios for Transtec and Norspan

Species	Study	Dose (mg patch)	AUC0–72 h (ng·h/mL)	2×AUC0–72 h (ng·h/mL)	Exposure ratio [d] (Transtec)	Exposure ratio [e] (Norspan)
Rat (SD)	Fertility [Study NDSE-554]	1.25	197	394	3	5
		5	890	1,780	13	21

Species	Study	Dose (mg patch)	AUC0–72 h (ng·h/mL)	2×AUC0–72 h (ng·h/mL)	Exposure ratio [d] (Transtec)	Exposure ratio [e] (Norspan)
		20	2,938	5,876	42	70
	Embryofetal development [Study NDSE-527][a]	1.25	69.8	139.6	1	2
		5	234	468	3	6
		20	1,993	3,986	28	47
	Pre/postnatal [Study NDSE-555]	1.25	149	298	2	4
Rabbit (NZW)	Embryofetal development [Study DSE-395]	80	43.6[b]	87.2	0.6	1
Human (healthy subjects)	[PK402]	[70 µg/h BUP-TDP] 2 x 70 µg/h Transtec [c]	69.45[c]	–	–	–

[a] Data from evaluation report for application 99-3667-3; [b] Data from dose-ranging study; [c] MRHD from Transtec PI is 2 x 70 µg/h patches (34.723 ng.h/mL x2; see text); [d] at Transtec MRHD, animal AUC_{0-72h} :human AUC_{0-72h}; [e] results for Norspan 40 mg (40 µg/h) patch with AUC_{0-168h} of 84 ng.h/mL, 2× animal AUC_{0-72h} :human AUC_{0-168h} (application PM-2013-03232-1-1).

As with the rat carcinogenicity study, exposure ratios for Transtec are about half those for Norspan but are still considered adequate. Although the exposure ratio for the rabbit embryofetal development study is < 1, there were no adverse effects on embryofetal development in the subcutaneous (SC) dosing arm of this study (up to 10 mg/kg/day) and also NDSE-528-GLP (up to 5 mg/kg/day SC), which achieved much greater plasma exposures (≥ 38 x clinical exposure at the MRHD for Transtec).[7]

The conclusions drawn for Norspan were:

> no adverse effects on fertility or embryonic development were seen in rats when treated males and females were paired, and no adverse effects on embryofetal development were seen at the highest tested dermal doses in rats (20 mg patch), and in rabbits (80 mg patch). As with the previous Norspan evaluation, the drug related lower neonatal survival needs to be retained in the pregnancy section of the PI.

Nonclinical summary and conclusions

- Buprenorphine has been registered for many years and no additional safety concerns are predicted for Transtec. The nonclinical dossier included new pharmacology studies and two toxicity studies of excipients used in the transdermal patch adhesive matrix.

[7] Based on rabbit AUC_{0-24h} of 880 ng h/mL (on Day 19, 5 mg/kg/day SC; NDSE-528-GLP) and 1575 ng h/mL (on Day 6, 10 mg/kg/day SC; DSE-395-GLP) and a human AUC_{0-24h} of 23.15 ng h/mL.

- The proposed MRHD of buprenorphine is greater for Transtec (70 µg h/mL x 2 patches) compared to that for Norspan (40 µg/h total). The estimated plasma AUC at the Transtec MRHD is about 2 fold greater than at the Norspan MRHD, and the safety margins for the previously evaluated pivotal toxicity (carcinogenicity, reproductive toxicity) studies conducted for Norspan submissions were reduced by about half, but are still adequate. The Transtec patches are not expected to present any new or greater systemic toxicities than those observed with the currently registered Norspan patches.
- The results of several nonclinical pharmacology studies were consistent with the known pharmacology of buprenorphine. The issue of a 'ceiling effect' for analgesia will require assessment by the clinical evaluator.
- The additives Durotak 387-2051 and Durotak 387-2054 (previously evaluated) were found to comply with USP in a standard battery of toxicity tests, and as such raise no toxicity concerns.
- There are no nonclinical objections to the registration of Transtec patches at the proposed strengths.

The nonclinical evaluator also made recommendations regarding the PI but these are beyond the scope of the AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 1.

Introduction

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

Buprenorphine was first synthesised in the late 1960s, and introduced into worldwide clinical practice in a parenteral formulation in the late 1970s. Sublingual and transdermal formulations subsequently became available. Formulations of buprenorphine for intravenous and SL administration were first registered for use in Australia in 1991 with the indication of short term (not more than one week) relief of moderate to severe pain[8]. A transdermal form, Norspan (from the same sponsor as the current application), was registered in Australia in April 2005 for the indication of moderate to severe pain.[9] Sublingual dosing forms are also available for the management of opiate dependence.

The proposed indication of the new dosing strengths and regimen is the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids. The following dosage forms and strengths currently registered in Australia are shown in Table 6 below.

[8] Temgesic PI accessed February 2015
[9] Norspan PI. Date of last amendment 25 August 2009.

Table 6: Currently registered forms of buprenorphine

Tradename	Dosage form	Strengths	Indication
Temgesic	Sublingual, Intravenous	0. 2 mg tablet, 0.3mg ampoule	Acute moderate to severe pain
Norspan*	Transdermal patch changed every 7 days	5, 10, 15, 20, 25, 30 ,40 µg/hr	Moderate to severe pain
Bupadex	Sublingual (SL) tablet	0.2, 4, 8 mg	Management of opiate dependence
Subutex	Sublingual (SL) tablet	0.4, 2, 8, 16 mg	Management of opiate dependence
Bupradone, Subuxone	Sublingual (SL), combination with naloxone	various	Management of opiate dependence

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

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

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

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

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

Comment: The proposed patch strengths supplement the currently registered buprenorphine patches (Norspan), with substantially lower dose strengths available in the Norspan formulation (see Table 6 above). The recommendation of the draft Transtec PI that all patients, from the opioid naïve to those on moderate doses of opioids, commence on the Transtec 35 µg/h strength patch does not consider the availability of lower patch strengths in the Norspan formulation (see description below). Given the high

rate of discontinuations seen in the clinical studies due to opioid type adverse events (AEs) in opioid naïve patients, it may be more appropriate that opioid naïve patients commence on a lower strength Norspan patch; the Australian Therapeutic Guidelines: Analgesic[10] recommend initiating patients on a 5 µg/h strength patch. The full range of buprenorphine patches (both seven day and four day formulations) should be considered when determining the most appropriate starting point for patients already receiving opioids.

The PI proposes a maximum dose of two 70 µg/h patches although the maximum dose used in the clinical trials was 70 µg/h and the higher dose was rarely reported as being used in the post-marketing surveillance studies. The rationale for the maximum dose of 2 x 70 µg/h patches provided in the clinical overview is that this would allow for the additional SL buprenorphine tablets used in the clinical studies and because this dose would correspond to 240 mg of oral morphine. This was not further substantiated by an estimate of the additional buprenorphine tablets taken in the studies and whether this equated to a second 40 mg patch. Nor was there any reference for the statement regarding equipotency to 240 mg of morphine.[11]An upper dose limit of one 70 µg/h patch would be more in keeping with the dose tested in the studies.

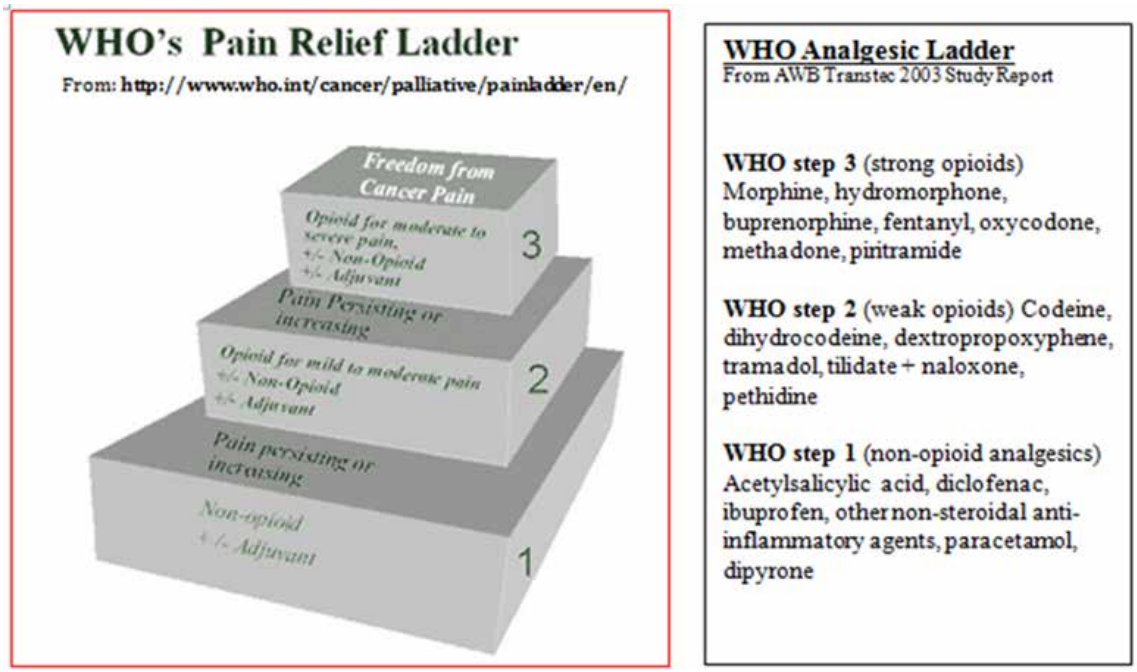
Clinical rationale

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

The World Health Organisation (WHO) proposed a simple stepwise approach to chronic pain (Figure 7): commencing with WHO Level 1 non opioid drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and/or paracetamol, progressing to WHO Level 2 with weak opioids for mild to moderate pain and then escalating to WHO Level 3 by adding a strong opioid for moderate to severe pain. At each level, drug administration was to be regular and options for breakthrough pain provided. This ladder was proposed in 1994 for use in cancer pain and has since also been used for chronic pain of all causes. Terminology related to the WHO Pain Relief Ladder is used throughout the report.

[10] Chronic pain: pharmacological management 113-134. Therapeutic Guidelines: Analgesic, Version 6, 2012.
[11] This issue was resolved during the second round of evaluation.

Figure 7: WHO's pain relief ladder



Buprenorphine is a potent opioid analgesic that has been used for several decades in the treatment of moderate to severe acute (for example, postoperative) pain, acute and chronic cancer pain, and severe chronic non cancer pain. In some countries, including Australia, buprenorphine has also been used in the management of opioid dependence, with doses well above the analgesic range.

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

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

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

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

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

The dossier prefers to refer to the different patches by their 'release rate'. This is the nominal average in vivo absorption rate. The term 'release rate' suggests an active controlled process by the patch, rather than the passive diffusion that is occurring. It also implies a consistency in absorption over time and between patients. It may be more correct to refer to the patches by the total amount of buprenorphine contained within the patch and the application time.[12]

The Seven Day Norspan Patch: Another buprenorphine product using the same transdermal delivery system, but with a seven day application time, was registered in Australia in 2005 under the tradename Norspan. This patch is not discussed in the dossier but needs to be considered given the close relationship between the two patch formulations and frequent reference to the 7 day product in this evaluation. The Norspan patches available at the time of Australian registration were 5, 10 and 20 µg/h with higher strength patches (30 µg/h and 40 µg/h) becoming available recently. The dosing interval for Norspan patches is 7 days and the indication is 'moderate to severe pain'. The seven day patch has been marketed in the USA since 2010 as Butrans that is sponsored by Purdue Pharma LP and manufactured by [information redacted].[13] The manufacturer of the buprenorphine patch that is the subject of the current submission is [information redacted] and the Australian sponsor is Mundipharma Pty Ltd.

Absorption of buprenorphine from a matrix patch worn over seven days is greater during the first few days of wear compared to the last few days. The use of a shorter dosing interval, such as 3 or 4 days, enables higher plasma concentrations to be achieved by exploiting this higher flux during the first few days. As an example, the 20 mg patch is common to both Norspan and Transtec and the area of active matrix in each is 25cm^2:

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

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

1. a beige coloured web backing layer of polyethylene terephalate (PET)

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

[13] http://www.drugs.com/pro/butrans-patch.html

2. an adhesive matrix rim without buprenorphine (provides a seal around the active drug matrix)
3. a separating layer ('foil') of PET over the adhesive matrix
4. the buprenorphine containing adhesive matrix
5. a release liner, this is removed and discarded before use.

See Figure 1 for a diagram of the structure of the Norspan/ Butrans patch.

Table 7: Patch strength and size

Purported Release Rate	Amount of Buprenorphine	Area of Active Matrix	Approximate size of patch as worn
35 µg/h	20 mg	25 cm^2	52 cm^2
52.5 µg/h	30 mg	37.5 cm^2	70 cm^2
70 µg/h	40 mg	50 cm^2	88 cm^2

Comment:

- This formulation was used in the clinical trials and is the same formulation as the currently registered Norspan patches.
- Buprenorphine 'release rates' calculated prior to clinical testing were found to be an over estimation in clinical pharmacokinetic studies. Example: the 20 mg patch release was found to have an average release rate of 35 µg/h rather than the estimated 50 µg/h. Many of the studies provided in the dossier use a terminology based on the initial estimates of release rates (TTS50, TTS70 and TTS100), as will be evident in tables and figures taken from the study reports.
- The dosing interval used in the clinical studies was 72 hours. An additional pharmacokinetic study and two population pharmacokinetic studies[14] were performed with the objective of showing bioequivalence for 72 hour and 96 hour dosing intervals.
- The post-marketing surveillance studies report patients wearing ⅛, ¼ and ½ of the 20 mg patch despite the advice in the consumer medicine information (CMI): 'Do not cut or divide the patch'.

Guidance

The guidance on clinical investigation of medicinal products for treatment of nociceptive pain [15] came into operation in the EU in 2003 and was adopted by the TGA in 2005. The guideline on clinical medicinal products intended for the treatment of neuropathic pain[16] was also adopted by the TGA in 2005. This latter guideline was replaced by a revision involving the paediatric section in 2009.

[14] Correction: there were 2 studies one was a population PK study and the other was a Wagner –Nelson analysis.
[15] CPMP/EWP/612/00 Note For Guidance On Clinical Investigation Of Medicinal Products For Treatment Of Nociceptive Pain
[16] CPMP/EWP/252/03 Guideline on Clinical Medicinal Products Intended for the Treatment of Neuropathic Pain

Contents of the clinical dossier

The submission contained the following clinical information:

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

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

Comment: Much of the clinical dossier appears to have been written and assembled almost 10 years ago, in 2005. The clinical overview, although dated August 2014, contains little information and no references more recent than 2005.The Summary of Clinical Safety is dated 15 November 2005 and has not been updated.[17] The Risk Management Plan (RMP) is dated 31 October 2014. There were considerable discrepancies and inconsistencies across the three documents. In particular, the RMP describes two major new safety issues. Neither of these is discussed in the clinical overview and only one is discussed in the Summary of Clinical Safety.

Grunenthal sponsored Phase III studies[17] and post marketing surveillance studies that were performed after 2005 (and described in the PSURs) were not included in the dossier.

None of the research involving the closely related 7 day buprenorphine patch was included in the dossier, despite the active and ongoing research

[17] Clarification; as no new clinical trials (or Phase III studies) had been performed there was no requirement to update the Summary of Clinical Safety.

programme conducted by [information redacted].[18] Not all cited references were provided. One frequently cited reference was only provided in German.[19]

Paediatric data

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

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

Good clinical practice

The submission states that the clinical trials, which were all conducted in Europe, were conducted in accordance with Good Clinical Practice[15]. Review of the study reports supports this.

Pharmacokinetics

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

Studies providing pharmacokinetic data

Summaries of the pharmacokinetic studies were provided. Table 8 shows the studies relating to each pharmacokinetic topic.

[18] Data from the 7 day patch was made available where it was relevant in response to TGA questions.
[19] This was corrected after the TGA notified the applicant.

Table 8: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	Primary aim of study*
PK in healthy adults	General PK- Single dose	LAB91206	PK*
		HP5303/01	Dose proportionality
		HP5303/04	72 h versus 96 h wear time
	General PK Multi-dose	HP5303/02	PK with repeated dose
	Bioequivalence† - Single dose	HP5303/01	
	Bioequivalence - Multi-dose		
	Food effect	Not applicable	
	Factors affecting absorption	Not included	
PK in special populations	Target population; § Single dose		
	Target population; Multi-dose	WIS-BUP02PK	PK with repeated dose
	Hepatic impairment	Not included	
	Renal impairment	Not included	
	Neonates/infants/children/adolescents	Not included	
	Elderly	Not included	
	{Other special population}	Not included	
Genetic/gender-related PK	Males versus females	WIS-BUP02PK	
	Other genetic variables	Not included	
PK interactions	Any	Not included	
Population PK analyses	Healthy subjects	PP0017P	Bioequivalence of 72 and 96 h wear times
	Healthy subjects	PK761	Bioequivalence of 72 and 96h wear times
	Target population, Other	Not included	

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

Pharmacokinetic results that were excluded

The PK results from Study WIS-BUP02PK were excluded from consideration due to study deficiencies. Study WIS-BUP02PK examined the PK of multiple dosing was excluded because the steady state and lack of accumulation with multiple dosing were not demonstrated.

For further detail of the studies and their evaluation please see Attachment 1.

Evaluator's conclusions on pharmacokinetics

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

Some specific issues related to the patches were not tested:

- Patch application to the infra clavicular region and upper back was described in the studies. No comparison of absorption from these sites was provided nor was there any investigation of the effects activity on adhesion and absorption.
- The dossier describes the possibility of increased absorption with increased heat (local and systemic). The draft CMI notes that the patch should not be exposed to excessive heat (for example sauna, infrared radiation). The dossier, however, does not include any testing of the effect of heat on the patch, although this information is apparently available for the sponsor's product Norspan.[20]
- Increased absorption from the patch was noted when there was only a three days gap before reusing a skin site in Study HP5303/02. The draft PI recommends that '*At least one week should elapse before a new transdermal patch is applied to the same area of skin*'. The dossier does not provide any evidence to support this as an adequate interval. The Australian PI for Norspan states that '*In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events*' and that '*A new patch should not be applied to the same skin site for 3 to 4 weeks*'.

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

The PK of buprenorphine after absorption is heavily dependent on existing literature regarding buprenorphine administered by other routes. Many of the studies on which the

[20] Clarification: The original dossier, however, did not include any testing of the effect of heat on the patch, although this information was subsequently supplied in full in response to questions (as previously provided for the sponsor's product Norspan).

PK information is based were performed in the 1980's and 1990's and involved small numbers of patients. Information regarding use in special populations and drug interactions is extremely limited and there is no evidence of consideration of the literature since 2006.[21] There is scant information provided regarding PK drug interactions and dependence appears to be on post-marketing surveillance over the 30 to 40 years of use to have revealed any major interactions or issues. There are also inconsistencies between the documents provided. For example, the Transtec PI states 'There is evidence of enterohepatic recirculation'. This PK property is not discussed in the nonclinical overview or the clinical overview of PK properties of buprenorphine.

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

Pharmacodynamics

Studies providing pharmacodynamic data

Two of the clinical PK studies, HP5303/01 and HP5303/02, also provided data on pharmacodynamics (PD) but only for the variable of pupil size. Table 9 shows the 2 studies. Neither of these studies had deficiencies that excluded their results from consideration.

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

Table 9: Submitted pharmacodynamic studies

PD Topic	Subtopic	Study ID	*Primary Aim
Primary Pharmacology	Effect on pupil size and reactivity	HP5303/01	Pharmacokinetics
		HP5303/02	Pharmacokinetics
Secondary pharmacology	QT prolongation	BUP101**	Evaluate QT prolongation

* Indicates the primary aim of the study. ** BUP1011 was not submitted in the dossier but was included in an appendix to a PSUR. It is included here due to its importance.

For further detail of the studies and their evaluation please see Attachment 1.

Evaluator's conclusions on pharmacodynamics

Limited information regarding the specific pharmacodynamics of the buprenorphine transdermal delivery system is provided. Information regarding pharmacodynamics is largely based on the literature available regarding the administration of buprenorphine by

[21] Clarification: regular review of the literature has not revealed any new relevant publications on Transtec since 2006.
[22] Data from the 7 day patch was made available where it was relevant in response to TGA questions.
[23] This study was subsequently provided, together with expert overviews, in response to the TGA's questions.

other routes. This section of the clinical overview appeared to have been compiled in 2006 and not subsequently updated. This resulted in significant gaps in the discussion provided, for example there was no discussion of the effect of buprenorphine at the Human Ether-a-Go-Go-Related Gene (HERG) potassium channel and the implication of this.[24]

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

A question mark remains over the potential for the life threatening arrhythmia of polymorphic ventricular tachycardia Torsades de Points (TdP). Of note is that the PI for the sponsor's 7 day patch Norspan[9] includes the following paragraph under Precautions:

> *In a study of the effect of Norspan patches on the QTc[25] interval in 131 healthy males, therapeutic dosages (10 µg/h) had no effect on the QTci[26] interval. Higher dosages (40 µg/h) and the active control (moxifloxacin 400 mg) each produced increases of 5.9 ms in the QTci interval. This observation should be considered when prescribing Norspan patches for patients with congenital QT prolongation and for patients taking antiarrhythmic medications in either Class 1A (for example quinidine, procainamide) or in Class III (for example amiodarone, sotalol) or any other medication which prolongs the QT[27] interval.*

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

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

The extent of the information provided regarding equipotent doses of buprenorphine and other opioid analgesics is the estimate of intramuscular buprenorphine being 25 to 50 times more potent than intra muscular morphine. Information regarding equipotent doses of buprenorphine and the formulations of other opioids used in the management of chronic pain (for example oral morphine) would be helpful with respect to advice

[24] Clarification: buprenorphine's potential to cause QT prolongation has been discussed in the RMP
[25] QTc = corrected QT interval
[26] QTci = individually corrected QT interval Definition of QTci Individually Corrected: A corrected QT interval which takes into account the physiologic shortening of the QT interval which occurs as the heart rate increases. Correction method applies regression analysis techniques to individual subject pre-therapy QT and RR interval data over a range of heart rates, then applies this correction to on-treatment QT values. This method theoretically corrects the QT interval to that which would be observed at a heart rate of 1 cycle per second.
[27] QT interval for heart rate; the measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. The QT interval represents the depolarisation and repolarisation of the ventricles.

regarding switching. The draft PI advises that '*Clinical experience has shown that patients who were previously treated with higher daily dosages of a strong opioid (in the dimension of approximately 120 mg oral morphine) may start the therapy with the next higher transdermal patch strength*'. The source of this information is not provided in the PI and the issue is not discussed in the clinical overview.

Genetic polymorphism sees a variation between ethnic groups in their sensitivity to the effects of opioids. This was not discussed in the dossier.

The discussion of pharmacodynamic drug interactions is limited and the publications referred to date from 1991 to 1993.[28] Given the frequency with which new drugs and new classes of drugs are developed, it is concerning that there is no evidence of a recent evaluation of pharmacodynamics drug interactions, for example potential interaction with other drugs known to prolong the QT interval.

The potential for naloxone to reverse the unwanted effects of buprenorphine, especially in overdose, also remains problematic. The draft PI recommends an initial bolus of 1 to 2 mg intravenously with this followed by an infusion. This initial dose may be inadequate and an initial bolus dose of 2 to 4 mg more appropriate, with a similarly high dose infusion rate (4 mg/hour) to follow. The Naloxone PI identified in the Transtec PI section on overdose indicates an inordinately high intravenous fluid rate of 1L/hour given the recommendation: 'For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9% or glucose 5% injection to produce a solution containing 4 micrograms/mL'.[29] It would be helpful if advice could be provided in the Transtec PI regarding the management of overdoses and the safety of a more concentrated solution of naloxone.

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

Dosage selection for the pivotal studies

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

- Three buprenorphine patch strengths are proposed, 20 mg, 30 mg and 40 mg. These are said to provide an average release rate of 35 µg/h, 52.5 µg/h and 70 µg/h on the basis of the findings in the 2004 Study PK1599. Prior to this study, the average release rates had been estimated to be 50 µg/h, 75 µg/h and 100 µg/h.
- The application period was 72 hours (three days) for each patch. This interval results from the patch technology, pharmaceutical and PK properties of the transdermal therapeutic system and from the skin physiology.

The dose provided over 24 hours by the range of three strength buprenorphine patches was estimated to correspond to 0.8 to 1.6 mg daily buprenorphine, as calculated from the average release rates determined in PK1599. A dose of 0.8 to 1.6 mg buprenorphine sublingually was said to be the daily dose in common practice (at the time and place of the trials; Europe in the late 1990s) in the treatment of moderate to severe chronic pain. This range was also said to represent the overlapping zone of WHO Level 2 to 3 and can be understood as an entrance dose range into WHO Level 3

[28] Clarification: The sponsor has advised that regular literature searches are conducted and were referred to in PSURs that were subsequently submitted. No further publications were identified.
[29] DBL Naloxone hydrochloride injection product information. Accessed Feb 2015

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

Comment: According to the original estimates of release rates from the three strength buprenorphine patches, the daily dose provided would have been 1.2 mg, 1.8 mg and 2.4 mg respectively. The rationale for this dose selection in the development of the patches was not provided in the dossier.[30]

The average release rates calculated in the PK Study PK1599, reported in 2004, were 35 µg/h, 52.5 µg/h and 70 µg/h, equating to an average daily dose of 0.84 mg, 1.26 mg and 1.68 mg for the 20 mg, 30 mg and 40 mg patch respectively. There was considerable inter patient variability in absorption from the buprenorphine patches shown in Study PK1599. Minimum and maximum daily doses can be calculated using the ranges measured for individual patients. This shows that the daily dose delivered from a 20 mg patch could range from 0.048 mg to 1.92 mg and the range for a 40 mg patch could be 0.036 mg to 3.10 mg.

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

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

The dose of 0.8 to 1.6 mg of SL buprenorphine was stated to be the daily dose in common practice (at the time and place of the trials) in the treatment of moderate to severe chronic pain. No references were provided nor could this be established in the dossier.

Tramadol is generally classed as a 'weak opioid', fitting in Level 2 of the WHO analgesic ladder (mild to moderate pain). The dossier seeks to position the buprenorphine patches as suitable for use in moderate to severe pain (WHO Level 3) or for patients transitioning from WHO Level 2 to WHO Level 3.[31]

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

Efficacy

Studies providing efficacy data

The sponsor sought to establish efficacy through the presentation of:

- 6 efficacy studies with

[30] The sponsor subsequently submitted literature to demonstrate that at the time of development of this product, total daily doses of buprenorphine were consistent with the doses proposed.
[31] This was addressed during TGA's evaluation of the company's response.

  - 3 pivotal placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) in patients with tumour or non tumour related pain
  - 1 placebo controlled withdrawal study (PB-TTC-02) in patients with tumour related pain
  - 2 non inferiority efficacy studies (PB-TTC-01 and BUP4201; both with prolonged release tramadol as a comparator) in patients with non tumour related pain
  - 1 post-hoc analysis of the 3 pivotal efficacy studies
- 2 uncontrolled extension studies (WIS-BUP-LTS and PB-TTC-01 follow-up)
- 10 non interventional post-marketing surveillance studies, 2 with comparator arms (tramadol, fentanyl patch).

Table 10: Efficacy studies

Study Identifier	Type of trial	Description provided in Attachment 1
WIS-BUP01	Placebo controlled, double blind, parallel group trial with run-in phase – three strength patches, tumour and non-tumour. Duration 15 days	Detailed
WIS-BUP02	Placebo controlled, double blind, parallel group trial – three strength patches, tumour and non-tumour. Duration 15 days	Detailed
WIS-BUP03	Placebo controlled, double blind, parallel group trial – 20 mg patch only, tumour and non-tumour. Duration 16 days	Detailed
PB-TTC-02	Placebo controlled, double blind parallel group trial with run-in phase - 40 mg patch only, tumour patients. Duration 30 days	Detailed
PB-TTC-01	Active controlled (Tramadol SR), double blind trial in patients with non tumour pain. Duration 4 weeks.	Detailed
BUP4201	Active controlled (Tramadol SR), double blind trial in patients with osteoarthritis. Duration 5-8 weeks	Detailed
WIS-BUP-LTS	Uncontrolled follow-up	Summary
PB-TTC-01 follow-up	6 month uncontrolled follow-up	Summary
AWB Transtec 2001/1*	Post-marketing surveillance study	Summary
PM Transtec 2001/2	Post-marketing surveillance study	Summary
AWB Transtec 2003*	Post-marketing surveillance study	Summary
AWB Transteconco 2003	Post-marketing surveillance study	Summary
AWB Transtec Pro 2005/2	Post-marketing surveillance study	Summary

Study Identifier	Type of trial	Description provided in Attachment 1
GRU-BUP-2002-01*	Post-marketing surveillance study	Summary
BIOC/11/03/04*	Post-marketing surveillance study	Summary
Cohort trial Transtec versus. Durogesic *	Post-marketing surveillance study – buprenorphine compared to fentanyl patch	Summary
TTC-MATRIX-AWB-2003*	Post-marketing surveillance study	Summary
BUP4202	Post-marketing surveillance study	Summary
Report WIS-BUP123	Combined efficacy analysis of WIS-BUP01, 02 &03	Brief

* Post marketing surveillance studies discussed in the clinical overview

Comment: The most recent clinical study provided in the dossier is from 2004. The most recent post marketing surveillance study discussed in the clinical overview is from 2004. It is apparent from the listings of new studies provided in the PSURs that more recent studies have been conducted (including 9 post-marketing surveillance studies from 2008 to 2013). Relevant clinical studies, including ones sponsored by [information redacted], dating from after 2004 have not been included in the dossier.[32]

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

Pivotal efficacy studies

- The dossier describes the three placebo controlled studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03 as pivotal studies, despite the pre-defined primary variable analysis failing to demonstrate efficacy in all three trials. The primary outcome in each was the response rate, with this defined by a composite endpoint of patient assessed pain relief and some measure of SL buprenorphine tablets taken for breakthrough pain during patch wearing.
- The three pivotal studies were performed some time ago: WIS-BUP01: 1995 to 1998; WIS-BUP02: 1996 to 1998; WIS-BUP03: 1995 to 1997. This transdermal buprenorphine system was first registered in 2000. The regulatory environment fifteen years ago was different. The guideline for guidance on clinical investigation of medicinal products for treatment of nociceptive pain [15] came into operation in the EU in 2003 and was adopted by the TGA in 2005. The guideline on clinical medicinal products intended for the treatment of neuropathic pain[16] was also adopted by the TGA in 2005. This latter guideline was replaced by a revision involving the paediatric section in 2009.

[32] The sponsor subsequently submitted additional studies in the PSURs. No interventional studies have been performed by the company since 2005.

- The studies share similar efficacy variables, randomisation and blinding methods and statistical analysis. However, the design of each study is different, as are some of the outcome measures.

Evaluator's conclusions on efficacy

Presented below are the clinical evaluator's conclusions on clinical efficacy for the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.

Efficacy and the pivotal studies: WIS-BUP01, WIS-BUP02, WIS-BUP03 and WIS-BUP123

The dossier presented 3 'pivotal' randomised, double blind placebo controlled efficacy studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03. The three studies were all performed in Europe between 1995 and 1998. No more recent placebo controlled studies on the whole target population were included in the dossier. The three studies shared similar efficacy measures but each had a different design.

Table 11: Summary of the 'pivotal' efficacy trials

Study Identifier	Type of trial	Patient group	Treatments	Patient Nos	Duration
WIS-BUP01	Placebo controlled, double blind, parallel group trial; 5 day open run-in phase (buprenorphine SL); 6 day (2 patches) double blind; 72 hours per patch	Chronic tumour and non tumour pain.	A: placebo B: 20 mg patch C: 30 mg patch D: 40 mg patch All groups: rescue medication buprenorphine SL	A: 37 B: 35 C: 41 D: 38 Total: 151	11 days
WIS-BUP02	Placebo controlled, double blind, parallel group trial; no run-in, 15 days (5patches); 72 hours per patch	Chronic tumour and non tumour pain.	A: placebo B: 20 mg patch C: 30 mg patch D: 40 mg patch All groups: rescue medication buprenorphine SL	A: 38 B: 41 C: 41 D: 37 Total: 157	15 days
WIS-BUP03	Placebo controlled, double blind, parallel group trial; 6 day open run-in (buprenorphine SL); 9 day (3 patches) double blind; 72 hours per patch	Chronic tumour and non tumour pain.	A: placebo B: 20 mg patch All groups: rescue medication buprenorphine SL	A: 90 B: 47 Total: 137	15 days

From review of the studies, all had appropriate randomisation, blinding and statistical analyses. Inclusion criteria were consistent with the proposed indication and exclusion criteria were consistent with the contra indications to the use of buprenorphine listed in the draft PI. All study participants were accounted for and there were no breaches in protocol that would invalidate the results.

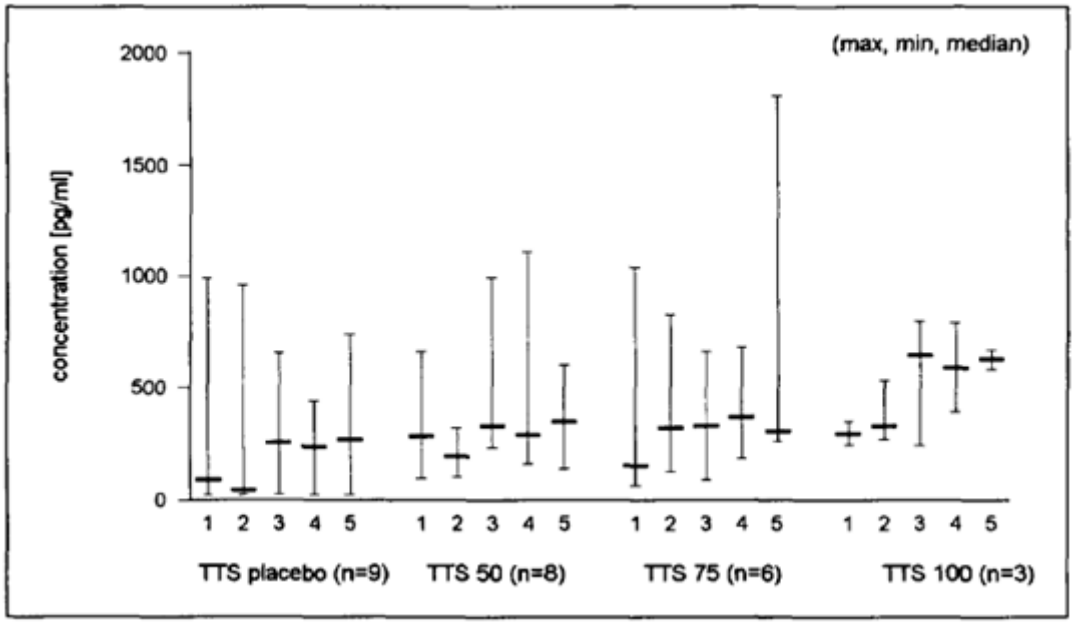
All three studies used a primary efficacy outcome of response rate with responders defined by the combination of the patient's retrospective perception of pain relief as being 'at least satisfactory' on a four point scale and the use of rescue medication being less than a pre-specified level ('not more than 1 additional SL buprenorphine tablet per day' in WIS-BUP01 and WIS-BUP02 and 'at least 40% fewer buprenorphine SL tablets than in the run-in phase' in WIS-BUP03). Secondary efficacy measures included retrospective pain relief, pain intensity, sleep duration, and the use of rescue medication.

There are a number of issues in the study design, and factors that limit generalisability, including:

- Sample size calculations: These were based on unexplained assumptions regarding response rates for both the active and the placebo groups. The estimated response rate in the active group that was used in the calculations was 40% (WIS-BUP02 and WIS-BUP03) and 55% (WIS-BUP01) for the 20 mg patch strength. Higher response rates were assumed for the other patch strengths. The estimated placebo response rate used was 15% (WIS-BUP02 and WIS-BUP03) and 20% (WIS-BUP01). There was no explanation provided for the estimates of the active group and placebo response rates, nor is it clear why they should differ between the studies. In each study, the decision was also made after the sample size calculations to analyse the groups according to tumour or non-tumour sources of pain. The final analysis was stratified by patch strength and source of pain, resulting in small patient numbers in some groups.
- Enrichment: Both WIS-BUP01 and WIS-BUP03 used a study design in which only those patients who had at least satisfactory pain relief on a regimen of SL buprenorphine tablets were able to be enrolled in the double blind assessment phase. This could potentially select out those patients who were likely to be responders for inclusion in the double blind phase.
- Participant number: The sample size calculations resulted in treatment groups that were around 40 patients in WIS-BUP01 and WIS-BUP02, although slightly larger in WIS-BUP 03. Response to therapies in chronic pain is recognised as being highly variable and it can be expected that only a minority of patients with chronic pain are likely to benefit from a specific therapy. Consequently, larger trials may be needed to demonstrate a treatment effect.[33]
- Use of SL buprenorphine as rescue medication in all groups; this potentially enabled patients in the placebo group to self-titrate until pain reached an acceptable level that is the 'placebo' effect may have been more of a SL buprenorphine effect and may have contributed to the high response rates seen in the placebo groups. The PK arm of Study WIS-BUP02 found that plasma buprenorphine levels (although highly variable) were not dissimilar in the placebo group compared to those achieved in the active patch groups.

[33] Moore RA et al. Editor's choice: Challenges in design and interpretation of chronic pain trials *Br. J. Anaesth.* 2013;111:38-45

Figure 8: WIS-BUP02PK: Plasma buprenorphine levels for patients taking none or one additional buprenorphine tablet prior to patch placement and then at removal of each of the 5 patches (transdermal and SL buprenorphine plasma concentrations (pg/mL)



- End point: The level of pain relief chosen in the response rate definition in the three studies was 'at least satisfactory' on a four point scale (unsatisfactory, satisfactory, good and complete). This is a relatively crude measure of pain relief and has largely been replaced by scales that allow finer discrimination with a greater number of points, for example the Box Scale 11[34], an 11 point scale used in PB-TTC-02. It could also be argued that, from a patient's perspective, the aim of pain relief that is 'at least good' would be more desirable. The use of retrospective assessment of pain relief may also introduce inaccuracy as it is dependent on the patient's memory of sensation.
- Prior pain and analgesics: no measure of pain intensity prior to study entry was provided. The majority of patients had been receiving opioids in each study.
- Duration: the studies were of relatively short duration (15 days or less). Medications for chronic pain can be assumed to have use that extends over months and years. Longer clinical trials are, therefore, essential to exclude a transient effect and to investigate such issues as tachyphylaxis, tolerance, dependence and safety. It is recommended that trials investigating therapies for chronic pain have duration of at least 12 weeks.
- Ethnicity: all participants were Caucasian (except for one or two of African descent). Opioids are generally accepted as being ethnically sensitive, with genetic polymorphisms resulting in different responses in different ethnic populations. Although over 90% of the Australian population has Caucasian ancestry there are other ethnic groups represented, including Aboriginal and Torres Strait Islanders (2.5%), Chinese (4%) and Indian (2%).[35]
- Age: only adults were included, although the elderly were not excluded.

[34] Also known as the 11 point numeric rating scale (NRS) with 0 = no pain and 10 = pain as bad as you can imagine.
[35] Reflecting a Nation: Stories from the 2011 Census, 2012–2013.

- Special populations: patients with any major organ disease were excluded from the studies. Concomitant disease was, however, common.
- Use of opioids: the majority of study participants had previously used opioids, for both tumour related and non-tumour related pain. The use of opioids for non-tumour pain such as osteoarthritis would be unusual in Australia.

Table 12: Results for the primary outcome measure (response rate)

Treatment Group	Response Rate (%)	95% Confidence Interval
WIS-BUP01		
placebo	31.4	16.9 – 49.3
20 mg patch	34.3	19.1 – 52.2
30 mg patch	36.6	22.1 – 53.1
40 mg patch	50.0	33.4 – 66.6
WIS-BUP02		
placebo	16.2	6.2 – 32.0
20 mg patch	36.6	21.2 – 53.1
30 mg patch	47.5	31.5 – 63.9
40 mg patch	33.3	18.6 – 51.0
WIS-BUP03		
Placebo	46.7	31.7 – 62.1
30 mg patch	57.5	46.4 – 68.0

As shown by the response rates (and 95% confidence interval (CI)) above, none of the three 'pivotal' randomised double blind placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) were able to show that the patch was significantly better than placebo for the primary efficacy outcome measure of response rate. Secondary efficacy measures in these three studies (including retrospective pain relief, pain intensity, and sleep duration) were, in general, suggestive of efficacy with the buprenorphine patch group showing some improvements over placebo, although there were inconsistencies across patch strengths.

Given that SL buprenorphine tablets were used for breakthrough pain, the placebo group may have had a higher response rate due to high consumption of these tablets. WIS-BUP01 and WIS-BUP03 included run-in phases during which SL buprenorphine was used to control pain. Comparing the baseline of rescue medication consumption during run-in to consumption during the randomised phase of WIS-BUP01, all groups had a similar average daily consumption of SL buprenorphine during the run-in phase (0.9 to 1.0 mg) and all groups had a lower consumption during the double blind phase (placebo group: reduced by 0.5 mg, all active patch groups: reduced by 0.6 mg). In WIS-BUP03, comparing the average daily doses of SL buprenorphine in the steady state phase to the run-in phase,

there was a reduction of 0.6 mg (from 1.1 mg to 0.5 mg) in the buprenorphine patch group and a reduction of 0.4 mg, (from 0.9 mg to 0.5 mg) in the placebo group (p = 0.0288). The reduction in consumption of SL buprenorphine seen in the placebo groups in both studies suggests that the placebo response in these two studies was not simply due to use of more SL buprenorphine. However, in WIS-BUP02, patients in the placebo group were found to take, on average, 2 more 0. 2 mg SL buprenorphine tablets per day: average daily dose of 0.7 mg compared to 0.3 mg for all active patch strengths.

There was no consistent dose response for the three patch strengths that were assessed in WIS-BUP01 and WIS-BUP02. For the secondary outcome measures in WIS-BUP01, the 40 mg patch performed better than the 20 mg patch, but the 30 mg patch was not better than the 20 mg patch. In WIS-BUP02, the performance of the 40 mg patch in the secondary outcome measures was worse than both the 20 mg patch and the 30 mg patch.

In most of the analyses there was no consistent difference between the non-tumour and tumour related pain, although interpretation is difficult given that the number of patients in the non-tumour groups was as low as seven.

WIS-BUP123

This post-hoc pooled analysis combined the data of the three pivotal studies. It used efficacy endpoints that were common to the three studies, although some manipulation was needed to enable roughly similar time-points to be used. Analysis was for each patch strength separately or the combined patch strengths. Outcome measures used were pain intensity and the use of rescue medications, analysed separately, and two combined outcome measures (pain intensity + the use of rescue medication and pain relief + the use of rescue medication).

The separate analyses of pain intensity and use of rescue medication was prompted by the UK Medicines and Healthcare products Regulatory Agency (MHRA) during the mutual recognition process in 2001and showed improvement in the active groups over placebo, although this was not consistent across the three studies or the three patch strengths:

- Pain intensity
  - in WIS-BUP01, pain intensity was significantly less than placebo for all patch strengths and for the combined patch strengths
  - in WIS-BUP02, pain intensity was not significantly less than placebo for any patch strength or the combined group
  - in WIS-BUP03, pain intensity was significantly less than placebo in the 20 mg patch group.
- Use of rescue medication
  - in WIS-BUP01, the use of rescue medication was only less than placebo for the combined patch strengths and not for the patch strengths individually
  - in WIS-BUP02, the use of rescue medication was less than placebo for all patch strengths
  - in WIS-BUP03, the use of rescue medication was less in the 20 mg patch group than placebo.

The combined outcome measures failed to show consistent improvement over placebo. Of note are the very wide confidence intervals in the results of these analyses.

Efficacy and the supportive Studies: PB-TTC-01 and PB-TTC-02, BUP4201

Supportive studies provided included the placebo controlled withdrawal Study, PB-TTC-02, and two non-inferiority studies that used prolonged release tramadol as comparator, PB-TTC-01 and BUP4201. These studies were performed in the early 2000's

and used a patch application time of 72 hours. The design details for these studies are provided in Table 13. Review of the study reports shows these studies to be well designed and well run.

These studies were performed on subgroups of the target population. The placebo controlled withdrawal Study PB-TTC-02, was performed on patients with severe chronic tumour related pain. The non-inferiority Studies PB-TTC-01 and BUP4201, were performed in patients with non-tumour pain: PB-TTC-01 included patients with various types of chronic non tumour pain and BUP4201 included patients with chronic pain due to osteoarthritis.

The choice of tramadol as the comparator is problematic. The dossier positions transdermal buprenorphine as suitable for patients transitioning from WHO Level 2 analgesics to WHO Level 3 analgesics (strong opioids). Tramadol has a mixed analgesic action with part of this due to agonist effects at the mu-opioid receptor. It is generally regarded as a weak opioid that fits into WHO Level 2. The use of tramadol as the active comparator in these non-inferiority studies is not consistent with the presentation of transdermal buprenorphine as a WHO Level 3 analgesics.

Table 13: Supportive efficacy studies

Study Identifier	Type of trial	Patient group	Treatments	Patient Number	Duration
PB-TTC-02	Placebo-controlled, double blind parallel group withdrawal study: 15 day open label run-in, 15 day (5 patches) double blind; 72 hours per patch	Chronic tumour pain	A: placebo B: 40 mg patch All groups: rescue medication buprenorphine SL	A: 88 B: 88 Total: 176	15 day run-in then 15 day double blind
BUP4201	Active-controlled (Tramadol SR), double dummy, double blind, non-inferiority trial; titration period up to 3 weeks; assessment period of 4 weeks; 72 hours per patch	Chronic pain due to osteo-arthritis	A: patch of any marketed strength B: Tramadol PR 150 or 200 mg bd.	A: 159 B: 154 Total: 313	31 to 59 days
PB-TTC-01	Active-controlled (Tramadol SR), double dummy, double blind, non-inferiority study; no run-in; 72 hours per patch	Chronic non tumour pain	A: 20 mg patch B: Tramadol PR 100 mg BD All groups: rescue medication paracetamol	A: 284 B: 276 Total: 560	28 days

PB-TTC-02

PB-TTC-02 used a withdrawal design and recruited patients with severe tumour related pain who had previously received opioids at an equianalgesic dose range equivalent to 90 to 150 mg morphine orally per day (the study report and protocol did not indicate how the morphine equivalences were determined). Patients were stabilised on 40 mg (70 µg/h) buprenorphine patches over a 1 to 3 week period, with SL buprenorphine tablets as required for breakthrough pain. If adequate pain control on the buprenorphine patch was

achieved, patients were then randomised to continue on an active patch or a placebo patch. All patients continued to use SL buprenorphine tablets for breakthrough pain during the double blind withdrawal phase.

The primary efficacy measure was the proportion of responders, where a responder was defined by a combination of three efficacy variables:

1. completion of at least 12 days of the double blind period
2. pain intensity less than 5 on an 11 point scale (scale from 0 to 10, where '0 was no pain' and '10 was pain as bad as you can imagine')
3. use of rescue medication of less than 2 tablets on average per day.

Of the 289 patients enrolled in the initial titration phase, 189 were randomised into the withdrawal phase, with the efficacy analysis including only those patients in the randomised withdrawal phase. Of the 100 patients who were not randomised, 28 withdrew due to lack of efficacy and 50 did not meet the criteria for adequate pain control using the patch in the titration phase, suggesting that likely non-responders to buprenorphine had been selected out prior to the withdrawal phase. Supportive of this is the analysis of pain intensity during the titration phase for the two groups (those that met the criteria for randomisation and those that did not meet the criteria). This showed that the mean pain intensity had decreased by approximately 2 points in the group that was subsequently randomised compared to virtually no change for the non-randomised patients.

The active and placebo groups were evenly matched on baseline characteristics, including the number with advanced malignancies (as shown by the presence of metastases). The overall mean (± SD) baseline pain intensity (11 point numeric rating scale (NRS))[36] at the end of the titration phase was comparable across treatment groups and analysis sets: 1.3 ± 1.3 in the buprenorphine group and 1.6 ± 1.4 in the placebo group for the per protocol (PP) set; 1.5 ± 1.4 in the buprenorphine group and 1.7 ± 1.4 in the placebo group of the full analysis set. Overall response rates (using the three part responder definition described above) showed that buprenorphine performed significantly better than placebo for the full analysis set of 188 patients: buprenorphine response rate 74.5% (95% confidence interval (CI) 65.7 to 83.3%) compared to placebo response rate 50.0% (95% CI 39.9 to 60.1%). Similar results were obtained for the PP set and modified PP set.

The secondary efficacy measure of twice daily assessment of the pain intensity showed that the differences to baseline were 0.24 ± 1.19 (95% CI -0.01 to 0.49) for buprenorphine and 1.10 ± 1.90 (95% CI 0.66 to 1.54) for placebo in the full analysis set. Similar results were found for the other analysis sets, but with some overlap of confidence intervals. The difference to baseline in use of rescue medication (average rescue medication during double blind period minus the average rescue medication during 4 days preceding randomization visit) indicated that the intake of rescue tablets was lower in the buprenorphine group (-0.52 ± 1.28) than in the placebo group (-0.01 ± 1.78), with no overlap of the 95% confidence. The mean amount of rescue medication used on Day 1 was similar for both groups (buprenorphine: 1.0 ± 1.3 tablets; placebo: 1.1 ± 1.4 tablets). By Day 14, mean use of rescue medication was lower in the buprenorphine group (0.8 ± 1.1 tablet compared 1.2 ± 1.2 tablets). Median and mean times to withdrawal were similar for buprenorphine and placebo in the full analysis set and modified PP set. Of the patients withdrawing due to lack of efficacy, there were 4 in the buprenorphine group compared to 14 in the placebo group of the full analysis set.

[36] The 11 point NRS is a numeric scale from 0 to 11 with no pain at zero to pain as bad as you can imagine at 11.

The results of Study PB-TTC-02 demonstrate efficacy of the 40 mg buprenorphine patch in a very select group of patients that is those patients with severe cancer related pain previously requiring high doses of strong opioids and who had achieved adequate pain control using a 40 mg buprenorphine patch. Of note is that one third of patients who entered to study (100 out of 289) were unable to meet the criteria for continuing in the double blind withdrawal phase, and that the most common reasons for this were lack of efficacy and inadequate pain control (78 out of 100).

BUP4201

The non-inferiority Study BUP4201 was performed in patients with chronic pain due to osteoarthritis of the spine, knees or hips and used a double dummy design with two phases, each of up to 4 weeks in duration. At study enrolment, patients were randomised to either buprenorphine patch with 72 hour application time or prolonged release tramadol twice daily and entered a titration phase of up to four weeks during which the analgesic medications were titrated as required (to maximum dose of 40 mg patch or 200 mg prolonged release tramadol). Patients who had a stable analgesic dose, acceptable pain control, and no significant adverse effects, continued into the 4 week assessment phase. Paracetamol was used for breakthrough pain in all patients. Long-term (> 4 weeks) NSAIDs could be continued at the same dose as prior to study entry.

A total of 319 patients were enrolled and 313 were randomised: 159 in the buprenorphine group and 154 in the tramadol group. A total of 175 patients (57%) discontinued from the study: 110 patients (70%) in the buprenorphine group and 65 (43%) in the tramadol group. Most of the discontinuations occurred during titration period and the most common reason was AEs. Of the discontinuations, 9 out of 110 of the buprenorphine group and 11 out of 65 of the tramadol group withdrew due to lack of efficacy.

The primary efficacy endpoint was the mean Box Scale 11 (BS-11)[37] pain scores recorded during the last 12 days of the assessment period. Equivalence between buprenorphine patch and prolonged release tramadol was to be assumed if the 95% CI for the mean treatment difference (buprenorphine - tramadol) for the primary efficacy endpoint fell within the range (-1.5, 1.5) boxes on the BS-11 scale. The rationale for the selection of this range (-1.5 to 1.5) was not provided and may be clinically excessive. The Study PB-TTC-01 used the range of 1.0 box on an 11 point scale to demonstrate non inferiority.

Baseline mean BS-11 pain scores (SD) were 7.3 ± 1.26 for the buprenorphine group and 7.3 ± 1.37 for the tramadol group and consistent with poor pain control prior to study entry. The mean scores during the assessment period were 4.3 ± 2.16 for the buprenorphine group and 4.3 ± 2.24 for the tramadol group. The test for non-inferiority, using the mean BS-11 pain scores recorded during the last 12 days of the assessment period compared to the mean baseline scores, showed that the buprenorphine patch was statistically non inferior to prolonged release tramadol for both the intention-to-treat (ITT) and PP populations. This result must, however, be interpreted with caution given the high withdrawal rate, with this disproportionately affecting the buprenorphine group.

PB-TTC-01

The other non-inferiority Study PB-TTC-01, compared the 20 mg buprenorphine (35 µg/h) patch (applied every three days) to prolonged release (SR) tramadol 100 mg orally twice daily (BD) over a 4 week period. Patients were included in the study if they had chronic non tumour pain that was inadequately controlled by treatment with weak opioids or NSAIDs, or poorly tolerated NSAID treatment. Patients were randomised to either 20 mg buprenorphine patch applied every three days or to tramadol SR 100 mg taken orally as a

[37] BS-11 pain scores. Patients recorded their pain intensity using the BS-11 pain scale, where 0 = no pain and 10 = pain as bad as you can imagine. Patients recorded scores in their PABs every evening before going to bed by circling the box on the BS-11 scale that indicated their level of pain during that day.

tablet BD over a 4 week (28 day) period. Paracetamol (up to 2000 mg per day) was used for breakthrough pain. No other analgesics were allowed.

The primary efficacy variable was the mean actual pain intensity, as rated by the patient using an 11 point NRS, twice daily during blinded treatment compared to the pain intensity rating at the beginning of the study. Non inferiority was to be assumed if the treatment difference between the buprenorphine group and tramadol group was less than 1 unit on the 11 point scale as this was 'the largest difference that can be judged as being clinically acceptable'. No further rationale for this choice was provided.

Of the 560 patients who were enrolled and randomised, 372 patients completed the study, with the buprenorphine patch patients disproportionately represented amongst the discontinuations. Of the patients randomised to the buprenorphine patch, 117 out of 284 (42.5%) withdrew, 97 out of 117 due to AEs and 8 out of 117 due to lack of efficacy. Of the 275 patients randomised to tramadol, 71 out of 275 (25.7%) withdrew with 51 out of 71 due to AEs and 14 out of 71 due to lack of efficacy.

There was no major difference in the baseline mean average pain on the 11 point NRS in the FA data set between the two treatment groups (6.99 ± 1.44 points in buprenorphine group and 7.02 ± 1.55 points in the tramadol group). The mean pain reduction from Day 2 to 28 was 2.00 ± 2.06 points for buprenorphine and 2.06 ± 2.03 points for tramadol.

The 95% CI for the difference of means in the PP data set and the FAS was within the predefined therapeutic equivalence range. Therefore, the buprenorphine patch was statistically non inferior to prolonged release tramadol. Statistical significant superiority of the 20 mg buprenorphine patch compared to tramadol could not be shown.

Other Studies

Open Follow-up Studies

Two open follow-up studies were provided

PB-TTC-Follow Up

PB-TTC-Follow Up included patients from PB-TTC-01 for up to 6 months. Patients were treated with buprenorphine patches titrated to effect

- 307 patients entered the follow-up phase
- 145 completed the 6 months (49.5% withdrawal rate)
- 61% of withdrawals were due to AEs, 12% due to lack of efficacy
- After some titration in the first month, the patch dose strength remained unchanged for most patients for the rest of the study
- Analysis of the mean actual pain intensity, as rated twice daily by the patient using the 11 point NRS showed that there was a small decline in pain intensity of around 0.3 across the six months in both the ITT and PP populations. This change is too small to be clinically relevant but does suggest that any analgesic effect of the buprenorphine patch is sustained for up to six months.

WIS-BUP-LTS

WIS-BUP-LTS included patients from WIS-BUP01, WIS-BUP02 and WIS-BUP03. It was initially planned for 6 months but ended up continuing for up to 5 years in a small number of patients. Patients were treated with buprenorphine patches titrated to effect.

- 241 patients were enrolled but this number rapidly declined: 134 remained at 2 months, 37 at one year and 4 at 3 years. Mean duration of non-tumour patients was 6.5 months and tumour patients, 3.3months

- Efficacy was determined by the patient's retrograde assessment of pain relief on a 4 point verbal rating scale (VRS)[38] at the regular investigator appointments. 188 patients conformed to patch wearing requirements and were analysed: 42.7% had complete and good pain relief and 47.3% satisfactory pain relief
- The 37 patients who completed 12 months showed a constant level of efficacy without any indication of the development of tolerance.

Both follow-up studies had a rapid drop off in participants. However, those patients who remained in each study for 6 or 12 months appeared to experience reasonably constant analgesia without development of tolerance.

Post-Marketing Studies

Nine post-marketing surveillance studies were provided, with study duration of 6 to 8 weeks in general, although some continued for up to 12 months. Two studies provided a comparator: SR tramadol in the six month Study BUP4202 and fentanyl patch in the 12 month Study PMS Transtec versus Durogesic cohort study. In one Study, AWB Transtec Pro 2005/2, the buprenorphine patch was worn for 96 hours. In all of the studies, patients who were to be commenced on buprenorphine patches for the management of moderate to severe tumour or non-tumour pain were recruited from general practice clinics, specialty clinics, and hospital out patients. Prescription and dosing were to be in accordance with the summary of product characteristics (SmPC). Large numbers (in the 1,000's) were recruited to most of these studies. Discontinuation rates ranged from 18 to 46%.

These studies made varying assessments of efficacy. In AWB Transtec 2001/1, 13,179 patients were recruited and 25% discontinued. Immediately before starting the patch, 6% of all patients reported 'good' or 'very good' pain relief using a four point VRS. This increased to 71% of all patients at the first review after commencing the patch, with this persisting to the final study visit. The analysis of a further 2,077 patients from this study was reported in PM Transtec 2001/2; the efficacy result was similar to the main group. In AWB Transtec 2003; 3,644 patients were recruited and 23.5% discontinued during the 10 week study. The efficacy analysis of 3,340 patients found that pain relief, using a four point VRS, was 'very good' or 'good' in 2,941 (88.1%) patients at the end of the study. In AWB Transteconco2003, 412 patients with cancer related pain were enrolled. The efficacy analysis of 361 of these patients found that pain relief on a 4 point VRS was assessed as 'good' or 'very good' by 8 out of 361 patients prior to enrolment with this increasing to 238 out of 361 patients at the end of the 8 week study. In Study AWB Transtec Pro 2005/2, a subset of 256 patients who had previously been taking morphine or fentanyl was analysed. Using an 11 point scale for pain intensity and evaluation after 20 days of buprenorphine patch wearing, it was found that 248 of 256 patients (97%) achieved pain intensity that was equal to or better than pain intensity prior to buprenorphine patch. In Gru-BUP 2002/01; 1,223 patients were recruited and 535 (44%) did not complete the 3 month study. The proportion of patients who experienced good to very good pain relief increased significantly from 3.57% at baseline to 70.55% at one month and to 85.82% after 3 months of treatment with the patch. The Study TTC-MATRIX-AWB-2003 recruited 10,810 patients of whom 2,881 (26.7%) discontinued buprenorphine patches during the 6 week study. Baseline mean pain intensity, as measured with an 11 point Numeric Rating Scale (11 point NRS), was 6.6. At Visit 2 this had decreased to 3.7 and at Visit 3, after an average of 6 weeks follow-up the pain intensity was 2.6 ($p < 0.0001$). The Study BIOC-110304, enrolled 1,648 patients and 82.8% of patients reported excellent or good pain reduction at the end of the 9 to 10 week period.

[38] Pain relief was assessed at each visit by the patient using a four point verbal rating scale with the following items: 1=complete, 2=good, 3=satisfactory and 4 = poor.

Dose Dependent Response

WIS-BUP01 and WIS-BUP02 compared the three patch strengths. Inconsistent results were found across the two studies such that dose dependent responses cannot be established. For example, all patch strengths in WIS-BUP01 had a reduction of 0.6 mg in the amount of SL buprenorphine in the randomised phase compared to the run-in phase; plotting of the mean pain intensity scores across 15 days in WIS-BUP02 showed no clear separation in the scores of the doses at all of the time points; however, the overall proportion of patients in WIS-BUP02 with 'no' or 'mild' pain increased in a dose dependent fashion: placebo patch: 40.3%; 20 mg patch: 47.3%; 30 mg patch: 58.7% and 40 mg patch: 62.2%.

Proposed Maximum Dose

The draft PI proposes a maximum dose of two 40 mg patches worn simultaneously. This dose was not tested in any of the efficacy studies and its use was only rarely described in the post-marketing surveillance studies (134 patients of 33,673 patients). There is insufficient evidence to support the proposed maximum dose and there would appear to be little clinical need for it.

Special Populations

Children, pregnant or lactating women and patients with severe hepatic impairment were excluded from the efficacy studies. Patients with renal impairment and other major organ disease were excluded from most of the clinical efficacy studies. The draft PI advises against use in these groups, except for patients with renal impairment.

Opioid Naïve

The efficacy studies predominately enrolled patients who had previously taken opioids. The most common reason for patient withdrawals in most of these studies was AEs typical to opioids. Analysis in some studies, such as PB-TTC-01, showed that withdrawal due to AEs was more common in opioid naïve patients. It was not uncommon for the post-marketing surveillance studies to describe the use of doses smaller than the 20 mg patch (545 of 33,673 patients), with these delivered by cutting the patch into smaller pieces, despite advice in the SmPC that this should not be done. These two factors would seem to indicate that this formulation of buprenorphine patch may be 'too strong' for opioid naïve patients. In support of this, the Therapeutic Guidelines: Analgesic recommend a buprenorphine patch starting dose of 5 µg/h; this dose can be delivered using one of the lower strength patches available in the 7 day Norspan version.

Summary

The dossier does not provide sufficient evidence to convincingly establish efficacy of the buprenorphine patch in the management of moderate to severe chronic pain The pivotal studies did not establish superiority over placebo for the pre-specified primary efficacy outcome measures. The wide confidence intervals seen in the results for the primary outcome variable for the three studies, and the pooled analysis, suggest that they were underpowered to show a response. The studies did show some efficacy for the secondary measures, but this was not consistent across the patch strengths. The guideline that was developed by the European Medicines Agency (EMA), and adopted by the TGA in 2005, expresses the opinion that: '*In pivotal clinical trials where pre-defined primary variable analysis has failed to demonstrate efficacy, favourable results on secondary variables will not be enough to grant a marketing authorisation*'. This guideline was adopted some 8 years after these studies were performed but it is appropriate that the studies be judged according to current regulatory standards.

The supportive studies were suggestive of efficacy but only in select groups and the results must be interpreted with caution. In the placebo controlled withdrawal study, the highest strength patch did appear to be superior to placebo in patients with severe cancer related

pain but the study design was such that there is the strong possibility of enrichment bias with non-responders not entering the withdrawal phase. The two active controlled studies suggest that the buprenorphine patch was non inferior to the WHO Level 2 opioid, tramadol, but interpretation of both of these studies is difficult due to high withdrawal rates with the buprenorphine group disproportionately affected. The patients receiving buprenorphine had a much higher incidence of adverse events (AEs) resulting in early discontinuation compared to the patients receiving prolonged release tramadol. This suggests that the buprenorphine patch may be non-inferior in efficacy to a WHO Level 2 analgesic but is considerably worse with regard to tolerability.

The post hoc pooled analysis of the three conventional placebo controlled studies showed efficacy using the separate analyses of pain intensity and use of rescue medication but not for these two measures combined. There were also inconsistencies across patch strengths. The open studies were also limited by high withdrawal rates but suggest that, in those patients who found the buprenorphine patch efficacious, this effect could continue for some months without development of tolerance.

Of note is that the dossier submitted for the related product Norspan also had difficulties in establishing efficacy in its initial evaluation. In this case, review of the dossier through the appeal process, led to two of the pivotal studies being categorised as 'failed' rather than 'negative' and considerable weight was placed on supportive studies to establish efficacy.[39]

Conclusion

The buprenorphine patch may be efficacious but this has not been satisfactorily established by the dossier for the proposed indication.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Efficacy studies:

- Placebo controlled, WIS-BUP01, WIS-BUP02 and WIS-BUP03
- Placebo controlled withdrawal PB-TTC-02
- Non inferiority studies PB-TTC-01 and BUP4201.

Follow-up studies:

- WIS-BUP-LTS (Follow-up study for WIS-BUP01, WIS-BUP02 and WIS-BUP03)
- PB-TTC-01 Follow-Up (Follow-up study for PB-TTC-01)
- Some 10 non interventional post-marketing surveillance studies (from the years 2000 to 2005). Two of these studies had comparator arms (tramadol, fentanyl patch).

Table 14: Post marketing surveillance studies

Study Identifier	Duration	Safety Data
AWB Transtec 2001/1	Up to 10 weeks	ADRs

[39] ACPM Minutes: Item 2.8 Buprenorphine Transdermal Patch, Mundipharma Pty Ltd and Item 3.4 Buprenorphine hydrochloride (Norspan TDS) – Mundipharma Pty Limited - Section 60 Appeal.

Study Identifier	Duration	Safety Data
AWB Transtec 2001/2	Up to 10 weeks	ADRs
AWB Transtec 2003/2	10 weeks, 6 months	AEs, ADRs
AWB Transtec onco2003/01	Up to 8 weeks	ADRs
GRU-BUP-2002-01	12 weeks	AEs
BIOC/11/03/04	10 weeks	AEs, Global evaluation of tolerability
TTC-MATRIX-AWB-2003	6 weeks	AEs, Patient satisfaction
AWB Transtec Pro 2005/2 (subset analysis)	Up to 8 weeks	ADRs
BUP4202	Up to six months	AEs
PMS Transtec versus Durogesic Cohort Study	Up to 12 months	AEs

The sponsor seeks to demonstrate safety of the buprenorphine transdermal delivery system through the reporting of AEs for this route of administration and through the existing literature regarding the safety of buprenorphine administered by other routes. There were no studies using safety as the primary variable. The clinical PK studies looked at safety variables other than AEs (vital signs and laboratory variables) but these short-term studies were performed in healthy volunteers. The summary of clinical safety comments: '*The safety evaluation plan included ongoing routine collection and evaluation of case reports, signal detection and generation of periodic safety update reports. It was considered adequate, because the product is a new application form of an established compound with a well-known safety profile.*' ' This safety profile was not otherwise substantiated: there was no review or summary of the currently available literature provided to support the safety profile of buprenorphine administered by other routes. This is not adequate.[40]

Exposure

This buprenorphine patch was first registered in Switzerland in 2000, with the development programme occurring in the late 1990s and early 2000s. In the controlled clinical trials 1,053 patients were exposed to the patch, with another 370 exposed to placebo patches. Of the 1,053 patients, 546 continued into open follow-up phases. In the post marketing surveillance studies from the early 2000s that were included in the dossier, over 30,000 patients were exposed to the buprenorphine patch. According to the RMP, the total cumulative post authorization patient exposure to this buprenorphine patch is 505.6 million patient treatment days since first registration in Switzerland in June 2000.

[40] The following references were subsequently submitted by the sponsor; Kress HG. Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur J Pain*. 2009; 13: 219-230.; and Pergolizzi J, et al. Current knowledge of buprenorphine and its unique pharmacological profile. *Pain Pract*. 2010; 10: 428-450.

The duration of exposure documented in the studies provided is short for a drug proposed for long term use. No patients in the controlled studies were treated with the patch for more than 3 months. Of all the patients in the open studies, including the post-marketing surveillance studies, only 238 patients were treated with the patch for longer than 6 months. The sponsor proposes a maximum dose of 140 µg/h (2 x 40 mg patch, 2 x 70 µg/h). No patients in the controlled studies received this dose. The number treated with this dose in the post-marketing surveillance studies could not be determined as only the dose range of 71 to 140 mg was provided. Ninety three patients were exposed to this dose range but only 2 of these for longer than 6 months. No separate analysis of patients exposed to the proposed maximum dose is provided in any of the studies or in the dossier.

Adverse Events

Adverse events were common in the clinical studies and were typical of opioid analgesics acting as mu-opioid receptor agonists. They included nausea, vomiting, constipation, dizziness and fatigue in rough order of frequency. A common adverse effect that is specific to the patch was application site reaction, most commonly itch and redness. Application site reactions were common with both active and placebo patches.

The frequency with which these opioid type AEs were observed varied considerably across the studies provided. Rates, overall, tended to be highest in the healthy volunteers in the clinical PK studies and in the two active controlled studies. Not surprisingly, the rates were lower in the post marketing surveillance studies where patients are less closely observed and there was a much higher discontinuation rate. Rates are lower again in the company core data sheet (CCDS), which is largely influenced by voluntary reporting.

Table 15: Frequency of adverse events according to type of trial

	Frequency of Adverse Events (%)							
	Placebo Controlled			Active controlled				
Adverse Event	WIS BUP 01, 02, 03	WIS BUP LTS	PB TTC 02	PB TTC 01	BUP 4201	PK studies	Post marketing surveillance studies	Company Core Data Sheet 2013
Nausea	17	13	12.5	46	53	10-20	4-17	≥ 10
Vomiting	9	6	9	34	38	10-20	1-8	≥1, <10
Dizziness	7	7		20	33	11-30	2-13	≥1, <10
Tiredness	6	5	2	6		9	1-10	≥1, <10
Constipation	5	4	9	30	24	11	1-10	≥1, <10
Pruritus	2			0.7		7-12	0.7-4	≥ 10
Headache	1.5			7	17	9-18	0.3-7	≥1, <10
Hyperhidrosis	4	6	1	5	16	3	0.4-5.5	
Application Site reaction	30			30	17		6	< 0.1

Occurrence of AES did not vary considerably between patients with tumour or non tumour pain and patients aged more or less than 70 years. AEs were, however, observed to be more common in patients who had not previously been exposed to opioids (and a more common reason for discontinuation in these patients). In those studies that used prolonged release tramadol as a comparator, AEs were observed to occur considerably more frequently in the buprenorphine patch group.

The 6 month open follow-up phase of PB TTC 01 suggests that the rate of gastrointestinal AEs seemed to decrease over time (nausea from 12.5% to 7%; vomiting from 9 to 6% and constipation from 9 to 2%) although it was not clear whether this was due to patients adjusting to these effects or to the use of antiemetics and laxatives, or from patients with

these side effects dropping out of the study. This study also found that application site reactions increased over time (from 40 to 50%) and were a common reason for patients discontinuing patch treatment.

Deaths were common in most studies involving the target population, but this was to be expected given the number of patients with serious malignancies included in these studies. No deaths in the clinical studies were assessed as related to the study drug and review of the narratives provided did not reveal any anomalies. Serious adverse events (SAEs) described in the studies, and assessed as related to the study drug, were severe forms of the AEs described above. These included:

- severe nausea and vomiting, with this resulting in severe dehydration in one patient and a Mallory-Weiss tear in another
- confusion and respiratory depression
- severe somnolence
- generalised pruritus
- severe constipation
- severe application site reaction.

AEs resulting in discontinuation from the study were also those opioid type AEs described above. Nausea and vomiting, dizziness and application site reactions were some of the common AEs causing discontinuation from the studies.

Laboratory Testing and Other Variables

The summary of clinical safety stated: '*Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine*'. In support of this, the clinical overview refers to a general review article from 2002[41] (sponsored by [information redacted]), an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine, from 1994[42] and 2005[43] respectively. Evidence of a more substantive assessment, with this including the past 10 years, is essential to determining the risks associated with the use of this product.

Potential effects of the study drug on vital signs, ECG, as well as laboratory variables, were not tested in the target population and only for a short period of time (up to 15 days) in healthy volunteers. Other parameters such as respiratory function, skin absorption from different sites, factors affecting absorption (local and general) were not assessed.[18] Safety in special populations was not assessed.

Post Marketing Experience

Periodic safety update reports (PSURs) covering the years 2000 to 2013 were provided. During this time, the buprenorphine patch has gone from being marketed in one country to twenty six countries. Unsurprisingly, the number of case reports received each year has increased from less than 200 per year to over 1,000 per year. As discussed in the section

[41] Budd K. Buprenorphine: a review. Evidence Based Medicine in Practice 2002, 1-24
[42] Walsh SL, et al. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther* 1994; 55: 569-80.
[43] Dahan A, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth* 2005; 94 :825-834.

above, some of these case reports describe serious AEs attributable to the buprenorphine, patch.[44] Of these the most concerning are:

- Multiple reports of overdose symptoms requiring hospitalisation but occurring with doses as small as ½ of the lowest strength patch.
- Multiple reports of depressed conscious state and/or respiratory failure requiring hospitalisation and occurring with co-administration of buprenorphine patch and other sedating agents. These included one death.
- Several concerning cardiac events including syncopal episodes and tachyarrhythmias.

There were, however, few reports of drug abuse and only a small number of case reports of physical dependence developing with prolonged administration.

It is important to remember that these case reports result from voluntary reporting. The number of reports received is likely to represent only a fraction of the actual number of cases that occur in clinical practice.

Safety issues with the potential for major regulatory impact

There are a number of real or possible adverse effects that are concerning. These are mainly derived from the PSURs and represent real world experience. The only information provided to counterbalance these reports is the AE reporting in a number of short term studies of select populations.

One concern is the potential for side effects to occur with such severity as to require hospitalisation with therapeutic dosing (even as low as half a 20 mg patch). As noted above, there are a number of case reports in the PSURs in which patients treated with therapeutic doses were hospitalised due to AEs such as: severe nausea and vomiting; respiratory failure and stupor requiring treatment with naloxone; and acute confusional states including one culminating in a suicide attempt. Similar hospitalisations occurred when excessive doses were taken inadvertently or through activities that increased absorption from the patch.

Another concern is the number of patients in whom co-administration with other potential sedating agents resulted in respiratory depression and unconsciousness requiring hospitalisation and resulting in death from hypoxic injury for one patient. These cases occurred despite clear warnings in the SmPC and consumer information leaflets. Unfortunately, patients with chronic pain are likely to be on a variety of agents to control pain, with these commonly including benzodiazepines, anti-depressants and anti-psychotics, all of which are potentially sedating.

Cardiovascular safety is another concern. The track record of buprenorphine over the decades of use would indicate that this is very low risk but it cannot be ignored. The nonclinical studies indicating inhibition of the HERG potassium channel together with the QT prolongation observed with the use of 2 x 20 mg patches (average dose 70 µg/h) in a 'thorough QT study' and the PPR (Proportional Reporting Rate for the combination of a particular drug and particular ADR) signal of disproportionate reporting for sudden death with buprenorphine require serious consideration and close ongoing monitoring. It is worrying that this risk would appear to have been dismissed to the extent that it is not mentioned in the clinical overview and relevant documents only provided in appendices in the PSURs.

It is not possible to assess the risk of coronary vasospasm with use of the buprenorphine patch on the information available ('two well documented individual case safety reports'). It is unclear why this risk should only have been mentioned in the RMP and not have been

[44] Many of the AE's attributable were also related to either unknown or sublingual formulation.

addressed in the clinical overview. Coronary vasospasm is of serious concern in that it may require hospitalisation with invasive investigations and may be a precursor to acute myocardial infarction.

There is also the potential for abuse of this opioid. There are reports of the active drug being extracted from the patch in a variety of ways (descriptions of techniques can be readily found with a simple internet search). How frequently this may occur cannot be determined. It would be unusual for this to be reported as an AE, although it was in 3 reports. The other way it can be suspected is through the routine toxicology in the investigation of unexpected deaths. Detectable buprenorphine levels do not, however, indicate the source of the buprenorphine. Despite this concern, buprenorphine is a restricted drug that, together with the added difficulty of extracting it from the matrix, should make abuse a relatively low risk.

Other Safety Issues

No specific data is provided regarding the use in special populations, except the elderly. The high mean age in most of the clinical studies and a subgroup analysis in one of the large post marketing surveillance studies suggest that there is no difference in safety in the elderly. This may need to be interpreted with caution in the extreme elderly as they were over represented in the case reports in the PSURs.

There are concerns with administration of buprenorphine to pregnant or breastfeeding women, based on nonclinical studies. This has not been tested in clinical studies. The dossier refers to reported safe use in observational studies of pregnant women in opioid dependence programmes, but correctly advises against the use of the buprenorphine patch in the draft PI.

Children were excluded from the clinical studies. The PI appropriately states that the use of the buprenorphine patch in patients below 18 years of age not recommended. The post marketing surveillance studies and case reports in the PSURs indicates that the product is used in children. This is not surprising given the convenience of a transdermal preparation in this age group and such off-label use can be expected to continue. The RMP refers to an article describing use in children but this article was not included and is not referred to elsewhere.

Reference is made to the existing literature to guide use in liver and renal failure. As discussed in the pharmacodynamic section above, studies of the use of buprenorphine in patients with severe renal failure have not indicated any accumulation of the drug or its active metabolite. The recommendation that the buprenorphine patch may be used with close observation in liver disorders is based on PK studies that indicate most of its clearance is by biliary excretion and only 30% via hepatic metabolism. The safety of use in patients with liver impairment was not demonstrated.

The high rate of adverse drug reactions and discontinuation of buprenorphine seen in opioid naïve patients would indicate that this medication should be used with care in this group. The need for lower dose preparations is also suggested by the use of patches cut into quarters and halves, as described in the post marketing surveillance studies and PSURs. It may be more appropriate for opioid naïve patients to be commenced on the lower strength 7 day patches where these are available.

Drug-drug interactions, in particular the potential for life threatening respiratory failure and unconsciousness with co-administration of other sedating agents, are of obvious concern. Standard measures such as advice against this practice in the SmPC and CMI have not eliminated the problem.

Evaluator's conclusions on safety

A limited presentation of the safety of buprenorphine is provided in the dossier. Reliance is placed on the existing literature regarding administration by other routes to demonstrate safety but a review and summary of this literature is not provided.

There are substantial safety concerns regarding the product.

The response to even low doses is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter patient variability in absorption from the patch demonstrated in the PK studies.

Potentially life threatening co-administration with other sedating drugs is likely given the target population and given that many co-analgesics may cause sedation. This is a particular concern with the buprenorphine patch given the long half-life even after patch removal.

The still unknown risk of Torsades de Pointes (TdP) and coronary vasospasm also indicate the possibility that life-threatening cardiac complications may occur.

Tolerability of the buprenorphine patch is another issue. Adverse event reporting in the clinical studies indicate that side effects such as nausea and vomiting were extremely common and one of the main reasons for patients discontinuing from the studies. That these side effects could be serious is shown by the SAEs in the clinical studies and the reports of hospitalisations due to adverse drug reactions (ADRs) in the case reports of the PSURs, although this was infrequent. Application site reactions were also common and, although categorised as mild to moderate with itching and erythema, were also a common reason for patients discontinuing the medication.

First Round Benefit-Risk Assessment

First round assessment of benefits

The dossier did not provide sufficient evidence to convincingly establish efficacy of the buprenorphine patch in the management of moderate to severe chronic pain. Given this, the advantages associated with transdermal drug delivery such as avoidance of first pass metabolism, achievement of constant drug plasma levels, an improved patient compliance and improved pain control due to less variation in therapeutic plasma levels may not be realised.

The three randomised double blind placebo controlled studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03) proposed as 'pivotal' by the sponsor were unable to show that the buprenorphine patch was significantly better than placebo for the primary efficacy outcome measure of response rate, with this defined by a combination of pain relief and use of rescue medication. Secondary efficacy measures in these three studies (including retrospective pain relief, pain intensity, sleep duration, use of rescue medication) were, in general, suggestive of efficacy for the 20 mg and 30 mg patches. The 40 mg patch did not perform as well in the two studies that included it (WIS-BUP01 and WIS-BUP02).

Study PB-TTC-02 used a withdrawal design and recruited patients with severe tumour related pain who had previously been receiving high dose opioids. Of the 289 patients entering the run-in phase only 189 were randomised to the withdrawal phase. The most common reason for not continuing was lack of efficacy. The results of the withdrawal phase demonstrated efficacy of the 40 mg buprenorphine patch in a very select group of patients (patients with cancer related pain who had previously required strong opioids and who had achieved adequate pain control using the buprenorphine patch in the run-in phase).

The two active controlled non inferiority studies, PB-TTC-01 and BUP4201, used the WHO Level 2 weak opioid, tramadol, as comparator although the proposed indication would class buprenorphine as a WHO level 3 analgesic. Both of these studies had high discontinuation rates, with this disproportionately affecting the buprenorphine patch group; the most common reasons for discontinuation were ADRs. Both of these studies showed that the buprenorphine patch was non inferior in efficacy to prolonged release tramadol in the treatment of chronic non tumour pain but less well tolerated.

The post-hoc analysis, WIS-BUP123 combined the data of the three studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03. The separate analyses of pain intensity and use of rescue medication showed improvements in the buprenorphine patch groups over placebo, but these improvements showed some inconsistencies across the three studies and the three patch strengths. . The combined outcome measures failed to show statistically significant improvement over placebo.

At best, efficacy has been shown to be non-inferior to the weak opioid, prolonged release tramadol, with this occurring at the cost of a higher rate of side effects resulting in discontinuation of the buprenorphine patch.

First round assessment of risks

Clinical safety was inadequately dealt with in the dossier. Reliance was placed on experience with buprenorphine administered by other routes but a current review and summary of the relevant literature to support this was not provided. Important risks described in the RMP were not discussed in the clinical overview.

There is little information to guide some aspects of safety, in particular the use in special populations, PK drug interactions, safety of long-term exposure, the potential for overdose at therapeutic doses and the dose relationship of reversibility of life threatening effects with naloxone.

From the information available, the main risks of the buprenorphine patch in the proposed usage are:

- Safety Concerns
  - The response to even low doses is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter patient variability in absorption from the patch demonstrated in the PK studies
  - Potentially life threatening co-administration with other sedating drugs is likely to continue to occur, given that many co-analgesics may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  - The still unknown risk of TdP and coronary vasospasm also indicate the possibility that life threatening cardiac complications may occur
  - The potential for abuse and misuse also exists, although this is probably at low risk of occurrence.
- Tolerability Concerns
  - Use of the buprenorphine patch of these strengths is frequently associated with such side effects of nausea, vomiting, constipation, dizziness and fatigue. These were sufficiently distressing for many patients to discontinue use of the buprenorphine patch (discontinuation rates of 18 to 46% were described in the post marketing surveillance studies)

- Application site reactions frequently occurred and were of sufficient severity to be a common reason for patients to discontinue use of the product, particularly with long-term use.

First round assessment of benefit-risk balance

The benefit-risk balance of the buprenorphine patch for the proposed usage is unfavourable. Given the uncertain efficacy, the risks outweigh any potential benefit. These risks range from potentially life threatening, although rare, adverse drug reactions to the less severe but very common and distressing opioid type side effects.

First Round Recommendation Regarding Authorisation

It is recommended that the submission be rejected on the grounds that:

- efficacy has not been satisfactorily demonstrated for the proposed indication of the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids
  - the placebo controlled studies failed to demonstrate efficacy, using current regulatory and study design standards
  - the active controlled studies demonstrated non-inferiority to prolonged release tramadol, a WHO Level 2 opioid, although the buprenorphine patch is proposed as a WHO Level 3 opioid
  - if reliance is to be on other supportive studies, then a thorough and current literature review and summary should be provided
- safety has not been satisfactorily demonstrated
  - the clinical overview and summary of clinical safety need to be updated to include all of the risks identified in the RMP
  - for those aspects of safety that the submission relied upon the 'well known' safety profile of buprenorphine administered by other routes, a summary of the relevant literature should be provided
  - the risk of Torsades de Pointes needs to be reviewed. The scientific evaluation from 2006 (currently available only in the Appendix to a PSUR) should be included in the main part of the dossier and updated
  - the risk of coronary vasospasm needs to be discussed within the clinical overview and summary of clinical safety. More information regarding this risk should be provided.

Clinical Questions

Pharmacokinetics

1. The PI describes buprenorphine as poorly soluble in water. It is elsewhere described as soluble and highly soluble in water. The major review by Budd[41], frequently referred to in the clinical overview, describes it as highly soluble. Could the water solubility of buprenorphine be better quantified?
2. Inspection of individual patient data in PK1599 appears to show considerable inter-patient variability. The plasma concentrations achieved during the wearing of a patch (HP5303/01, HP5303/02 and HP5303/04) also seem to show similar inter-patient

variability. The inter-individual coefficient of variation is described as 'relatively low (about 40% at the plateau level)'for HP5303/01. Inter patient variability is an important factor to consider in determining appropriate dosing recommendations and the expectation of response during patient counselling. It would be helpful to have a more comprehensive description of inter patient variability with respect to release rates and plasma concentration with, for example:

- Frequency histogram of calculated release rates from PK1599
- Inclusion of median with min, max in the residual amounts and release rates in the summary table for PK1599
- Inclusion of median with min, max for C_{max}, and AUC in the table of PK parameters of buprenorphine for HP5303/01 and HP5303/02.

An assessment of intra-patient variability in the crossover studies HP303/01 and HP303/04 would be useful as visual inspection of the individual patient concentration time graphs for HP5303/01 shows considerable variation in the amount of rise going from the 20 mg to the 40 mg patch.

3. The Transtec PI recommends that a skin site be left for at least one week before another patch is applied there. Study HP5303/02 demonstrated that re use of a site at 3 days resulted in increased absorption. The Australian PI for the sponsor's product Norspan, a buprenorphine patch that is structurally almost identical to Transtec (although worn for 7 days not 4) states that '*In a study of healthy subjects applying Norspan patches repeatedly to the same site, immediate reapplication caused increased absorption, without clinical adverse events'* and that '*A new patch should not be applied to the same skin site for 3 to 4 weeks*'.

   Norspan and Transtec are structurally almost identical. Could the study of the effect of re using skin sites on absorption from the Norspan patch be provided? What is the evidence/rationale for the recommendation that it is appropriate to re-use a skin site after one week for Transtec?

4. The PI for the sponsor's product Norspan provides additional important information of the effect of local application of heat on absorption*: In another study in healthy subjects, application of a heating pad directly on the Norspan patch caused a transient, 26 to 55% increase in blood concentrations of buprenorphine. Concentrations returned to normal within 5 hours after the heat was removed.* This is not consistent with the draft Transtec PI advice that: '*Fever and the presence of heat may increase the permeability of the skin. Theoretically in such situations buprenorphine serum concentrations may be raised during Transtec treatment*'. Could the study of the effect of heat on absorption from the Norspan patch be provided and the effect of locally applied heat on the absorption of buprenorphine from the patch be clarified?

5. Bioequivalence of the 72 hour and 96 hour application times was demonstrated in healthy volunteers. Could the following study be provided to enable evaluation of the bioequivalence in the target population: Likar R et al., Transdermal Buprenorphine Patches Applied in a 4 Day Regimen Versus a 3 Day Regimen: A Single Site, Phase III, Randomised, Open label, Crossover Comparison*. Clin Ther* 2007; 29: 1591- 1606.

6. The information provided by the National Library of Medicine on the sponsor's product Butrans (a trademark clone of Norspan) provides additional important information regarding drug interactions: *'certain protease inhibitors with CYP3A4 inhibitory activity such as atazanavir and atazanavir/ritonavir resulted in elevated levels of buprenorphine and norbuprenorphine when buprenorphine and naloxone were administered sublingually.* C_{max} *and AUC for buprenorphine increased by up to 1.6 and 1.9 fold, and* C_{max} *and AUC for norbuprenorphine increased by up to 1.6 and 2.0 fold respectively, when sublingual buprenorphine was administered with these protease*

inhibitors. Patients in this study reported increased sedation, and symptoms of opiate excess have been found in post-marketing reports of patients receiving buprenorphine and atazanavir with and without ritonavir concomitantly. It should be noted that aatazanavir is both a CYP3A4 and UGT1A1 inhibitor.'[45] The evaluator was unable to find any reference to these studies in the dossier. Could the effects of protease inhibitors on buprenorphine metabolism be clarified and a current review of PK interactions of buprenorphine be provided?

7. The draft Transtec PI states 'There is evidence of enterohepatic recirculation'. This PK property was not described in the nonclinical overview or the clinical overview of PK properties of buprenorphine. Could this be clarified?

Pharmacodynamics

8. The potential for naloxone to reverse the unwanted effects of buprenorphine, especially in overdose, is problematic. The study by van Dorp [46] showed that doses of 2 to 4mg followed by an infusion rate of 4 mg/h were required to reverse the respiratory depressant effects of a therapeutic dose of intravenous buprenorphine. The Transtec PI recommends an initial bolus of 1 to 2 mg intravenously with this followed by an infusion. This initial dose may be inadequate and an initial bolus dose of 2 to 4mg more appropriate, with a similarly high dose infusion rate (4 mg/h) to follow. The Naloxone PI that is referred to in the Transtec PI section on overdose does not allow for this high infusion rate, except at inordinately high intravenous fluid rate of 1 L/h given the recommendation: '*For continuous intravenous infusion, 2 milligrams of naloxone hydrochloride may be diluted in 500 mL of sodium chloride 0.9% or glucose 5% injection to produce a solution containing 4 micrograms/mL'*.[47] Could advice be provided regarding the safety of a more concentrated solution of naloxone?
9. The references provided for pharmacodynamics interactions are over 10 years old. Could an updated review be provided?

Efficacy

10. In the protocol violations section of each of the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 it was noted that skin site assessments had occurred earlier than required by the protocol. The statement is then made that the patients were checked for skin reactions and that in all of the patients either no reaction was observed or the skin reaction lasted '*for longer than 30 minutes*'. No further information is provided. Is this an error and should it read '*the skin reaction lasted for no longer than 30 minutes*'?
11. In WIS-BUP02, the study report provides an estimate of the amount of opioids (as an average daily dose of 'buprenorphine equivalent') being taken by the patients prior to entry into the study. No detail is provided regarding how the buprenorphine equivalent doses were determined. Could the method of determining the 'buprenorphine equivalents' be described?
12. The inclusion criteria for study PB-TTC-02 includes:

    § *Patients pre-treated with opioids and requiring an equianalgesic dose range equivalent to 90 to 150 mg morphine per oral (p.o.) per day.*

    Could the method of determining equianalgesic doses be provided?

[45] NLM DailyMed advice regarding transdermal buprenorphine. Accessed March 2015 at: http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm
[46] van Dorp E, et al. Naloxone reversal of buprenorphine-induced respiratory depression. *Anesthesiology* 2006; 105: 51-57
[47] DBL Naloxone hydrochloride injection PI.

13. A number of the post-marketing observational studies, in which prescription of buprenorphine patches was said to be in accordance with the SmPC, describe patients using ½ or ¼ (and even ⅛) of the 20 mg patch. Does cutting a patch into smaller pieces change its properties (for example, release rates, adhesion) and is this a recommended practice?
14. The post marketing surveillance study, AWB Transtec Pro 2005/2, describes Transtec Pro as a 'more advanced form of Transtec' and a 'new form with an application period of up to 96 hours'. From the PK studies it appeared that the patch used for 96 hours was identical to the patch used for 72 hours. Could this be clarified?

Safety

15. The summary of clinical safety states: '*Clinical laboratory evaluations were not performed during the clinical development of buprenorphine transdermal patch because no clinically relevant changes had been reported for orally or intravenously administered buprenorphine*'. In support of this, the clinical overview refers to a review article from 2002 (sponsored by [information redacted][41], an editorial by the same author and two articles reporting research into the respiratory depressant effects of buprenorphine, from 1994[42] and 2005[43] respectively. Could a substantive review of the safety of buprenorphine as evidenced in the literature, with this including the past 10 years, be provided?
16. The RMP states in the section on local tolerability and sensitization that: '*Two types of skin reactions can be observed in general: Irritative/toxic reactions or allergic skin reactions. Long term occlusion of the skin increases the risk for skin sensitisation and development of an allergic skin reaction*.' These effects of transdermal drug delivery systems are not elsewhere discussed. Could a review of the interaction between human skin and the buprenorphine patch be provided?
17. Pre-clinical data show that buprenorphine inhibits the HERG channel in in vitro models. The potential for Torsades de Pointes, using the surrogate marker of QT prolongation, was investigated in the Phase I study BUP1011. The report of this is provided in PSUR 10 and the conclusion of the study is that the dose of 2 x BTDS 20 mg (40 mg) prolongs QTci[26] to an extent comparable to 400 mg of moxifloxacin. A maximal dose of 140 mg of transdermal buprenorphine is proposed in this submission. The risk of Torsades de Pointes is not discussed in the clinical overview or the summary of clinical safety. It is briefly addressed in the RMP. With regard to the results of study BUP1011, this concluded that: '*Several limitations around study design and data recording, which possibly confounded the results, were identified during an independent re-assessment of the electrocardiographic data'* and that *'Aside from the trends of mean QTci values, no QTci outlier was identified which could be considered a concern with regard to pro-arrhythmic potential*'. Despite this conclusion, the Australian PI for the sponsor's closely related product Norspan includes:

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

    Could a more comprehensive scientific evaluation of the risk of Torsades de Pointes (including for the proposed maximum dose of transdermal buprenorphine 140 µg/h)

be provided? Could the rationale for not including a warning regarding QT prolongation in the draft PI be provided?

18. According to the RMP, two well documented individual case safety reports were received during post marketing surveillance that were suggestive of vasospastic angina induced by buprenorphine. Both cases were reported as serious, requiring hospitalisation, and both recovered. No further information was able to be located in the dossier. This risk is not addressed in the clinical overview or the summary of clinical safety. Could further information regarding these case reports be provided?
19. Re exposure during the clinical trial programme: According to the summary of clinical safety: '*More than 1,250 patients were exposed to any buprenorphine transdermal patch during controlled clinical studies*'. According to the RMP: In total 1,318 subjects have been exposed in interventional clinical trials with buprenorphine transdermal patch. The RMP also states that: *'48 subjects in the clinical trial program were exposed to a 17.5µg/h patch*'; this dose was not used in any of the studies provided (except as 'medication errors' in some of the post-marketing surveillance studies). Please clarify: have additional studies been included in the RMP that have not been provided or discussed in the dossier?
20. Could the following documents that are in the Appendix of PSUR10 Volume 2 be provided as separate electronic copies:
    - BUP1011 Study Report
    - Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006
    - EMA document 'Points to Consider: The Assessment Of The Potential For QT Interval Prolongation By Non-Cardiovascular Medicinal Products
    - International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use ICH Harmonised Tripartite Guideline: The Clinical Evaluation Of Qt/Qtc Interval Prolongation And Proarrhythmic Potential For Nonantiarrhythmic Drugs E14 from 2005
    - Fenichel RR, Malil M, Antzelevitch C, Sanguinetti M, Roden M, Prioir SG, Ruskin JN, Lipicky RJ, Cantilena LR. Drug-Induced Torsades de Pointes and Implications for Drug Development. *J Cardiovasc Electrophysiol*, Vol. 15, pp. 475-495, April 2004.

Second Round Evaluation of clinical data submitted in response to questions

For detail of the second round evaluation of the clinical data submitted in response to questions please see Attachment 1.

Second Round Benefit-Risk Assessment

Second round assessment of benefits

The responses provided to the clinical concerns by the sponsor provide no new information related to efficacy. The clinical evaluator's opinion is unchanged from the first round assessment that the sponsor does not provide sufficient evidence to convincingly establish efficacy the of the Transtec patch in management of moderate to severe chronic pain on the basis that:

- The three 'pivotal' placebo controlled studies failed to demonstrate efficacy, using current regulatory and study design standards
- The post hoc analysis of the three under powered placebo controlled studies found inconsistent results across the three patch strengths and three studies and also failed to demonstrate efficacy
- The fourth placebo controlled withdrawal study demonstrated efficacy but only in a sub group of the target population; those patients with severe cancer pain who had already demonstrated a response to the Transtec patch
- The active controlled studies demonstrated non-inferiority to prolonged release tramadol, a WHO Level 2 opioid, although the Transtec buprenorphine patch is proposed as a WHO Level 3 opioid. This is not consistent with the proposed indication.

Given this, the advantages associated with transdermal drug delivery such as avoidance of first pass metabolism, achievement of constant drug plasma levels, an improved patient compliance and improved pain control due to less variation in therapeutic plasma levels may not be realised.

In the responses to the clinical concerns, the sponsor has indicated that the 'ceiling effect' on respiratory depression should be considered a safety related advantage of the use of the buprenorphine patch. It is important to remember that this postulated ceiling effect on respiratory depression with buprenorphine was demonstrated by the administration of intravenous buprenorphine, to healthy volunteers with an average age of 22 years. It has not been demonstrated in the target population, who will vary in age, co-morbidities and concomitant medication. Note that many of these patients will be taking co analgesics that have sedating effects (for example antidepressant, carbamazepine).

The process of raising clinical concerns and evaluating the sponsor's responses has highlighted a number of gaps in the clinical development programme of the Transtec patch with these including:

- establishing the minimum effective therapeutic concentration
- establishing the equivalence of 72 hour and 96 hour application times in the target population
- establishing dose responsiveness
- investigating drug-drug interactions
- investigating the factors that affect absorption and inter-patient variability in absorption.[18]

Second round assessment of risks

The responses provided by the sponsor, including a considerable number of publications that are more recent than 2005 and that were not included in the original submission, has provided a greater depth to the descriptions of aspects of the product. Access to the studies from the clinical development programme of the 7 day Norspan patch has also provided a greater understanding of the performance characteristics of the transdermal buprenorphine delivery system together with safety concerns related to the 7 day patch.

These concerns include the safety aspects of an appropriate interval before re use of an application site, the effect of heat on absorption and potential drug-drug interactions. The lack of information regarding these factors in relation to the Transtec patch means that the information available for the 7 day Norspan patch must be used as the best available guide. This would suggest that the risks associated with re-use of an application site

within 21 days, application of heat to the patch and potential interactions with drugs such as protease inhibitors need to be acknowledged in the PI for Transtec.

Additional information was also provided regarding the potential safety concerns of QT prolongation and vasospastic angina. The 2015 review of the risk of QT prolongation with transdermal buprenorphine was reasonably comprehensive and suggests that this risk is, at most, extremely low. However, the 2015 review was not as thorough as the review performed in 2006 and failed to follow up on the safety signal of increased 'sudden death' that was identified by a broad search of the WHO Vigibase in the earlier review.[48]

The safety and tolerability concerns identified in the first round evaluation remain and several more have been added following the second round evaluation:

- Safety concerns;
  - The response to even low doses is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter patient variability in absorption from the patch demonstrated in the PK studies
  - Potentially life threatening co administration with other sedating drugs is likely to continue to occur, given that many co analgesics may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  - The clinical evaluator's concern regarding the risk of Torsades de Pointes is lower following the second round evaluation but this concern has not been eliminated
  - Coronary vasospasm remains a serious potential risk
  - The potential for abuse and misuse also exists, although this is probably at low risk of occurrence.
- Tolerability Concerns;
  - Use of the buprenorphine patch of these strengths is frequently associated with such side effects of nausea, vomiting, constipation, dizziness and fatigue. These were sufficiently distressing for many patients to discontinue use of the buprenorphine patch (discontinuation rates of 18 to 46% were described in the post marketing surveillance studies)
  - Application site reactions frequently occurred and were of sufficient severity to be a common reason for patients to discontinue use of the product, particularly with long-term use.
- Additional concerns identified through the second round evaluation;
  - Increased absorption from the patch, with resulting increase in opioid type adverse effects may occur with
    - § re-use of an application site between 7 and 21 days
    - § local application of heat to the patch
    - § external heat and physical activity
    - § application to an area of damaged skin

[48] The MAH of Transtec have performed several comprehensive scientific evaluations (including the Scientific Evaluation of the Effect of Transtec on Myocardial Repolarisation dated 27/02/2006 provided in PSUR 10 Appendices) of buprenorphine transdermal patch and QT prolongation, the latest in Mar 2015, which considers all the data available for on this topic and concludes that there is no signal that buprenorphine may have a pro-arrhythmic effect in the range of exposure achieved with transdermal systems or even the higher doses of oral buprenorphine used in opioid substitution therapy.

- Use in opioid naïve patients should be avoided due to the likely occurrence of distressing opioid type adverse effects. Use of one of the lower strength 7 day Norspan patches should be considered instead
- The proposed maximum dose of 2 x 40 mg patches (estimated dose of 140 µg/h) is not supported by the clinical study programme. Insufficient use of this dose has been described in the post-marketing surveillance studies and available literature to provide support for this proposed maximum dose
- The possibility of drug-drug interactions with drugs that affect CYP3A4 (including protease inhibitors)
- Risk of medication errors through the availability of two buprenorphine patches with different application times. Patients may inadvertently apply the 7 day patch for 4 days and receive a higher than intended dose.

Second round assessment of benefit-risk balance

The clinical evaluator's assessment of the benefit-risk balance is unchanged: the benefit-risk balance of the buprenorphine patch for the proposed usage is unfavourable. Given the uncertain efficacy, the risks outweigh any potential benefit. These risks range from potentially life threatening, although rare, adverse drug reactions to the less severe but very common and distressing opioid type side effects.

Second round recommendation regarding authorisation

The evaluator's recommendation regarding authorisation is unchanged from the first round.

It is recommended that the submission be rejected on the grounds of:

- Efficacy has not been satisfactorily demonstrated for the proposed indication of the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids
- Safety concerns such as;
  - Unpredictable response to even low doses (including part patches) that can result in symptoms requiring hospitalisation
  - Potentially life threatening co administration with other sedating drugs is likely to continue to occur, given that many co analgesics used in the target population may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  - Poor tolerability with high rates of discontinuation due to adverse effects
  - Cardiac risk due to possible QT prolongation and coronary vasospasm.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan EU-RMP Version 1.0 (dated 31 October 2014, DLP 30 July 2014) and Australian Specific Annex Version 0.3 (dated December 2014) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown in Table 16.

Table 16: Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Respiratory depression Drug abuse Addiction Overdose
Important potential risks	Vasospastic angina
Important missing information	None

Pharmacovigilance plan

The sponsor concludes that routine pharmacovigilance activities are sufficient to address all ongoing safety concerns.

Risk minimisation activities

The sponsor concludes that routine risk-minimisation activities are sufficient to address all ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 17 outlines the reconciliation of issues outlined in the second round RMP report.

Table 17: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
1. Safety considerations may be raised by the nonclinical and clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor has addressed the specific safety concerns under the respective questions. The sponsor does not consider any of these safety concerns significant new safety information and therefore no updates are required to the Transtec RMP.	The clinical evaluator has made recommendations regarding the RMP.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
2. The RMP provided in support of the current application differs significantly from the RMP provided for the application to register Norspan 5 µg/h, 10µg/h and 20 µg/h. Of significance, the RMP provided for the current application differs from the RMP previously evaluated in the table of ongoing safety concerns, the pharmacovigilance and risk-minimisation activities. Although, it is noted that the indication between Norspan and Transtec are slightly different, this is considered unacceptable as the application refers to the same product but in different strengths and therefore, it is expected that the RMP for Norspan being equally applied for Transtec. Consequently, the RMP in its current version is deficient and has to be corrected prior to potential approval.	The difference seen in the safety profile of Transtec in comparison to Norspan accurately reflects the different way these two products are used. Although the buprenorphine patch itself is the same, the differing indication, patient population, strengths and duration of wear of both products all contribute to a differing safety profile between the products. The global safety database of each product therefore accurately reflects the safety profile of its respective product. Safety concerns identified for Norspan are considered for Transtec and vice versa, however they cannot be automatically applied to both products as this may not reflect the safety profile of each product as per its global safety database. Therefore the RMP for Norspan cannot be applied to Transtec. Further detail on the differing risks is provided in response to Recommendation 4 which clarifies that there is very little or significant difference between the identified Norspan and Transtec risks.	This is partially acceptable. The characterisation of some safety concerns, for instance, medication error might be specifically related to a particular formulation type. However the entire safety profile of a product cannot be sufficiently characterised without consideration of risks relating to other formulations of the medicine, particularly where the other formulations have substantially more post-market experience. The deficiencies in the summary of safety concerns are further discussed below (see recommendation 4).
3. It is recommended that the sponsor reworks the structure and content of the ASA, to provide all relevant information outlined in the TGA ASA template. This document will be revisited prior to the Advisory Committee on Prescription Medicines (ACPM).	The ASA has been reworked to provide the information as outlined in the TGA ASA template. The ASA now includes a summary table of the safety concerns and the risk minimisation measures in the Australian context. This table includes the actual wording of the EU SmPC and proposed Australian PI and CMI for all of the safety concerns.	The evaluator acknowledges the sponsor's revisions.
4. The sponsor should add all ongoing safety concerns which were accepted and requested for Norspan patches to the table ongoing safety concerns for Transtec, or provide compelling justification for not doing so. Pharmacovigilance and risk-minimisation activities should be	A comparison and justification for the difference in the ongoing safety concerns of the Transtec RMP compared to the Norspan RMP is provided in Table 18. Based on the justifications in the above table and the response to recommendation 2 the sponsor does not think any alterations are required to the Transtec RMP.	The evaluator accepts the sponsor's handling of the risks Drug Abuse and Addiction which are included as identified risks in the Transtec RMP/ASA.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
assigned to all ongoing safety concerns and the pharmacovigilance and risk-minimisation plan of the EU-RMP/ASA be amended accordingly.	The ongoing safety concerns that the TGA requested to be added as potential risks for Norspan were: 1. The interaction with CYP3A4 inhibitors. 2. CNS depression, in particular the effects on driving ability. 1. The interaction with CYP3A4 inhibitors. The sponsor believes that the addition of this risk to the Transtec RMP is not justified. In general, Buprenorphine is subject to metabolism by CYP3A4. However, as outlined in RMP Part II Module SII Non-clinical part of the safety specification buprenorphine itself is not expected to have relevant effects on CYP3A4 or CYP2D6: Buprenorphine and its main metabolite norbuprenorphine have in vitro inhibitory effects on CYP3A4 at concentrations that were 2000-fold above clinically relevant concentrations. Inhibitory concentrations (Ki) for effects on CYP2D6 in the in vitro studies were estimated to be about 5,000 to 10,000 times higher than the total peak plasma concentrations of buprenorphine under steady-state conditions at the highest recommended dose for the marketed transdermal patch. Therefore, clinically relevant changes in the activity of these enzymes due to treatment with buprenorphine transdermal patch are unlikely in humans. Although the non-clinical data suggests this interaction is unlikely for Transtec the potential for the interaction buprenorphine and CYP enzymes is well-recognised therefore the Transtec label does contain the following suitable statement regarding this interaction: 'Administered together with inhibitors or inducers of CYP 3A4 the efficacy of Transtec may be intensified (inhibitors) or weakened (inducers)'. Furthermore the Australian Public Assessment Report for Buprenorphine/Naloxone does not recognise this as a safety concern for Suboxone in the table of safety concerns. Considering that the dose of buprenorphine in this product is significantly higher than that received via the Transtec patch (maximum daily does is 32mg compared to 140mcg) the sponsor therefore considers that the pharmacovigilance activities and risk minimisation measures currently in	The evaluator accepts that accidental overdose will continue to be monitored under the umbrella identified risk Overdose. This is not accepted. Medication error, including accidental exposure is possible. This is important as due to the residual medicine available on the patch after use, safe disposal is paramount. The evaluator accepts that the Norspan risk 'psychological dependence' is sufficiently covered by the identified risk 'Addiction'. In concordance with the draft PI, this product *has not been studied in patients under 18 years of age.* Paediatric use should be included as an item of missing information. In concordance with the draft PI, *there are no adequate data from the use of Transtec in pregnant women*. Use in pregnant or breastfeeding patients should be included as an item of missing information. The clinical evaluator has recommended that the draft PI include additional information

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	place are adequate to minimise this risk and that the addition of this as a safety concern for the Transtec patch is unjustified. 2. CNS depression, in particular the effects on driving ability. The sponsor believes that the addition of CNS depression, in particular the effects on driving ability, to the table of ongoing safety concerns is not justified. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published a literature review in 2014 on Drug use, impaired driving and traffic accidents which provides a comprehensive report on the relationship between drug use, impaired driving and traffic accidents. The Strand et al. article[49] referenced in the evaluator comment was included as a source in the review conducted by the EMCDDA[50] to evaluate the relationship between buprenorphine administered for opioid maintenance therapy and impaired driving. The conclusion for this association is that 'maintenance therapy buprenorphine users have not generally shown impairment, except at high doses' and 'Long-term use of transdermal buprenorphine for the treatment of chronic non-cancer pain does not impair driving ability, but, because of the individual variability of test results, an individual assessment is recommended.' although neither of these statements specifically refer to the Transtec product (it being neither high dose buprenorphine or transdermal buprenorphine for the treatment of chronic non-cancer pain) this paper concludes that buprenorphine can have an effect on driving ability but this is limited to high doses (2 to 8mg) which is above the maximum dose of Transtec (140µg). The epidemiological studies available are limited and provide inconclusive evidence for the accident risk associated with opioid use. The potential effect of buprenorphine transdermal on the ability to drive and operate machinery is	regarding CYP3A4 drug interactions. Should the sponsor include this information then not including it as a specific safety concern may be acceptable. CNS depression is a concern for any opioid. Respiratory Depression is listed as an identified risk which is an important manifestation of CNS depression. It is noted that the PI already contains driving advice.

[49]Strand, M. C., et al. Psychomotor relevant performance: 1. After single dose administration of opioids, narcoanalgesics and hallucinogens to drug naïve subjects, 2. In patients treated chronically with morphine or methadone/buprenorphine. 2011 DRUID Deliverable 1.1.2c, Bundesanstalt für Strassenwesen, Bergisch-Gladbach.

[50] EMCDDA (2014), Drug use, impaired driving and traffic accidents, EMCDDA Insights No 16, European Monitoring Centre for Drugs and Drug Addiction, Lisbon.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	well-recognised and covered in the product labelling. The sponsor therefore considers that the pharmacovigilance activities and risk minimisation measures currently in place are adequate to minimise this risk and that the addition of this as a safety concern for the Transtec patch is unjustified.	
5. It is recommended to the delegate to assess whether the difference in the statement in the 'dose titration' section in the Norspan- and the Transtec-PI, is justified on the basis of the slightly different indication for Norspan and Transtec.	The indication for Transtec is moderate to severe cancer pain and severe pain which does not respond to non-opioids in comparison to the indication for Norspan which is the treatment of pain of moderate to severe intensity when an opioid is necessary for obtaining adequate analgesia. Considering pain levels will be higher in patient with moderate to severe cancer pain and severe non-malignant pain, the 140 µg/h Transtec dose is a valuable option for prescribing physicians to manage these patients. In order to titrate the Transtec dose up to a level that meets the patient's needs, high doses such as 140 µg/h may be required. Arbitrary maximum dose limits are not recommended, but there is a practical limitation to 140 µg/h Transtec dose due to the number of patches required. This dose level has been safely used in clinical practice, as documented in the post marketing data and open label extension studies included in the Transtec submission, and reported in the medical literature.	Dose titration advice in the PI is subject to final consideration by the Delegate. From a risk minimisation perspective, it would be helpful if titration advice was harmonised across Norspan and Transtec as appropriate.

Table 18: A comparison and justification for the difference in the ongoing safety concerns of the Transtec RMP compared to the Norspan RMP

Norspan risks	Corresponding Transtec risk	Justification for difference
Important identified risk; Drug withdrawal syndrome	Important identified risk; Drug abuse, Addiction	As outlined in Section II.SVI.3 of the Transtec RMP – Potential for misuse for illegal purposes and Section II.SVII.3 – Details of important and potential risks from clinical development and post-authorisation experience (including newly identified) the Norspan risks of physical and psychological dependence and drug withdrawal syndrome are regarded as included under the Transtec risks of abuse and addiction.
Important identified risk; Physical dependence		

Norspan risks	Corresponding Transtec risk	Justification for difference
Important identified risk; Accidental overdose	Important identified risk; Overdose	Section II.SVI.1 – Potential for harm from overdose and II.SVII.3 – Details of important identified and potential risks from clinical development and post-authorisation experience (including newly identified) of the Transtec RMP summarise the data for Transtec. The Norspan risk of accidental overdose is included under the Transtec risk of overdose.
Important potential risk; Medication error	No corresponding risk identified for Transtec	Section II.SVI.4 of the Transtec RMP Potential for medication errors summarises the data for Transtec. No important safety concern was identified based on the data provided. Cutting the plaster into pieces was the most often observed medication error for Transtec. As no safety concern was identified in the cases related to the topic, this is not regarded to provide a basis for an important potential risk.
Important Potential Risk: Off label use (cutting of the BTDS patch to achieve an intermediate dose)		
Important potential risk: Psychological dependence	Important identified risk: Addiction	The Transtec RMP covers the important potential risk 'psychological dependence' under it important identified risk of 'addiction'.
Missing information: use in pregnant and breastfeeding patients	No corresponding missing information for Transtec	As outlined in the Transtec RMP Section II.SV.3- post authorisation use in populations not studied in clinical trials there is considerable experience with the use of buprenorphine during pregnancy derived from opioid maintenance therapy and there is data on the use of transdermal buprenorphine in paediatric patients.
Missing information: paediatric use		

Summary of recommendations

Outstanding issues

Issues in relation to the RMP

1. New recommendations

The *'Potential for medication errors or other risks if applicable'* section of the revised ASA is not satisfactory in that it does not consider risks of inadvertent exposure, including exposure to used patches. Even after the specified treatment time a clinically significant residual amount of buprenorphine may remain on the patch. Such an amount may be very

harmful (even fatal) for example if a child was inadvertently exposed to the patch. Ensuring appropriate storage and disposal of the patch is paramount to the safe use of this medicine.

- Therefore it is recommended to the Delegate that the sponsor should consider implementing the following activities to mitigate the risk of accidental exposure:
- Include 'medication error/accidental exposure' as a safety concern in the RMP and/or ASA.
- Amend the risk minimisation plan to accommodate this risk as follows:
  - The existing disposal instructions in the CMI should include an explanation of the rationale for safe disposal as follows (or similar): After removing the used patch, fold it over on itself so that the adhesive side of the patch sticks to itself, and dispose of it safely where children cannot reach it. Safe disposal is important as the used patch may be harmful, even fatal to people not prescribed the patch, especially children.
  - The CMI should additionally include the following (or similar) in a prominent and appropriate location: '*Accidental exposure to even one dose of <tradename>, especially by children, can be fatal. It is important that you ensure that <tradename> is stored, used and disposed of out of the reach of children as directed*'.
  - The dosage and administration section of the PI should be revised to include a statement as follows (or similar)*: After use it is possible that the patch will still contain a substantial amount of buprenorphine. Such an amount can be harmful, even fatal to opioid naïve individuals, especially children. Therefore, to avoid accidental exposure, patients should be directed to remove the used patch and fold it over on itself so that the adhesive side of the patch sticks to itself. The patch should then be disposed of safely where children cannot reach*.
  - The Delegate may also wish to consider inclusion of advice similar to above as a specific PI precaution.
  - The packet of buprenorphine patches should include a prominent statement for how to dispose of the patches such as (or similar): '*After use the patch must be disposed of safely according to instructions (see package insert)*'.
  - The patch could include a printed warning such as (or similar): '*After use the patch must be disposed of safely*'
  - The CMI should be included in every box; if not already proposed
  - It is noted that for a transdermal buprenorphine product in the US a 'disposal unit' is included in each pack to assist the safe disposal and minimise risk of accidental exposure. As an additional risk minimisation measure the sponsor should also consider including a disposal unit in the product packet that used patches can be wrapped up and sealed safely in prior to disposal.
- From a risk minimisation perspective it is also noted that the feature of substantial residual medicine after standard use may be desirable to those patients who wish to misuse buprenorphine. This is a challenging risk to mitigate.

Regarding the risk of medication error, the clinical evaluator has detailed concerns relating to patients switching between the Transtec patch and the existing buprenorphine 7 day patch. The concern is that confusion in switching between regimes may result in under or over dosing. The RMP evaluator supports the inclusion of clear statements in the PI and CMI of the existence of other products with different dosing/duration regimes and the importance of ensuring that the appropriate duration is explained and confirmed by the prescriber to the patient.

The RMP evaluator also supports the clinical evaluator's recommendation to improve concordance with the Norspan PI. From a risk minimisation perspective this would improve clarity and communication of risk for both buprenorphine transdermal products.

Any changes made to the risk minimisation plan should be included in an updated ASA document, revised to incorporate any new activities.

2. Recommendations maintained from the RMP evaluation report

In concordance with the draft PI, *this product has not been studied in patients under 18 years of age*. Paediatric use should therefore be included as an item of missing information in the RMP.

In concordance with the draft PI*, there are no adequate data from the use of Transtec in pregnant women.* Use in pregnant or breastfeeding patients should therefore be included as an item of missing information in the RMP.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Comments on the safety specification of the RMP

Clinical Evaluation Report

- The Safety Specification in the draft RMP is not entirely satisfactory and should be revised, having regard to the table provided in section 18.2.8. Comments relate to Module 1, Section 13 RMP, Risk management system Transtec 35/52.5/70. Individual file name: riskmgtsystem-transtec3552570
- The evaluator has reviewed Part II.SVI.4 Potential for Medication Errors, Part II: Module SVII - Identified and potential risks and Part II: Module SVIII – Summary of Safety Concerns.
  - Re Part II.SVI.4 Potential for Medication Errors
    - § Wrong application time: If the 4 day Transtec patch is approved, then there is the potential for patients previously exposed to the 7 day patch to use this application time with Transtec, with this possibly resulting in less analgesic effect than expected. Patients prescribed the 7 day patch may also mistakenly use a 4 day application time, resulting in greater than planned dose and risk of adverse effects. To avoid these drug errors, the evaluator is of the opinion that some acknowledgement in the CMI and PI that two buprenorphine patches, each with a different duration of application, are available would be helpful. This should be accompanied by a recommendation that the consumer and prescriber confirm that the appropriate patch is being used.
    - § Confusion in both prescribers and patients due to differences in the PI and CMI regarding precautions, interactions and adverse effects. Concordance between the PIs and CMIs of Norspan and Transtec would be important.

    Future use of buprenorphine patches in patients with escalating analgesic requirements may involve patients being up-titrated through the available range of patch strengths, with considerable potential for confusion and medication errors.
  - Re Part II: Module SVII - Identified and potential risks

    The evaluator is of the opinion that greater specificity is required for the section II.SVII.4.1 Overview of potential for interactions: This should include information similar to that provided for the 7 day buprenorphine patch
    - § Potential for interactions: CYP3A4 inhibitors:

CYP inhibitors and inducers

Buprenorphine is both a substrate for, and an inhibitor of, CYP3A4. Caution is advised when buprenorphine patches are administered concurrently with inhibitors of CYP3A4 (e.g. protease inhibitors, some drug classes of azole antimycotics, calcium channel antagonists and macrolide antibiotics) as this might lead to increased levels with increased efficacy of buprenorphine with concomitant increased toxicity. Co-administration of buprenorphine patches and enzyme inducers (for example, phenobarbitone, carbamazepine, phenytoin, rifampicin) could lead to increased clearance which might result in reduced efficacy

Potential for interaction with CNS depressants:

Buprenorphine patches, like all opioid analgesics, should be used with caution in patients who are currently taking other CNS depressants or other drugs that may produce additive depressant effects, for example, respiratory depression, hypotension, profound sedation or potentially result in coma or death. Such agents include opioids, sedatives, hypnotics, general anaesthetics, phenothiazines, tranquillisers, skeletal muscle relaxants, sedating antihistamines and alcoholic beverages.

– Re Part II: Module SVIII – Summary of Safety Concerns

  The evaluator is of the opinion that Part II: Module SVIII: Summary of safety concerns should include QT prolongation as an 'Important Potential Risk'.

If the 4 day Transtec patch is approved, then the evaluator is of the opinion that concordance between the PIs and CMIs of Norspan and Transtec would be important. Some acknowledgement that two patches, each with a different duration of application, to be available in the CMI and PI would be essential, with the recommendation that the consumer and prescriber confirm that the appropriate patch is being used. Future use of buprenorphine patches in patients with escalating analgesic requirements may involve patients being up-titrated through the available range of patch strengths, with considerable potential for confusion.

Key changes to the updated ASA

Australian Specific Annex Version 0.3 (dated December 2014) has been superseded by: Australian Specific Annex version 0.4 (dated August 2015).

Table 19. Summary of key changes to the ASA.

Summary of key changes	
Pharmacovigilance activities	Now presented to align with TGA guidance. Nil significant
Risk minimisation activities	Now presented to align with TGA guidance.

Suggested wording for conditions of registration

RMP; Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

No suggested wording can be provided until the outstanding issues are satisfactorily addressed.

VI. Overall conclusion and risk/benefit assessment

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

Background

Buprenorphine is a potent opioid analgesic. It was first registered in 1991 in a parenteral formulation for short term use in moderate to severe pain. Sublingual tablets were subsequently registered for treatment of acute pain and for management of opiate dependence. Additional registrations have been of a transdermal drug delivery system (first approved as Norspan in 2005) for the management of moderate to severe pain and in combination with naloxone as SL tablets and film (first approved in 2011 as Suboxone) for treatment of opioid dependence.

The proposed patch is almost identical to Norspan patches in that it contains the same amount of buprenorphine however the dose regimen is different. Transtec is proposed to be applied every 3 to 4 days rather than every 7 days as is recommended for Norspan. This results in a substantially higher average release rate of buprenorphine. The Transtec range of transdermal patches have mean buprenorphine release rates of 35 µg/h to 70 µg/h compared to 5 to 40 µg/h for the Norspan range. The indication proposed for Transtec is slightly different from that of Norspan in that it is proposed for the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids whereas Norspan is approved for management of moderate to severe pain.

The Australian Therapeutic Guidelines Analgesic (v.6; e-TG)[51] states that buprenorphine patches are suitable first line opioid treatment for chronic non cancer pain and recommends a starting dose of 5 µg/h, increasing to a maximum of 20 µg/h. Thus the minimum dose available from these buprenorphine patches is higher than the currently recommended maximum dose of buprenorphine for patients with chronic non cancer pain.

The indication for Fenpatch (transdermal fentanyl) is '*Management of chronic pain requiring opioid analgesia*'. The indication for Norspan is '*Management of moderate to severe pain*'. Those indications were approved in 2009 and 2005 respectively. With Fenpatch doses of up to 300 µg/h may be given, this is equivalent to 1,035 to 1,124 mg oral morphine daily. The SmPC for Transtec states that the relative potency of buprenorphine in different application forms and in different clinical settings has been described in literature. Morphine p.o.: BUP TTS as 1: 75 to 115 (multiple dose, chronic pain). Using that conversion, the proposed maximum dose of 140 µg/h buprenorphine is equivalent to 252 to 386 mg oral morphine daily.

Quality

There were no objections to registration based on chemistry grounds. The quality evaluator has noted that the design of the Transtec and Norspan transdermal patches are identical.

For each series of products the same buprenorphine adhesive matrix is used with the amount of this matrix increasing proportionally with strength. The surface area of the matrix is also increased proportionally. These two things combine to result in the average release rate increasing proportionally with the strengths.

[51] The Australian Therapeutic Guidelines Analgesic (v.6; e-TG) from www.tg.org.au

When comparing one strength of Norspan to same strength of Transtec there is only a very slight difference in the formulations. That is in the amount of Duro Tak 387-2054, an excipient. The amounts of the other excipients and the surface areas are the same however there is a very large difference in the average release rate due wholly to be duration of application. While the release rates from the 2 products are very similar during the first 4 days after application Norspan remains in place for 7 days while Transtec is proposed to be replaced after 3 to 4 days. This shorter application period results in a higher average release rate over the course of an application. The quality evaluation summary compares the formulations release rates of the 2 products.

As a result of the reduced time a Transtec patch is left in place compared with a Norspan patch (that is when two patches are used per week rather than one patch) the steady state concentration is higher for Transtec than for the same surface area of a Norspan patch.

The quality evaluator has noted that the amount of buprenorphine remaining in the discarded patches will be slightly higher with Transtec than Norspan. For example with the 40 mg patch this will be approximately35 mg if the Transtec patch is discarded at 3 Days and approximately33.3 mg when the Norspan patch is discarded at 7 Days.

Nonclinical

There were no nonclinical objections to the registration of Transtec patches at the proposed strengths. The nonclinical evaluator noted that the proposed maximum recommended dose of buprenorphine from Transtec is (70 µg/h/mL x 2 patches) compared to that for Norspan (40 µg/h total). The estimated plasma AUC at the Transtec maximum is about 2 fold greater than at the Norspan MRHD, and the safety margins for the previously evaluated pivotal toxicity (carcinogenicity, reproductive toxicity) studies conducted for Norspan submissions were reduced by about half, but are still adequate. This was an error. The proposed maximum AUC is approximately 4 fold higher than the current AUC from the maximum recommended dose of Norspan patches.

Clinical

Clinical evaluator's recommendation

The clinical evaluator recommended that the submission be rejected on the grounds of:

- Efficacy has not been satisfactorily demonstrated for the proposed indication:

  of the management of moderate to severe cancer pain and severe pain that does not respond to non-opioids

- Safety concerns such as:
  - Unpredictable response to even low doses (including part patches) that can result in symptoms requiring hospitalisation
  - Potentially life threatening co-administration with other sedating drugs is likely to continue to occur, given that many co-analgesics used in the target population may cause sedation. This is a particular concern with the buprenorphine patch due to its long half-life even after patch removal
  - Poor tolerability with high rates of discontinuation due to adverse effects
  - Cardiac risk due to possible QT prolongation and coronary vasospasm.

Pharmacology

Five clinical pharmacology studies were included in the submission with reliance placed on existing literature regarding buprenorphine delivered by other routes to describe its PK and pharmacodynamic characteristics. Buprenorphine is subject to extensive first pass metabolism such that oral administration is ineffective. Estimated transdermal bioavailability is approximately 50%. Volume of distribution (Vd) is 430 L and it is highly protein bound (approximately96%). Buprenorphine passes the blood brain and placental barriers.

The main route of elimination of buprenorphine is as unchanged drug in faeces following biliary excretion and to a lesser extent by glucuronide conjugation followed by biliary excretion. Buprenorphine primarily undergoes N-dealkylation by CYP3A4 to norbuprenorphine and glucuronidation by uridine diphosphate glucuronosyltransferase (UGT)-isoenzymes (mainly UGT1A1 and 2B7) to buprenorphine 3β-O-glucuronide. Norbuprenorphine, the major metabolite, is also glucuronidated (mainly UGT1A3) prior to biliary excretion. Metabolism by the enzyme CYP3A4 accounts for about 30% of the total metabolism of buprenorphine. Renal clearance is thought to account for less than 30% of the excretion of buprenorphine. Clearance of buprenorphine is not significantly altered in patients with renal impairment.

The Phase III studies were conducted with patches applied every 72 hours rather than up to 96 hours as has been proposed. Bioequivalence of the 72 hour and 96 hour application was demonstrated in healthy volunteers and is discussed in the clinical evaluation report (see Attachment 1). Dose proportionality of the 3 strengths was demonstrated on single and multiple applications.

After patch removal and application of a new patch, a small transient decrease in plasma concentrations was observed. The ongoing increases in C_{max} and AUC with each patch indicate that the steady state of buprenorphine was not fully reached with the third patch (Day 9). The population PK study, PP017P was used to demonstrate steady state after three 96 hour sequential applications of the patch or four x 72 hour sequential applications of the patch and that accumulation with multiple applications did not occur. On multiple dosing the mean terminal phase half-life was between 33 and 37 hours.

There is wide inter-patient variability in absorption rates and plasma concentrations of buprenorphine for a given transdermal application, as shown in the clinical evaluation report (see Attachment 1). This was further explored after the sponsor provided additional information on the variability of plasma buprenorphine concentrations within the same patient given differing dose patches and between patients. As a result the clinical evaluator stated that '*inter-patient and intra-patient variability raises the question as to whether the patches are best described by their putative release rates. It may be more accurate to describe them by the amount of buprenorphine contained within the patch and the application time.'*

The clinical evaluator considered it was very important that this individual variability be highlighted in the product information as it is relevant to an individual's analgesic response and also relevant when switching from another opioid to buprenorphine patches, and from one buprenorphine patch to another. The inter-patient variability would indicate that it is most prudent to commence on the lowest available patch strength for all patients and that increasing the patch strength should be done with care.

No specific studies on skin tolerance, effect of temperature or of different body sites or skin characteristics were performed. Limited assessment of application site rotation showed increased absorption if a site was re-used with only a 3 day gap between applications. Given this lack of assessment the evaluator recommended the same restrictions on re-use of an application site as are recommended for Norspan, given the almost identical composition. This is 3 to 4 weeks rather the 7 days proposed for Transtec.

The effect of increases in temperature has been explored with Norspan and there was a substantial increase in the plasma concentration of buprenorphine when a heating pad is applied as shown in Figure 34 in Attachment 1.

A thorough QT study was not performed for this product. The thorough QT study performed to support registration of Norspan showed a transdermal dose of 40 µg/h prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2 to 13.3) msec.

Information on equipotency estimated a broad dose range of buprenorphine in transdermal patch preparations as being approximately equipotent with a given dose of morphine. Small switching studies had flaws in both design and execution. Information in published literature suggests 35 µg/h is equivalent to 60 mg oral morphine daily and 25 µg/h of transdermal fentanyl. The SmPC for Transtec cites conversation rates of 1: 75 to 115 for chronic pain. The Australian Therapeutic Guidelines: Analgesic[51] advises that the 7 day 20 µg/h buprenorphine patch is approximately equi-potent to 50 mg oral morphine per day. Further information on the daily delivered dose of buprenorphine was obtained by determining the residual buprenorphine in patches after application to healthy volunteers (see PKs Question 6 in the clinical evaluation report; see Attachment 1).

Table 20: Approximate daily dose of buprenorphine from Transtec patch (calculated from residual buprenorphine in used patches)

	Calculated release rate over 72 hours (mcg/h)		Approximate 24 hour dose (mg)	
	minimum	maximum	minimum	maximum
Study HP5303/01				
20mg patch	2	80.2	0.0	1.9
40mg patch	21	208.6	0.5	5.0
Study HP5303/02				
20mg patch	3.2	69.3	0.1	1.7
30mg patch	5	101.3	0.1	2.4
40mg patch	1.5	129.2	0.0	3.1

The range of daily dose estimated for the 40 mg patch was 0.04 to 5.0 mg. The sponsor estimate was for a daily dose of 1.7 mg daily with the 40 mg patch. It is important to note that the residual buprenorphine in the patches is similar to the residual in Norspan patches because most of the active drug is not absorbed from either product over the application course. This was referred to in the quality evaluation.

No interaction studies were performed. Given the interaction with SL buprenorphine and protease inhibitors with strong CYP3A4 inhibitory activity the clinical evaluator recommended this be included in the PI. The sponsor responded to this by clarifying that the possibility of drug-drug interactions for Transtec with drugs affecting CYP34A is inaccurate, given that the reported in vitro inhibitory effects on CYP3A4 only occurred at concentrations that were 2,000 fold above clinically relevant concentrations, or only seen with SL buprenorphine. That clarification assumes the drug levels achieved with SL buprenorphine could not be attained with the proposed Transtec dose schedule, however, as noted absorption is highly variable and may be to some extent dependent on skin temperature. Furthermore the clinical trial program based initial dose selection on buprenorphine levels achieved via SL buprenorphine.

Efficacy

There were no, dose finding studies with the doses tested apparently based on SL doses of buprenorphine in use for the management of pain in Europe when the studies were performed. A post-market surveillance study used the 96 hour dose interval.

Three double blind, randomised, placebo controlled studies were described as pivotal. These were short term studies with double blind periods of up to 5 patch applications (15 days). The application period between patches was 72 hours rather than the 3 to 4 day proposed in the draft PI. The pivotal studies were performed 18 to 20 years ago and their design may reflect clinical trial requirements at the time they were conducted. A further 3 double blind studies were performed between 2002 and 2005, two of these had sustained release tramadol as an active comparator and the other was a placebo controlled, randomised withdrawal study.

None of the studies nominated as pivotal demonstrated superiority of buprenorphine patches over placebo. Design features of the studies are likely to have contributed to this. A post hoc exploratory analysis of data from the 3 pivotal studies was performed at the request of the MHRA in 2001 as part of an application for mutual recognition within the EU. That analysis combined results from all doses of buprenorphine in each study and compared them with the placebo results from that study. The main efficacy variables in the post hoc analysis were change from baseline in mean pain intensity and use of rescue medication. Baseline was the last value prior to treatment. Results for these variables by study are shown in Table 37 in Attachment 1. The clinical evaluator has noted that WIS-BUP123 was a post-hoc analysis of the pooled results of three under powered studies each with a different design. Timeframes and end-points were manipulated to enable the results to be pooled. The results did not show a clear and consistent dose response for all groups and all patch strengths.

A statistically significant difference in mean change from baseline pain intensity between placebo and each strength of buprenorphine patch was demonstrated in studies WIS-BUP01 and WIS-BUP03 but not in WIS-BUP02. The mean differences from placebo in change from baseline pain intensity were in the region of 0.2 to 0.45 on a 4 point scale. Rescue medication was statistically significantly less likely to be required in patients given buprenorphine compared with placebo in each study overall and in each buprenorphine dose group in Studies WIS-BUP02 and WIS-BUP03 but not in any dose group in WIS-BUP01. Additional exploratory analyses of combined response pain relief and rescue medication and combined response pain intensity and rescue-medication were also performed.

The pivotal studies are summarised below:

WIS-BUP01

WIS-BUP01 was performed to determine the analgesic efficacy and safety of three buprenorphine patch dosages compared to patch placebo. During a 6 day run-in phase all patients took regular SL buprenorphine tablets at doses between 0.8 and 1.2 mg daily with additional 0.2 mg doses for breakthrough pain. On the 6th day patients were assessed for participation in the randomised component of the study. Only patients reporting at least satisfactory pain relief using a 4 point scale (unsatisfactory; satisfactory; good; and complete) were eligible for randomisation to one of three doses of Transtec (20 mg, 30 mg and 40 mg content of buprenorphine delivering 35 µg/h, 50 µg/h and 70 µg/h respectively) or placebo for 2 patch applications (6 day treatment period and a further 3 days of SL buprenorphine prior to the final assessment of Day 15). Breakthrough analgesia with buprenorphine SL tablets continued to be available.

The primary efficacy measure was the percentage of patients responding to treatment with a 'responder' defined as having at least satisfactory pain relief at each investigator

visit in the double blind phase (excluding Final Examination Visit) and taking a mean of not more than 1 additional SL buprenorphine tablet daily from the second day of buprenorphine patch application to the last day of patch wearing (Day 7 to Day 12; total 5 days).

A total of 151 patients were randomised into the double blind phase. Some 121 (77.1%) had cancer related pain and 22.9% had non cancer related pain. The study report did not provide the proportion of patients who were opioid naïve prior to study or patient's baseline level of pain however the baseline average daily opioid intake prior to study is presented in Table 16 in Attachment 1. The response rates in the buprenorphine patch groups were higher than the placebo group however, this difference in an ordered analysis, was not statistically significant ($p > 0.05$) and the primary endpoint was not reached. There was no evidence of a dose response.

- 16.2 % in the placebo group
- 36.6 % in the 20mg (TTS 50; 35 µg/h) group
- 47.5 % in the 30mg (TTS 75; 52.535 µg/h) group
- 33.3 % in the 40mg (TTS 100; 70 35 µg/h) group

WIS-BUP02

WIS-BUP02 was also performed to determine the analgesic efficacy and safety of 20 mg (TTS 50), 30 mg (TTS 75) and 40 mg (TTS 100) transdermal buprenorphine patches with placebo. This study enrolled patients with continuous severe tumour related and non-tumour related pain that could not be adequately managed with regular weak opioids according to WHO step 2 of tumour pain drug treatment. Patients previously treated with morphine up to a daily dose of 30 mg orally or 10 mg parentally or with another potent opioid in an equivalent dose prior to the start of the study were excluded.

This study had no run-in/washout period. On Day 1 of the first patch application patients were permitted to administer the analgesic medication of the previous day. Five patches were to be applied consecutively at 72 hour intervals. Buprenorphine 200 µg SL tablets were provided for the management of breakthrough pain. The primary efficacy assessment was the response rate, defined as in Study WIS-BUP01, though the initial protocol had required no additional SL buprenorphine. A total of 157 patients were randomised and 154 were included in the efficacy analysis. The response rates were: placebo 16.2 %, TTS 50 36.6 %, TTS 75 47.5 %, TTS 100 33.3 %. As in the previous study no dose response was demonstrated and statistical significance was not reached for the primary efficacy comparison, as shown in Table 17 in Attachment 1.

WIS-BUP03

WIS-BUP03 compared the analgesic efficacy and safety of the 20 mg (TTS 50) buprenorphine patch with placebo. Patients required more baseline pain relief than those in WIS-BUP02. The study enrolled patients with severe or very severe pain of benign or malignant origin, requiring the administration of a strong opioid such as buprenorphine. During a 6 day run-in phase patients received regular SL buprenorphine. Patients who obtained at least satisfactory relief with a daily dose of 0.8 to 1.6 mg buprenorphine were eligible for randomisation to the double blind phase. Because there is a time lag before an effective serum level of buprenorphine is obtained with the TTS the duration of adhesion of the first patch (Days 7 to 9) was described as the influx phase. The usual morning dose of SL buprenorphine was to be taken on the first day the TTS was applied. Three successive patches were to be applied at three day intervals from Day 7 until Day 13. The final examination was carried out on Day 16 at the removal of the third patch. Sublingual buprenorphine was available for breakthrough pain management.

The primary efficacy measure was the response rate with 'responders' defined as those patients who, during the steady state phase required at least 40 % fewer buprenorphine SL tablets than in the run-in phase and who stated that the pain relief was at least satisfactory (using the same 4 point scale as in WIS-BUP01 and WIS-BUP02) during the steady state phase. A total of 137 patients were randomised to double blind treatment with 90 receiving the 20 mg buprenorphine patch and 47 receiving placebo patch. Most patients had been taking opioids prior to the study (85.6% of the buprenorphine patch group and 87.2% of the placebo group). Tramadol was the most commonly prescribed opioid (33.6%), followed by tilidine (14.0%), codeine (9.5%) and morphine (8.0%). There were some differences in the distribution of patients with pain associated with cancer and with pain due to other causes and patients in the placebo group required on average 0.9 mg SL buprenorphine daily compared with 1.1 mg daily for the active group. Overall, 50 (57.5 %) of the buprenorphine patch group and 21 (46.7 %) of the placebo group were considered to be responders, a difference that did not reach statistical significance.

A further 3 randomised, double blind, controlled studies were subsequently performed.

PB-TTC 02

PB-TTC 02 examined the efficacy and safety of the 40 mg buprenorphine patch (TTS 100) in patients with severe chronic tumour related pain requiring treatment with opioids at an equianalgesic dose range equivalent to 90 to 150 mg morphine orally per day. This was a randomised withdrawal study conducted in 2 phases. In a 15 day run-in phase patients were treated with the 40 mg buprenorphine patches applied consecutively every 3 days. Randomisation criteria for entry into the double blind phase were: In the 4 days preceding the Randomisation Visit there were:

- At least 6 (of a possible 8 assessments) pain assessments in the patient's diary
- The pain score was less than 5.0 on average on an 11 point NRS. A level of 5 or more was said to be regarded by pain experts as indicative of a need to review the patient's pain management
- The consumption of rescue medication was ≤ 8 tablets (≤ 2.0 tablets on average per day) SL buprenorphine.

Sublingual buprenorphine was available for breakthrough pain throughout the study. Pain intensity using an 11 point NRS[36] was assessed twice daily. The primary efficacy outcome was of responders, defined as patients who completed at least 12 days of the double blind period, and who had an average pain intensity < 5.0 during the last 6 days of treatment, and who did not use more than 2 x 0.2 mg SL buprenorphine as rescue medication/day on average during the double blind period.

A total of 289 patients were enrolled into the run-in phase with 188 randomised to withdrawal and with a pain assessment available. No assessment of pain intensity prior to the run-in phase was provided. Mean baseline (that is last 4 days of the run-in phase) pain intensity prior to randomization was comparable across treatment groups and analysis sets, ranging from 1.3 ± 1.3 in the buprenorphine group of the per protocol set to 1.7 ± 1.4 in the placebo group of the full analysis set indicating generally good pain control with the 40 mg buprenorphine patch. The responder rate during the double blind period was 74.5% for patients given the 40 mg buprenorphine patch and 50.0% for patients given placebo (p = 0.0031).

BUP4201

BUP4201 compared the efficacy and safety of buprenorphine transdermal therapeutic system (TTS) with tramadol sustained tablets in patients with severe pain due to osteoarthritis. Patients were required to have been taking a WHO Step 2 analgesic prior to study entry. They were excluded if they had received full opioid agonists, buprenorphine

or tramadol in the last three months. Paracetamol and NSAIDS were permitted during the study. During an initial titration period of 1 to 3 weeks the dose regimen was titrated to one of three levels until acceptable pain control was achieved. If acceptable pain control was achieved patients could progress to a 4 week assessment period. The 3 dose groups were as shown in Table 21.

Table 21: Dose groups for Study BUP4201

Dose Level	Buprenorphine patches			Tramadol prolonged release tablets
	Loading dose	Release rate	Daily dose	
1	20 mg	35 µg/h	0.8 mg	100 mg twice-daily
2	30 mg	52.5 µg/h	1.2 mg	150 mg twice-daily
3	40 mg	70 µg/h	1.6 mg	200 mg twice-daily

This study was designed to show non inferiority of titrated buprenorphine TTS applied every 3 days with oral sustained release tramadol given BD. The primary efficacy measure was the mean BS-11[34]pain scores recorded during the last 12 days of the assessment period in the PP population. Analgesic equivalence between the two treatments was to be assumed if the 95% CI for the mean treatment difference fell within the range (-1.5, 1.5) boxes on the BS-11 scale. No rationale was provided for this range.

A total of 313 patients were randomised with 309 included in the ITT analysis (157 to buprenorphine TTS; 154 to tramadol slow release (SR)). The discontinuation rate was 57% and differed between the study groups. Of patients given buprenorphine TTS 110 (70%) discontinued compared with 65 (43%) given tramadol SR. The major difference in discontinuation rates was due to a greater proportion of patients given buprenorphine TTS discontinuing due to adverse effects. Mean pain scores at baseline, titration and primary assessment are shown in Table 32 of Attachment 1. The predefined criteria for equivalence of the two treatments were met for the ITT population. The PP population comprised 25 out of 159 (15.7%) of patients randomised to buprenorphine TTS and 78 out of 154 (50.6%) of patients randomised to tramadol SR.

PB-TTC-01

PB-TTC-01 compared the efficacy and safety of buprenorphine 20 mg patch applied every 3 days with tramadol SR 100 mg BD over 4 weeks. There was no dose titration and no run-in period. This was a non-inferiority study. Patients had chronic non tumour related pain with pain intensity at study commencement of at least 4 on an 11 point NRS[36] while receiving treatment with weak opioids including combinations such as codeine, dihydrocodeine, dextropropoxyphene, or tilidine/naloxone or who had pain that was insufficiently treated with NSAIDs, or poorly tolerated NSAID treatment.

The primary efficacy variable was the mean actual pain intensity, as rated by the patient using an 11 point NRS, at 08:00 hours and 20:00 hours of each day of blinded treatment compared to the pain intensity rating at the beginning of the study. The first day of patch use were excluded from the analysis due to the latency period of the patch. Non-inferiority was to be concluded if the treatment difference between the buprenorphine group and tramadol group was < 1 unit on the 11 point pain scale.

As in the previous study there was a higher discontinuation rate in patients randomised to buprenorphine compared with tramadol. The overall discontinuation rate was 188 out of 560 (33.5%) comprising 117 out of 284 (42.5%) patients randomised to buprenorphine 20 mg TTS and 71/276 (25.7%) randomised to tramadol SR. Most of the discontinuations in both treatment groups were due to AEs. This study concluded non-inferiority for efficacy of the two treatments.

Safety

A total of 1,708 individuals received Transtec patches in the clinical development program, 109 in pharmacology studies and 1,599 in safety and efficacy studies. Of these 37 patients were treated for at least 12 months. No patients in these studies received the proposed maximum dose of 2 x 40 mg patches every 3 to 4 days (140 µg/h). The post-market program provided surveillance information on a further 33,673 patients.

As noted by the evaluator interpretation of AEs in the placebo controlled studies is made difficult by the use of SL buprenorphine tablets for breakthrough pain in all phases of the studies and in all treatment groups. Analysis of the plasma buprenorphine levels in a small number of patients in the PK arm of WIS-BUP02 showed that plasma buprenorphine levels in the placebo group were not dissimilar to those achieved in the active patch groups.

The most frequently reported AEs are listed in Table 47 of Attachment 1 and include nausea, vomiting, dizziness, tiredness and constipation. The nature and frequency of AEs were similar across the treatment groups, including the placebo group. The use of rescue SL buprenorphine is likely to have contributed to this result. Mild to moderate application site reactions, mostly erythema and pruritus and occurred in about 30% of patients in the pivotal studies. No deaths were attributed to Transtec patches in the clinical development program. Of particular note the discontinuation rate due to AEs was much higher in the studies where Transtec was compared with tramadol though the level of analgesia was similar.

Risk management plan

The RMP is being finalised and will be dependent on whether this product is registered and any conditions of registration. Any changes to which the sponsor agrees would become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

No suggested wording can be provided at this time until a decision on registration is made and the outstanding issues are satisfactorily addressed.

The RMP evaluator considered that the '*potential for medication errors or other risks if applicable*' section of the revised ASA is not satisfactory in that it does not consider risks of inadvertent exposure, including exposure to used patches. Even after the specified treatment time a clinically significant residual amount of buprenorphine may remain on the patch. Such an amount may be very harmful (even fatal) for example if a child was inadvertently exposed to the patch. Ensuring appropriate storage and disposal of the patch is paramount to the safe use of this medicine.

The RMP evaluator recommended that the sponsor:

- Include 'medication error/accidental exposure' as a safety concern in the RMP and/or ASA.
- Amend the risk minimisation plan to accommodate this risk as follows:
  - The existing disposal instructions in the CMI should include an explanation of the rationale for safe disposal as follows (or similar): '*After removing the used patch, fold it over on itself so that the adhesive side of the patch sticks to itself, and dispose of it safely where children cannot reach it. Safe disposal is important as the used patch may be harmful, even fatal to people not prescribed the patch, especially children*.'
  - The CMI should additionally include the following (or similar) in a prominent and appropriate location: '*Accidental exposure to even one dose of <tradename>,*

especially by children, can be fatal. It is important that you ensure that <tradename> is stored, used and disposed of out of the reach of children as directed'.

- The dosage and administration section of the PI should be revised to include a statement as follows (or similar): After use it is possible that the patch will still contain a substantial amount of buprenorphine. Such an amount can be harmful, even fatal to opioid naïve individuals, especially children. Therefore, to avoid accidental exposure, patients should be directed to remove the used patch and fold it over on itself so that the adhesive side of the patch sticks to itself. The patch should then be disposed of safely where children cannot reach.
- The Delegate may also wish to consider inclusion of advice similar to above as a specific PI precaution.
- The packet of buprenorphine patches should include a prominent statement for how to dispose of the patches such as (or similar): '*After use the patch must be disposed of safely according to instructions (see package insert*)'.
- The patch should include a printed warning such as (or similar): '*After use the patch must be disposed of safely*'
- The CMI should be included in every box; if not already proposed.
- It is noted that for a transdermal buprenorphine product in the US a 'disposal unit' is included in each pack to assist the safe disposal and minimise risk of accidental exposure. As an additional risk minimisation measure the sponsor should also consider including a disposal unit in the product packet that used patches can be wrapped up and sealed safely in prior to disposal.

- From a risk minimisation perspective it was also noted by the RMP evaluator that the feature of substantial residual medicine after standard use may be desirable to those patients who wish to misuse buprenorphine.

The RMP evaluator noted that regarding the risk of medication error, the clinical evaluator has detailed concerns relating to patients switching between the Transtec patch and the existing buprenorphine 7 day patch (Norspan). The concern is that confusion in switching between regimes may result in under or over dosing. The RMP evaluator supports the inclusion of clear statements in the PI and CMI of the existence of other products with different dosing/duration regimes and the importance of ensuring that the appropriate duration is explained and confirmed by the prescriber to the patient. The RMP evaluator supported the clinical evaluator's recommendation to improve concordance with the Norspan PI. From a risk minimisation perspective this would improve clarity and communication of risk for both buprenorphine transdermal products.

Risk-benefit analysis

Delegate's considerations

This product is essentially the same as the current buprenorphine patch with the only clinically significant difference being the time between re-application of each patch (7 days for Norspan vs. 3 to 4 days for Transtec). The many design flaws in the pivotal studies which were identified to the sponsor early in the evaluation process could not be fully addressed by the post-hoc analyses that were performed. These include:

- The pivotal studies were designed more than 20 years ago and do not conform to current recommendations. The supportive studies are at least 12 years old and have similar, though less serious design flaws that limit the usefulness of their results

- The 2 non cancer pain studies designed to demonstrate equivalence/ non-inferiority used inappropriate comparators given the dose of buprenorphine. A high dose of a strong opioid (buprenorphine) was compared with a moderate or higher dose of a weak opioid (tramadol). This strongly suggests that lower doses of buprenorphine would also be effective in that patient population. Lower doses would also be safer. A justification for the equivalence interval in these studies was presented on request to the sponsor but was not included in the study reports. The studies satisfactorily demonstrated that these higher dose buprenorphine patches provided equivalent pain relief to tramadol SR given at its maximum dose, though with a higher discontinuation rate
- In the cancer pain study only responders to the 70 µg/h buprenorphine patch were included in the ITT population of a randomised withdrawal study. As noted by the clinical evaluator, this study was the only placebo controlled study presented in the dossier in which efficacy of the patch over placebo, as shown by a statistically significant difference in the primary end point, was demonstrated. The evaluator also agreed with the sponsor's description of the opinion expressed by the FDA: '*The FDA guidance (2012) also states that enrichment studies are best if they comprise only part of the body of evidence, as is the case for Transtec*.' An enrichment study may be necessary and appropriate in some circumstances but it provides only weak evidence for efficacy by itself
- Dose response was not demonstrated. In response to this contention the sponsor has proposed that evidence of dose response was seen in post-market surveillance. This is not accepted. The pivotal studies did not demonstrate a clear dose response. Nor was the safety and efficacy of the highest proposed dose of 2 x 40 mg patches (140 µg/h) assessed. The sponsor has responded to the effect that in order to titrate the Transtec dose up to a level that meets the patient's needs, high doses such as 140 µg/h may be required. Arbitrary maximum dose limits are not recommend, but there is a practical limitation to 140 µg/h Transtec dose due to the number of patches required. This dose level has been safely used in clinical practice, as documented in the post marketing data and open label extension studies included in the Transtec submission, and reported in the medical literature
- There was no exploration of the comparative effectiveness of a lower dose of buprenorphine. This is of concern given the lowest of the proposed dose recommendation is 75% higher than the maximum transdermal buprenorphine dose recommendations of the Australian Therapeutic Guidelines – Analgesics.[51] The highest proposed dose (2 x 70 µg/h) is 7 fold higher than the currently recommended maximum dose of transdermal buprenorphine
- There were no long term comparative data. While long term data for other lower buprenorphine dose regimens are available it is not clear that the safety of the much higher doses proposed would be similar. There is concern that this would not be the case. In response to this concern the sponsor has noted that there were open extension studies. However these studies had extremely high discontinuation rates and served only to demonstrate that patients receiving acceptable relief without intolerable side effects from Transtec continue using it. As noted in Table 46 of Attachment 1 there were 238 patients who used Transtec patches for longer than 6 months and 37 patients who Transtec for ≥ 12 months in open follow-up studies, including post-market studies. Given the studies selected only patients who responded to buprenorphine for enrolment it is not possible to estimate the proportion of patients requiring opioid analgesia who are likely to both tolerate and obtain acceptable pain relief from Transtec patches in the longer term using data from the clinical development program.

- The proposal to administer these transdermal patches to opioid naïve patients is completely unacceptable given the delivered doses and need for titration from a low initial opioid dose.

The sponsor has provided detailed responses to the above concerns and these responses are comprehensively discussed in Attachment 1. In summary the responses have not allayed the concerns.

It is possible a case could be made for use of Transtec in patients with cancer related pain who had inadequate analgesia with maximum doses of Norspan patches or other opioids that provided similar levels of analgesia. The randomised withdrawal study demonstrated efficacy of Transtec over placebo in this patient group. If Transtec were to be approved the PI would need to be extensively amended to reflect an amended indication and to highlight the safety concerns raised by the clinical and RMP evaluators.

Delegate's summary of issues

- The pivotal studies were designed more than 20 years ago and do not conform to current requirements. The supportive studies are at least 12 years old and have similar, though less serious design flaws that limit the usefulness of their results.
- The two 12 year old studies in patients with non-cancer pain were designed to demonstrate non-inferiority however the comparator was inappropriate. A high dose of a strong opioid was compared with moderate and maximum doses of a weak opioid. This strongly suggests that lower doses of buprenorphine would also be effective for these patients. Lower doses would also be safer.
- Steady state is not achieved until day 9. Some adjunctive treatment is likely to be required during a transition period from other treatments and/or during a titration period. Because of this prolonged time to achieve steady state, and therefore time to assess the effect of a given dose Transtec is not suitable for the management of acute pain however the proposed indication does not specify acute or chronic pain.
- Dose response was not demonstrated in the pivotal trials.
- There was no exploration of the comparative effectiveness of a lower dose of buprenorphine. This is particularly of concern given the lowest dose in the proposed dose recommendations is 75% higher than the maximum transdermal buprenorphine dose recommendations of the Australian Therapeutic Guidelines – Analgesics[51]. The highest proposed dose (2 x 70 μg/h) is 7 fold higher than the currently recommended maximum dose.
- The 2 x70 μg/h dose was not tested in any of the clinical studies and no justification for this dose regimen was provided.
- The proposed indication does not specify duration of use. There were no controlled data for long term use.
- The product has been proposed for use in opioid naïve patients, though it was not administered to these patients in clinical trials.

Proposed action

The Delegate is not in a position to say, at this time, that the application for buprenorphine transdermal delivery system (Transtec and other trade names) 35 μg/h, 52.5 μg/h and 70 μg/h should be approved for registration.

An alternative indication restricting use to patients with moderate to severe cancer related pain who have been stabilised on equianalgesic doses of an alternative opioid may be considered.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Given the composition of these patches is almost identical to products already on the market would it be more appropriate to identify transdermal opioid products primarily by the total opioid content rather than by the mean release rates if applied as directed?
2. If these products are identified primarily by the total quantity of buprenorphine contained in each patch should the same approach be taken for other transdermal opioid preparations?
3. Does the committee consider that the evidence submitted supports use of Transtec in patients with cancer-related pain who have been stabilised on equianalgesic doses of an alternative opioid?
4. If the indication was restricted to patients with cancer-related pain as above, would the proposed 2 x 70 µg/h dose be acceptable given the absence of clinical trial data for this dose?

The committee is (also) requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from Sponsor

Delegate's summary of issues; sponsor comments

Design of pivotal and supportive studies

It is important to note that at the time of conducting these and later Transtec studies, most of the current relevant guidelines for clinical trials in pain treatment did yet not exist. However, the studies were compliant with the respective standards at the time and also fulfil key recommendations of today's guidelines, for example WIS-BUP01, WIS-BUP02 and WIS-BUP03 were randomised, double blind, parallel group studies that included provision for rescue medication, and had pre-defined responder criteria.

Appropriateness of comparator

Oral tramadol was used as a comparator to Transtec in studies PB-TTC-01 and BUP4201 as it was anticipated that Transtec would be used in place of oral tramadol in future. The studies followed accepted practice at the time, which was to use an equipotency table to determine the equivalent opioid dose (Transtec SmPC, 2006). Doses lower than 35 µg/h Transtec would have been inappropriate for the indications of the patients in these studies, and inappropriate for the proposed Transtec indication.

The equivalence intervals used in these studies were less than the published clinically important difference in pain intensity, which is 2 points on an 11 point NRS. [52] The thresholds for clinical equivalence used in these studies were differences less than or equal to 1.5 NRS points (BUP4201) and 1.0 NRS points (PB-TTC-01). In study PB-TTC-01 the equivalence interval was also conservative by the 'half of the standard deviation'

[52] Farrar JT, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94: 149‑158

approach to determining the minimal relevant change.[53] This approach is supported by the FDA Draft Guidance for Industry on Patient Reported Outcome Measures.[54].

The TGA acknowledge that these studies satisfactorily demonstrated that higher dose buprenorphine patches provided equivalent pain relief to tramadol SR given at its maximum dose, but note that buprenorphine patches had a higher discontinuation rate. However, the discontinuation rate in these studies does not relate to the safety of Transtec in normal clinical practice, particularly when considering the proposed revised indication, for the reasons outlined in the following paragraphs:

1. The revised indication proposed below excludes opioid naive patients. These patients have a higher relative risk of stopping treatment: In study PB-TTC-01 the relative risk between treatment groups in opioid naive patients was 1.74 (the likelihood of stopping treatment under Transtec was 1.74 times that under Tramadol). The relative risk for opioid experienced patients was far lower, at 1.18. This suggests that the majority of discontinuations were among opioid naive patients, who are not included in the alternative proposed indication below. This might be explained by the reduced likelihood of commonly seen opioid side effects in opioid experienced patients, which are generally well known and can be managed by the treating physician. These side effects and the tolerability of Transtec are discussed further below under the heading '*Tolerability of Transtec*'.
2. The discontinuation rate under Transtec treatment in PB-TTC-01 was not directly representative of the number of patients who discontinued due to AEs. The number of patients who discontinued due to withdrawal of consent (which could be unrelated to treatment) is far higher under Transtec (12 patients) than under Tramadol (4 patients), although discontinuation due to lack of efficacy is notably higher in the tramadol arm.
3. PB-TTC-01 was a fixed dose study and thus not representative of normal clinical practice. In normal clinical practice, Transtec would be titrated to an appropriate dose by the treating physician. Studies PB-TTC-01 and PB-TTC-02 provide information about Transtec as compared to Tramadol, but as these fixed dose studies do not represent normal clinical practice, the discontinuation rates in these studies may not be reflective of discontinuation rates for Transtec.

Dose response not demonstrated in the pivotal trials

Dose response of Transtec was demonstrated in the retrospective combined analysis of 3 placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 (WIS-BUP123), which was acceptable to the MHRA. The analysis demonstrated that each of the underlying individual studies was insufficiently powered to demonstrate a clear dose response relationship. Using the combined data set, a clear dose response relationship could be determined for the response rates based on pain intensity and on mean consumption of rescue medication. In addition, Transtec dose response in daily clinical practice was demonstrated by the large non interventional study AWB Transtec 2001/1.

Comparative effectiveness of lower doses

One concern raised about the proposed Transtec doses relates to the dose recommendations in the Australian Therapeutic Guidelines (ATG).[51] It is important to note that:

[53] Norman GR, et al. (2003) Interpretation of changes in health-related quality of life: the remarkable universality of half a standard deviation. *Med. Care* 2003; 41**:** 582‑592

[54] FDA Patient reported outcome measures: Use in medical product development to support labelling claims. *Food Drug Adm.*2009

- the ATG recommendations provide general guidance for first choice opioids in the management of chronic non cancer pain, and
- the ATG recommend specialist advice should be sought when prescribing buprenorphine transdermal patch doses above 20 µg/h (ATG, 2015).

Under the revised indication proposed below, Transtec would not be available as first line opioid therapy and is limited to cancer pain patients. Therefore the recommendations in the ATG would not be applicable in the context of this revised indication.

Administration in opioid naïve patients

The sponsor acknowledges the TGA's concerns regarding the administration of Transtec in opioid naive patients and agrees to limit the administration of Transtec in this patient population (see proposed indication below).

Delegate's advice sought; sponsor comments

1. Given the composition of these patches is almost identical to products already on the market would it be more appropriate to identify transdermal opioid products primarily by the total opioid content rather than by the mean release rates if applied as directed?

2. *If these products are identified primarily by the total quantity of buprenorphine contained in each patch should the same approach be taken for other transdermal opioid preparations?*

(Appropriateness to identify transdermal delivery system (TDS) primarily by total opioid content.)

The sponsor does not wish to comment specifically regarding the identification of transdermal opioids at this point in time, as this recommendation would affect the labelling of TDS products beyond Transtec and would require other stakeholder involvement regarding the labelling of TDS products.

3. *Does the committee consider that the evidence submitted supports use of Transtec in patients with cancer-related pain who have been stabilised on equianalgesic doses of an alternative opioid?*

Considering the revised proposed indication (see below), the sponsor would like to highlight the demonstrated efficacy of Transtec to manage pain in moderate to severe cancer pain patients who had previously received opioid therapy. Clinically and statistically significant evidence for Transtec efficacy that is relevant to the revised proposed indication is provided by Study PB-TTC-02. The analgesic superiority of 70 µg/h Transtec over placebo used in patients with severe chronic cancer pain who had received prior opioid therapy was confirmed in this study. Major details of the study are outlined below.

In Study PB-TTC-02 the primary endpoint was a response definition: A patient was considered a responder if they completed at least 12 days of the double blind period, had a pain intensity < 5.0 on average on an 11 point NRS[36] during the last 6 days of treatment, and did not use more than 2.0 tablets of rescue medication per day on average during the double blind period.

The observed difference of response rates between the groups was found to be statistically significant (p = 0.0003, see Table 22 below). Thus, the efficacy of 70 µg/h Transtec was clearly demonstrated in comparison to placebo.

Table 22: Response rates (in %) in randomised withdrawal study PB-TTC-02

	Placebo	TRANSTC (70 µg/h)
FAS [n]	94	94
Responders [n]	47	70
Responders [%]	50.0	74.5
95% CI [%]	39.9-60.1	65.7-83.3

p-value between groups = 0.0003

The efficacy was further supported by the parametric analysis of the secondary variables (pain intensity, consumption of rescue medication) and the fact that many more patients dropped out due to lack of efficacy from the placebo group than from the 70 µg/h Transtec group. Initially, in the 15 day open label phase there was a significant reduction of pain intensity which was maintained in the active group during the 15 day double blind phase. Consumption of rescue medication was on a stable level during both study phases indicating adequate pain control with 70 µg/h Transtec. By contrast, pain intensity as well as consumption of rescue medication both significantly increased in the placebo group. Therefore, the randomised withdrawal study PB-TTC-02 demonstrated the analgesic superiority of 70 µg/h Transtec over placebo during four weeks of treatment in patients with severe chronic cancer pain who had received prior opioid therapy.

The sponsor notes the TGA concerns regarding this study, namely only responders to the 70 µg/h Transtec were included in the ITT population of a randomised withdrawal study, thus assessment was limited to a limited population already assessed as responding to treatment. However, it is important to note the study design was such that:

1. It was designed in acknowledgement that the placebo effect is known to be large and unpredictable in pain studies, thus the study was required to show superiority of Transtec versus placebo.
2. It was designed to focus on the study population in question; patients requiring analgesia for severe cancer pain. Therefore, the inclusion of non-responders that is randomization of patients not responding to Transtec, would be unethical as it would be likely that those patients would be denied adequate pain treatment during the study.
3. Enrichment guidance provided by the FDA and ICH E8 statistical guidelines[55] and ICH E9[56] clinical trial guidelines all support the use of the study design in PB-TTC-02. It is noted that the TGA has highlighted that the FDA guidance states enrichment studies are best if they comprise only part of the body of evidence. However it is important to note that this study is accompanied by the integrated evaluation of efficacy (WIS-BUP123, of WIS-BUP01, WIS-BUP02 and WIS-BUP03), as well one uncontrolled extension study (WIS-BUP-LTS) and 7 additional non interventional studies involving cancer pain patients.
4. *If the indication was restricted to patients with cancer related pain as above, would the proposed 2 x 70 µg/h dose be acceptable given the absence of clinical trial data for this dose?*

The sponsor believes that the maximum proposed dose of 140 µg/h Transtec will be a valuable option or prescribing physicians to manage severe pain. There is evidence that high doses of Transtec are relatively safe. Finally, this proposed maximum dose has been safely and efficaciously used in clinical practice. These points are elaborated below:

[55] International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH E8 General considerations for clinical trials.
[56] International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use. ICH E9 Statistical principles for clinical trials.

High Transtec doses may be required

As a general treatment principle for cancer pain patients receiving opioids, the dose administered is titrated to the patient's needs, therefore high doses may be required. The revised proposed indication for Transtec (see below) includes moderate to severe cancer pain. Thus, for patients prescribed Transtec, it should be possible for the prescribing physician to provide up to 140 µg/h Transtec if appropriate to meet the patient's needs.

Australian cancer pain guidelines (Cancer Council of Australia, 2015)[57] do not stipulate a ceiling dose for opioids. The American Academy of Pain Medicine have stated that arbitrary dose limits disregard differences between patients, while setting a ceiling dose could be dangerously misleading as it implies that lower doses are inherently safer.[58] This is corroborated by the Faculty of Pain Medicine of the Australian and New Zealand College of Anaesthetists, who note that for opioid treatment of chronic pain the question of a 'ceiling dose' has not been settled.[59] There is a practical obstacle to recommending greater Transtec dose strengths when considering the administration of more than 2 patches to new skin sites twice a week. Thus the maximum proposed dose of Transtec is 140 µg/h (that is 2 x 70 µg/h patches).

Transtec is relatively safe, especially at high doses

Buprenorphine has a wide safety margin.[60] Due to the rate controlled delivery of small amounts of buprenorphine into the blood circulation from Transtec patches, high or toxic buprenorphine concentrations in the blood are unlikely.[61] The maximum serum concentration of buprenorphine after application of the 70 µg/h Transtec transdermal patch is about six times less than after intravenous administration of the therapeutic dose of 0.3 mg buprenorphine. Buprenorphine has a ceiling effect on respiratory depression but not analgesia, making it an excellent choice of opioid for use at high doses.[61,39]

There is evidence of safe and efficacious use of high Transtec doses

In both post-marketing use and open label extension studies, Transtec doses were titrated to patient's needs, including 140 µg/h Transtec. Extensive post-marketing data is described by 19 Periodic Safety Update Reports (PSURs) (PSURs 1 -17 provided in submission and the additional PSURs 18 and 19 submitted with this response). In addition, 16 post-marketing studies describing the use of Transtec up to doses of at least 140 µg/h were provided in the submission.

One example of a post marketing study that included a minority of patients who received the 140 µg/h dose is AWB Transtec Pro 2005. The number of patients receiving 140 µg/h Transtec increased throughout the study; from 11 patients before first check-up, to 18 patients between first and last check-up, to 25 patients after last check-up.

The open label extension study WIS-BUP-LTS also described several cases in which dose increases due to disease progression led to daily doses greater than 4 mg buprenorphine. Even at these high doses, the treatment showed a constant level of full efficacy after a long period without any indication of a ceiling effect in analgesia or development of tolerance.

[57] Cancer Council of Australia (2015) Cancer Guidelines Wiki. Available at http://wiki.cancer.org.au/australia/Guidelines:Cancer_pain_management/Pharmacological_management
[58] AAPM (2013) A Position Statement from the American Academy of Pain Medicine: AAPM Speaks on the Use of Opioids in the Treatment of Chronic Pain.
[59] ANZCA (2015) PM01: Recommendations regarding the use of Opioid Analgesics in patients with chronic Non-Cancer Pain.
[60] Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. *J. Support. Oncol.* 2013; 10**:** 209‑219
[61] Kress HG (2009) Clinical update on the pharmacology, efficacy and safety of transdermal buprenorphine. *Eur. J. Pain* 2009; 13: 219‑230

Pre ACPM preliminary assessment; sponsor comments

Alternative indication

The sponsor wishes to propose the following alternative indication:

> *Use in patients with moderate to severe cancer pain not adequately treated by previous opioids.*

The sponsor acknowledges the TGA's concerns regarding the use of Transtec in opioid naive patients. However, the TGA's proposed indication requires that a patient is stabilised on equianalgesic doses of an alternate opioid prior to commencement of Transtec. The sponsor notes that there is no medical need to change opioid treatment if a patient has been stabilised on equianalgesic doses of an alternative opioid. A change in treatment without medical need might be unethical. For example, it is a globally established approach in clinical research that ethical approval for an opioid study in opioid tolerant patients would only be granted if the patients have had inadequate efficacy or tolerability under previous treatment.

The alternative indication proposed above would allow a change to Transtec treatment for opioid experienced patients if the previous opioid treatment provided inadequate efficacy (for example, patients requiring higher doses or insufficient analgesic efficacy based on substance character and receptor binding characteristics) or tolerability (for example, intolerable adverse drug reactions or patients who may have swallowing difficulties).

Other issues raised in the body of the request for ACPM advice; sponsor comments

Safety concerns; concerns regarding co-administration of other sedating drugs, poor tolerability, and cardiac risk.

Sponsor responses to the above safety concerns are included under separate headings below:

Administration of Transtec in combination with other sedating drugs

Data are available from 3 non interventional studies (see below) initiated by the Spanish Pain Society, investigating efficacy and safety of Transtec as well as its combination with tramadol or morphine. In one of these studies, 93 patients with chronic pain of various aetiologies, pre-treated with oral morphine, were switched to Transtec.[62] Following the switch they were allowed to take immediate release (IR) oral morphine as rescue medication for breakthrough pain. During the first week of treatment with Transtec, 68% of patients used rescue medication for breakthrough pain with a mean morphine dose of 17.3 mg/day. At week four, 59% used morphine with a mean dose of 13.4 mg/day. At week six, at the end of the study, 56.5% required morphine with a mean dose of 16 mg/day. The overall efficacy of the combined treatment with the two opioids was classified as 'very good' or 'good' in 69.9% of the patients and 85.4% of the doctors at the end of the study. It can therefore be assumed that the combination of Transtec with oral morphine is effective in clinical use. Additionally, no increase in side effects was seen.

Buprenorphine is also compatible with tramadol as rescue medication since no interactions or undesirable effects were observed with this combination in a study with 297 patients with chronic pain of various aetiologies.[63] About 50% of patients in this study required IR oral tramadol for breakthrough as rescue medication. The mean tramadol doses were very low, from 114 mg in the first week to 60.3 mg at the end of the observation period.

[62] Gonzalez-Escalada J. Use of buprenorphine and oral morphine in patients with chronic pain. *Rev Soc Esp Dolor* 2004; 11: 3-10

[63] Barutell, C. D. E. The opioid study group of the Spanish pain society. Buprenorphine and tramadol. *Rev. Soc. Esp. Dolor*.2004; 11: 31-40.

The risk of interactions with other sedating drugs is well known, and is common to all opioids and is a risk commonly managed by physicians. This risk is minimised by the inclusion of details regarding interactions with central nervous system (CNS) depressants in the PI and CMI.

Tolerability of Transtec

The majority of related AEs in the studies described in the Transtec dossier were known side effects of opioid use. There are several reasons why the discontinuation rates in these studies did not relate directly to the safety of Transtec.

Most importantly, in the studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 the discontinuation rates were similar or greater under placebo than under Transtec treatment (see Table 23). This suggests that the discontinuation rates were a feature of the study population rather than a product-specific issue.

Table 23: Discontinuation rates under Transtec compared to placebo treatment

	Discontinuations	
Treatment	Placebo	TRANSTEC (all doses except placebo)
WIS BUP01	8.1% (3/37)	8.8% (10/114)
WIS BUP02	42.1% (16/38)	23.5% (28/119)
WIS BUP03	4.3% (2/47)	6.6% (6/90)

A substantial number of the patients who left the study did so during the run-in phase. These were termed screening failures. As Transtec had not yet been administered, the reason for leaving the study must have been unrelated to Transtec treatment. Indeed, in studies WIS-BUP01 and WIS-BUP03, the discontinuation rate due to AEs was greater under buprenorphine SL tablet treatment in the run-in phases (WIS-BUP01: 6.4%; WIS-BUP03: 7.5%) than under Transtec treatment in the double blind phases (4.4% in both studies).

It should also be noted that high discontinuation rates are not uncommon in clinical trials for opioid pain products.[64] [65] In light of this, managing the expectations of patients entering a pain clinical study is an important challenge. Due to lack of patient or clinician experience with transdermal patch formulations at the time of these studies, it was challenging or impossible to adequately manage patient expectations going into these studies. Patients likely expected the rapid pain relief characteristic of oral opioid formulations, whereas patch formulations are now known to generally take longer to reach the minimum effective concentration.

Cardiac Risk of Transtec

In some clinical trials it was noted that administration of Transtec might risk prolongation of QTc. This is not considered a safety risk for Transtec due to the absence of any clinically relevant effects. Buprenorphine has been used worldwide for over 35 years in a variety of formulations which provide doses of buprenorphine up to 32 mg (SL buprenorphine for opioid substitution therapy). To date no association between buprenorphine and clinical effects of QTc prolongation such as Torsades de Points has been identified.

The EU marketing authorisation holder of Transtec have performed several comprehensive scientific evaluations of Transtec and QT prolongation, the latest in March 2015,[66] which considered all the data available on this topic. It concluded that the

[64]Noble M, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst. Rev.*: 2010 CD006605

[65] Noble M, et al. Long-term opioid therapy for chronic non cancer pain: a systematic review and meta-analysis of efficacy and safety. *J. Pain Symptom Manage.* 2008; 35: 214‑228.

[66] Grunenthal GmbH Scientific evaluation of the effect of Transdermal buprenorphine on Myocardial repolarization. Version 4. 31 March 2015.

available data does not support a causal relationship between Transtec and QT interval prolongation or Torsades de Pointes.

Safety concerns; use of rescue sublingual buprenorphine likely to have contributed to nature and frequency of AEs

Treatment with IR formulations is standard therapy to manage breakthrough pain. These studies avoided excess use of SL buprenorphine which might have led to AEs by up titrating the Transtec dose to minimise rescue medication use, as directed by the Transtec SmPC. These points are described further below.

Rescue medication is required for the treatment of breakthrough pain, which is a serious problem in cancer patients. IR formulations have long been used as standard therapy for breakthrough pain.[67] In the studies described in the Transtec dossier the amount of rescue medication was reduced by up titrating the Transtec dose to meet the patient's needs. This was as directed by the Transtec SmPC: *'Patients requiring a supplementary analgesic (for example, for breakthrough pain) during maintenance therapy may take for example one to two 0.2 mg buprenorphine sublingual tablets every 24 hours in addition to the transdermal patch. If the regular addition of 0.4 to 0.6 mg sublingual buprenorphine is necessary, the next strength should be used'*.[68] The Transtec SmPC conforms to worldwide pain guidelines.

Risk management plan concerns; inadvertent exposure, medication error (that is switching between Transtec and Norspan)

The sponsor is amenable to working with the TGA to ensure RMP (RMP) concerns are appropriately addressed. Please refer to the sponsor comments on the PI summarising the changes made to the PI to address the RMP evaluator's concerns and also the Delegate's recommendations throughout the report. Amendments have been made to include more detail regarding interactions with CNS depressants and CYP interactions, inclusion of statements of the existence of other products with different dosing/ duration regimes, initiation of patients on the lowest patch strength, change to the length of time between application site reapplications, and inclusion of statements regarding inadvertent exposure.

Discussion section; Concerns regarding lack of long term comparative data and high discontinuation rates

The placebo controlled studies WIS-BUP01, WIS-BUP02 and WIS-BUP03 all started between 23 August 1995 and 16 January 1996. At that time long term studies were not routinely carried out. Even so, many patients from these 3 studies entered into open label extension phases; described in the WIS-BUP-LTS clinical study report. The TGA notes the long-term extension studies highlight the tolerability issues with Transtec given the high discontinuation rates observed. It is reiterated that the discontinuation rates need to be considered in the context of that period of time whereby there was limited clinical experience of transdermal buprenorphine formulations, which exacerbated the challenge of managing patient expectations to minimise discontinuation.

It is important to note that Transtec has been approved in most European countries since 2001. The extensive post-marketing data available over the period 2002 to 2014 is described by 17 PSURs included in the dossier together with an additional 2 PSURs (PSUR 18 and 19) submitted with this response. In addition to this, 16 post-marketing studies describing use of Transtec up to doses of 140 µg/h (in general the dose is set according to patient requirements by the prescribing physician) are reported (in the dossier). These data collectively provide substantial evidence of the clinical place of Transtec for the long-

[67] Patt and Ellison. Breakthrough pain in cancer patients: characteristics, prevalence, and treatment. *Oncology.* 1998; 12**:** 1035-1046.
[68] Transtec SmPC (2015) Napp Pharmaceuticals Limited. Electron. Med. Compend. Available at: https://www.medicines.org.uk/emc/medicine/8864 [Accessed August 2015]

term treatment of chronic pain and evidence that efficacy of Transtec is maintained over time with minimal changes in the safety profile of the product.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Transtec and additional 3 trade names transdermal drug delivery system containing 35 µg/h, 52.5 µg /h and 70 µg /h of buprenorphine has an overall negative benefit-risk profile for the proposed indication.

In making this recommendation the ACPM

- Was of the view that the data submitted lacked contemporary relevance
- Advised that the chosen efficacy endpoints were not clinically meaningful and that efficacy had not been demonstrated
- Noted that the duration of the submitted studies was too short to inform use in chronic pain
- Expressed concern that significant safety issues were not explored
- Was of the view that the safety data presented indicate toxicity which outweighs any potential benefit.

Specific Advice

The ACPM advised the following in response to the delegate's specific questions on this submission:

1. *Given the composition of these patches is almost identical to products already on the market would it be more appropriate to identify transdermal opioid products primarily by the total opioid content rather than by the mean release rates if applied as directed?*

The ACPM discussed the issue of how to identify the strength of this product. There was support for expression by total opioid content rather than release rates. However, the ACPM acknowledged that this might cause confusion with established products, would be inconsistent with international convention and noted all current products on the Australian market would have to be changed if this recommendation was accepted for this product.

2. *If these products are identified primarily by the total quantity of buprenorphine contained in each patch should the same approach be taken for other transdermal opioid preparations?*

See response to question 1.

3. *Does the committee consider that the evidence submitted supports use of Transtec in patients with cancer related pain who have been stabilised on equianalgesic doses of an alternative opioid?*

The ACPM was of the view that the evidence submitted was not sufficient to support use of Transtec in patients with cancer related pain who have been stabilised on equianalgesic doses of an alternative opioid. The ACPM considered that the dose selection rationale was not robust and noted that the clinical and post-marketing studies were at least 10 years old. In the three pivotal studies (WIS-BUP01, WIS-BUP02 and WIS-BUP03), the primary endpoint/outcome was not achieved and efficacy was not satisfactorily demonstrated. In addition the ACPM advised that there were quality issues with the studies.

The ACPM was of the view that the application was significantly deficient in presentation of safety profile. The ACPM considered that the age of data, incomplete referencing, inadequate examination and discussion of range of potential significant safety issues and unsubstantiated assumptions and extrapolations were major deficiencies. In addition, the RMP was poorly documented and deficient in scope.

The ACPM noted the following issues are still unresolved;

- Use in opioid naïve patients is not contraindicated
- Routine starting dose 20 mg is too high
- 96 hour dosing interval is not justified adequately
- Recommended maximum dose of 2 x 40 mg not substantiated
- Old and incomplete data with unsubstantiated extrapolations
- Short duration of clinical studies
- Doubtful clinical meaningfulness of pivotal outcomes
- Quality issues in clinical studies and submission: internal inconsistencies, power calculations, population characteristics, withdrawal rates, protocol violations, varied bias, endpoint and stats plan amendments post-commencement.

The ACPM considered that the sponsor's pre ACPM response did not address the evaluation issues or include any information that would materially alter advice from both rounds of the evaluation.

The ACPM therefore concluded that the benefit/risk was unfavourable due to lack of demonstrated efficacy along with significant potential toxicity which had been inadequately examined.

4. *If the indication was restricted to patients with cancer related pain as above, would the proposed 2 x 70 µg/h dose be acceptable given the absence of clinical trial data for this dose?*

The ACPM advised that insufficient evidence had been presented to support a maximum dose of 2 x 70 µg/h dose.

Outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration Transtec and additional trade names (buprenorphine) transdermal drug delivery system, 35 µg/h, 52.5 µg/h, 70 µg/h for the amended indication of:

> *Management of moderate to severe cancer pain not adequately controlled by previous opioids.*

This decision is based on the evaluation of information and data provided with the original submission letter and with any subsequent correspondence and submissions relating to the original submission. In making this decision, the Delegate has also considered the advice provided by the ACPM at its 307th meeting that Transtec and additional 3 trade names (buprenorphine) transdermal drug delivery system has an overall negative benefit-risk profile for the proposed indication.

The proposed indication was amended in the pre ACPM response.

In the submission the sponsor submitted different indications in the application form and in the draft PI included in Module 1. The initially proposed indication in the application form was;

> *Management of moderate to severe cancer pain and severe pain that does not respond to non-opioids.*

in the draft PI submitted by the sponsor the indication was;

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

These indications were also rejected.

Reasons for Decision

Overall the benefit/ risk balance was unfavourable due to the lack of demonstrated efficacy and significant potential toxicity which has not been adequately examined.

1. Dose titration

While the mechanism for delivery is essentially the same as the currently approved buprenorphine transdermal drug delivery system, Norspan, the proposed dose regimen takes approximately 9 days to achieve steady state levels of buprenorphine in the blood. This compares with 3 days for Norspan.

This delay in reaching steady state will result in a prolonged period of dose titration to achieve adequate analgesia.

Dose titration would also be prolonged due to high inter-patient variability of absorption of buprenorphine from the transdermal drug delivery system (TDS). Due to this variability the response is unpredictable. The Delegate noted that the frequency histograms for release rates from the PK study PK1599 which were provided in response to the TGA consolidated request for information show some individuals given the 20 µg/h patch had measured release rates of 70 to 80 µg/h. The comparison of an opioid dose with an equianalgesic dose of oral morphine cannot be relied on for an individual patient. Therefore the initial dose would need to be considerably less than the dose anticipated to be required by a patient who had 'average' absorption of buprenorphine from the TDS and then be titrated. Additionally, within patient absorption is likely to vary with skin thickness and temperature so that the rate and possibly extent of absorption will vary with the site of application. Neither of these factors were assessed in the submission.

Slow and careful dose titration would also be necessary to avoid the prolonged period of management necessary should an overdose occur. When the TDS is applied to the skin, buprenorphine diffuses from the matrix into the skin and subcutaneous tissues. A depot forms there from which buprenorphine is subsequently absorbed into the systemic circulation. Thus removal of the TDS, should symptoms of overdose occur, would not result in immediate cessation of absorption of buprenorphine into the systemic circulation. The apparent half-life of buprenorphine from the TDS is approximately 30 hours and, as noted by the sponsor, naloxone has a limited impact on the respiratory depressant effect of buprenorphine. These factors would result in a requirement for prolonged observation and treatment if overdose occurred or was suspected.

The proposed maximum dose of 140 µg/h was based on extrapolation of PK data and post-market evidence of use. This dose was not administered in clinical trials. The issues regarding the prolonged period for dose titration and the attendant risk of overdose during this period increase with increasing dose, therefore this dose has a less favourable benefit-risk profile than the doses that were assessed, though no dose has an acceptable benefit-risk profile for either of the proposed indications.

2. Dose response

Dose response was not demonstrated in the clinical trials submitted. While the sponsor has indicated that there is evidence of dose response in post-market surveillance this is

not considered sufficient to support registration, particularly given the established difficulties with dose titration.

3. Efficacy

None of the placebo controlled studies, WIS-BUP01, WIS-BUP02 and WIS-BUP03 nominated by the sponsor as pivotal studies showed a statistically significant difference from placebo for their predefined primary variable analysis. The primary outcome in each of these studies was the response rate. This was a composite end-point of patient assessed pain relief and some measure of SL buprenorphine tablets taken for breakthrough pain during patch wearing.

A subsequent exploratory analysis of pooled data from these studies combined the results from all doses of buprenorphine TDS in each study and compared them with the placebo results from that study. In that analysis the main efficacy variables were change from baseline in mean pain intensity and use of rescue medication. Timeframes and end-points were manipulated to enable the results to be pooled. The results did not show a clear and consistent dose response for all groups and all patch strengths.

While a statistically significant difference in mean change from baseline pain intensity between placebo and each strength of buprenorphine TDS was demonstrated in studies WIS-BUP01 and WIS-BUP03 but not in WIS-BUP02 that variable was not the primary efficacy measure. The mean differences from placebo in change from baseline pain intensity were in the region of 0.2 to 0.45 on a 4 point scale which is so small that the effect is unlikely to be of significant clinical benefit. Rescue medication was statistically significantly less likely to be required in patients given buprenorphine TDS compared with placebo in each study overall and in each buprenorphine dose group in Studies WIS-BUP02 and WIS-BUP03 but not in any dose group in WIS-BUP01.

The differences in change from baseline pain intensity between any dose of buprenorphine TDS and placebo are of limited clinical significance. While the extent of difference in pain intensity reduction between buprenorphine TDS and placebo in these studies may have been reduced by the use of SL buprenorphine as rescue medication, efficacy of buprenorphine TDS was not been clearly demonstrated. In any case, a post hoc exploratory analysis of three failed studies which used a combination of patients with cancer and non-cancer pain is an insufficient basis on which to conclude efficacy for patients with cancer pain.

One study examined patients with cancer pain only. It was the only placebo controlled study in the submission in which efficacy of buprenorphine TDS over placebo, as shown by a statistically significant difference in the primary end-point, was demonstrated. Only patients previously receiving opioid doses of 90 to 150 milli-equivalents (mEq) of oral morphine were considered for enrolment. Patients with severe chronic tumour related pain of predominantly neuropathic origin were excluded. Thus the TDS was assessed for safety and efficacy in only a subset of patients with cancer pain and at a fixed dose.

This was a randomised withdrawal study. It commenced with a 2 week run-in period when patients were switched to buprenorphine TDS. Only those patients with satisfactory pain relief (scores of less than 5.0 on average on an 11point NRS in the last 4 days of the run-in period) were randomised to the 2 week withdrawal phase of the study. Of the initial 289 selected for the run-in phase only 188 (65%) were randomised to the withdrawal phase and had at least one efficacy assessment. Thus the only efficacy study that met its primary endpoint selected a subgroup of patients with cancer pain and further selected that group to allow the efficacy assessment only in patients who had earlier demonstrated a response to the treatment. This is clearly insufficient evidence of efficacy for the patient group proposed to use buprenorphine TDS.

Long term efficacy has not been adequately assessed either in patients with cancer pain or in the initially proposed group of patients with cancer and non-cancer pain. Buprenorphine TDS is intended for long term use however efficacy was compared over a period of approximately 2 weeks in the pivotal studies. Long term comparative efficacy assessment was not performed. Long term non comparative data for other lower dose buprenorphine regimens are available however it is unlikely that the safety of the much higher doses proposed would be similar given the known dose related toxicity of opioids.

The open label extension studies had very high discontinuation rates and served only to demonstrate that patients receiving acceptable pain relief without intolerable side effects from buprenorphine TDS continued using it. A total of 238 patients received buprenorphine TDS for longer than 6 months and 37 patients for ≥ 12 months in open follow-up studies, including post-market studies.

These studies selected only patients who responded to buprenorphine for enrolment so it is not possible to estimate the proportion of patients requiring opioid analgesia who are likely to both tolerate and obtain acceptable pain relief from buprenorphine TDS in the longer term using data from the clinical development program.

4. Safety

The response to even low doses of buprenorphine TDS is unpredictable and can result in symptoms requiring hospitalisation. This unpredictability is consistent with the considerable inter-patient variability in absorption from the patch demonstrated in the PK studies. The unpredictable dose requirement, the prolonged period necessary for dose titration and the difficulty with management of overdose present safety concerns that are intrinsic to buprenorphine when administered as a TDS using the proposed dose regimens. Additionally potentially life threatening co-administration with other sedating drugs is likely given the target population of patients with cancer pain because many co-analgesics may cause sedation. This is a particular concern with the buprenorphine patch given the long half-life even after TDS removal.

The above safety concerns when combined with the lack of adequate demonstration of efficacy confirm that there is a negative benefit-risk profile for the buprenorphine TDS product range that had been proposed for registration.

Final outcome[69]

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act. The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's decision letter.

The Delegate of the Minister's findings of fact and reasons for decision

The three strengths of transdermal delivery system ('patches') have been described in the submitted data by the content of buprenorphine in each patch (20 mg, 30 mg, 40 mg) and by the nominal rates of release of buprenorphine (35 µg/hour; 52.5 µg/hour; 70 µg/hour). To avoid confusion, the Delegate of the Minister in this decision letter has referred to the patches by the content of buprenorphine (that is, 20 mg, 30 mg, and 40 mg).

The Delegate of the Minister noted that the sponsor modified its original proposed indications for use to be:

[69] The Sponsor has made an application to AAT for review the TGA decision.

'Use in patients with moderate to severe cancer pain not adequately treated by previous opioids.'

The change excludes from the indication use in patients with non-cancer pain and use in opioid naive patients.

The Delegate of the Minister's decision reflected the consideration of whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established as required under section 25 (1)(d) of the Act. That is, whether the quality, safety and efficacy of the goods for the purpose of use in patients with moderate to severe cancer pain not adequately treated by previous opioids have been satisfactorily established.

The sponsor's appeal documentation summarised the grounds for the appeal. The Delegate of the Minister addressed the issues of efficacy and safety first.

Efficacy

The sponsor has submitted:

- *'From the meta-analysis of the three pivotal studies as well as Study PB-TTC-02 conducted by [information redacted], it is clear that there is a large and highly statistically significant treatment effect with buprenorphine TDS. In addition, in their decision the Delegate has recognised that Study PB-TTC-02 was the only placebo controlled study in the submission in which efficacy of buprenorphine TDS over placebo, as shown by a statistically significant difference in the primary endpoint, was demonstrated. This particular study clearly assists in supporting the efficacy of buprenorphine TDS for the target population of the revised indication;*
- *Mundipharma also agrees with the Delegate that patients should be initiated on a low dose of transdermal buprenorphine and that each individual should have their dose titrated to optimise therapeutic effectiveness and tolerability. The selection of starting dose should be on the basis of prior opioid therapy in accordance with the revised indication. Mundipharma also acknowledges that slow and careful dose titration would be necessary to avoid the prolonged period of management necessary should an overdose occur;*
- *Mundipharma therefore contends that for the revised indication, the evidence clearly demonstrates that the statutory test fin' efficacy has been met.'*

The evidence submitted to support efficacy comes principally from four clinical studies in which Transtec patches were compared with placebo. Those studies were WIS-BUP01, WIS-BUP02, WIS-BUP03 and PB-TTC-02. Those studies have been submitted by your company as the pivotal studies. That they are the pivotal studies is supported by your company's statistical expert, [information redacted], in his report.

The three studies WIS-BUP01, WIS-BUP02, WIS-BUP03 were conducted in a mixture of patients, some of whom had cancer pain and others who had chronic pain of non-cancer origin. As reported, these studies failed to show a significant difference between an active treatment strength and placebo (WIS-BUP01; page 50 of Attachment 1; WIS-BUP02 -with an inconsistency in the response rates of the different active treatments; page 64 of Attachment 1; WIS-BUP03; page 79 of Attachment 1). In the three studies, as shown in Table 24 below, the percentage of randomised patients with cancer pain in a particular treatment arm ranged from 28.9% to 78.4%.

Table 24: The percentage of randomised patients with cancer pain in the treatment arms for Studies WIS-BUP01, WIS-BUP02, and WIS-BUP03

	Treatment Group				
Study	Number Randomised; % with cancer pain	Placebo	20 mg.	30 mg.	40 mg.
WIS-BUP01	151	37	35	41	38
	%	51.4	62.9	53.7	50.0
WIS-BUP02	157	n=38	n=41	n=41	n=41
	%	76.3	78.0	75.6	78.4
WIS-BUP03	137	n= 47	n=90		
	%	40.4	28.9		

(data extracted from Summary of Clinical Efficacy)

Given the wide variation in the number of patients with cancer pain between studies and between treatments it would not be expected that analyses of the subgroup of patients with cancer pain would consistently show significant differences between placebo and an active treatment. That is confirmed by the information in the tabulations at Table 10, Table 17 and Table 21 of Attachment 1. Only in one instance (WIS-BUP02, Table 17, 40 mg versus placebo) did the 95% CI of the difference not cross zero, mirroring the inconsistency seen in the primary efficacy outcome analysis for all patients.

Study WIS-BUP123 was undertaken at the request of a regulator. It involved an exploratory analysis of pooled data by combining the results of the three efficacy studies described above. The analyses are of both cancer pain and non-cancer pain patients. The analyses comparing an effect of an active treatment with placebo were performed for each treatment individually and for all active treatments combined ('verum'). The results are shown for combined response of pain relief and rescue medication ('pain relief response') (Figure 29 of Attachment 1) and combined response of pain intensity and rescue medication ('pain intensity response') (Figure 30 of Attachment 1). The results are only suggestive of an effect compared with placebo. Concerning the 'pain relief response', the results of analyses of pooled data for the 20 mg , 40 mg and verum treatments were statistically significant but not for tile 30 mg treatment. The results for 'pain intensity response' were not congruent with those for 'pain relief response'. Only the 40 mg treatment was statistically significant. Again, analyses of the subgroup of patients with cancer pain would not be expected to show significant differences between a treatment and a placebo.

A further study which examined only patients with cancer pain was titled 'A randomised, multicentre, double blind, placebo controlled, parallel group study assessing the analgesic efficacy and safety of buprenorphine TDS 70 µg/h in patients with severe chronic tumour related pain' (Study PB-TTC-02). This study compared the analgesic efficacy of the buprenorphine 40 mg patch; the highest strength patch, with placebo. The main inclusion criterion was for patients with malignant tumours requiring treatment with opioids at an equianalgesic dose range equivalent to 90 to 150 mg morphine orally per day. This study involved a two week run-in phase at the start of which patients were switched to the buprenorphine patch. Of 289 patients entering the run-in phase, only 189 were randomised to the subsequent double blind period. In this latter period they could be randomised to continue to use the 40 mg patch or to use a blinded placebo patch. The primary analysis was to compare the rates of withdrawal from the study with an expectation of a greater rate of withdrawal from the placebo group. The Delegate for the Minister has noted that there were high rates of withdrawal from both arms of the study. In particular, thirty of 94 subjects randomised to the continued active treatment withdrew

compared with forty of 94 subjects randomised to the placebo treatment. The Delegate for the Minister has reviewed the submitted study report and have not been able to locate a statement or tabulation that gives clear reasons for all thirty withdrawals in the 40 mg treatment group.

Efficacy was judged by the difference in withdrawal rates between those with continuing active patch treatment and placebo treatment. This study met its primary endpoint which was the proportion of patients classified as responders, where responders were defined as patients:

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

A statistically significant difference was reported for the analysis based on the Full Analysis Set of 188 subjects (p = 0.0003) and when based on a modified per-protocol set (p = 0.0031). Of the 188, only 118 finished at least Day 28 of treatment and had no major protocol violation (per-protocol set). An analysis based on the per-protocol set failed to reach statistical significance (p = 0.0626). This is likely attributable to too few subjects available for the per-protocol analysis.

A demonstration of statistical significance for efficacy in this study is not sufficient to support efficacy in all patients with moderate to severe cancer pain not adequately treated by previous opioids because the patients in this study who entered the double blind phase had already demonstrated a response to treatment with the highest of the three proposed strengths of patches.

As reported by the clinical evaluator, neither the submitted study report nor the study protocol indicated how the morphine equivalent doses in the inclusion criteria were calculated. It is implied that a dose of opioid equivalent to 90 to 150 mg orally per day of morphine is equivalent to the buprenorphine from the 40 mg patch. The Clinical Record Form (CRF) concerning inclusion into the study asked investigators to answer Yes if they judged a patient as being 'pre-treated with opioids and requiring an equianalgesic dose range equivalent to 90 to 150 mg morphine p.o. per day'. It would appear that inclusion into the study was thus based on an investigator judgment. The Table 14 of the study report at pages 131 to 133 of 2,297 gives summary data about the prior analgesic medication including opioids. For the subjects allocated to continue the active buprenorphine patch (n = 94) and those allocated to placebo (n = 95) buprenorphine or buprenorphine hydrochloride was being used by 6.4% and 3.2% respectively, fentanyl or fentanyl citrate (58.5%; 61.1%), morphine, morphine hydrochloride or morphine sulphate (35.2%; 44.2%) and tramadol or tramadol hydrochloride (28.7%; 25.3%). Small numbers were using other opioids. Any one patient may have been using more than one of these opioids.

The submitted information does not permit the TGA to assure itself that all the patients entering this study met the criterion of requiring an equianalgesic dose range equivalent to 90 to 150 mg morphine p.o. per day. If investigators entered patients whose immediately prior use of an opioid was at a dose less effective than buprenorphine from the 40 mg patch, the results of the study would be biased in favour of the buprenorphine patch. Yet to demonstrate, in support of the proposed indication, that a buprenorphine patch was appropriate to the treatment of moderate to severe cancer pain not adequately treated with previous opioids, patients whose prior use of an opioid was not adequate would be precisely the group of patients who should be investigated.

The Delegate for the Minister has concluded that study PP-TTC-02 may be biased to favour the Transtec 40 mg patch because of an inadequate inclusion criterion and that in any case the results do not support use in patients 'not adequately treated with previous opioids' because the comparison was with placebo, because the prior opioid treatment was not demonstrably with an equianalgesic dose of morphine, because the included patients were not necessarily not adequately treated with their previous opioid and , importantly, efficacy compared with placebo was demonstrated only in a subgroup of patents with cancer pain selected because they had already, in the run-in period, demonstrated a response to treatment.

Additionally, the study does not provide any evidence about the efficacy of the 20 mg and 30 mg patches and does not provide any evidence of efficacy to support the use of two 40 mg patches concomitantly to deliver a maximum dose rate of 140 µg per hour.

Your company's expert statistician, [information redacted], conducted a meta-analysis combining the data from the four trials to provide an overall estimate of efficacy. His Tables 2 (page 10 of Attachment 11 of the sponsor's appeal documentation) and Table 3 (page 11) give Odds Ratio Estimates for the combined (verum) doses from the four studies using two different response outcome parameters. These give results of Odds Ratios of 2.170 and 2.168 respectively. These support that the Transtec patches have some efficacy when compared with placebo.

[Information redacted] also conducted a meta-analysis combining the data from the four trials, for each strength of patch. The results are provided in Table 4 (page 12) and Table 5 (Page 13 of his report). He notes that there is a trend for the odds ratios to be greater for the high dose group than the low dose group. He notes that the confidence intervals for the mid dose group are wide 'indicating uncertainty about the effectiveness of this dose'. The Delegate for the Minister notes that in Table 4 for which the definition of primary outcome from the combined analysis (WIS-BUP123) was used the point estimate for the odds ratio for the 30 mg patch is considerably less than the other two strength patches. The Delegate for the Minister agrees with [information redacted]that there is no clear evidence of dose response from the meta-analysis. Both the clinical evaluator and [information redacted]have reported that the randomised controlled clinical trials have failed to demonstrate a dose response relationship.

Again, it is important to note that [information redacted]'s analyses relate (with the exception of study PB-TTC-02) to patients who did not solely have cancer pain.

Opioid analgesia for moderate to severe cancer pain will involve long term use in some patients. None of the four randomised controlled studies provided long term efficacy data. The open label extension studies had very high discontinuation rates and the patients with long term use were those with acceptable pain relief without adverse effects requiring discontinuation. At section 7.4 of Attachment 1 the clinical evaluator has tabulated synopses of a number of open efficacy and post-marketing studies. Concerning efficacy, the Delegate for the Minister could only identify one study in that tabulation in which the patients solely had cancer related pain. That is AWB Transteconco2003/0 and 2003/1. That was an open label uncontrolled study of up to 8 weeks with a possible extension of up to three months. The median duration of patch use was 63 days (range 4 to 405 days). Some 361 subjects were included in the efficacy analysis. Such a study is insufficient with respect to duration to satisfy about efficacy in long-term use in moderate to severe cancer pain.

The Delegate for the Minister has considered the issue of whether data about treatment of non-cancer pain can be used to support use in treatment of cancer pain. The Delegate for the Minister has noted that the Clinical Overview (page 32) and the Summary of Clinical Efficacy (page 82) reproduce a Figure which purports to show the responses by subgroup (cancer related pain versus non cancer related pain) for placebo and each of the three

strengths of Transtec patch. The Figure is in the form of a histogram and is unsatisfactory as it lacks basic information such as the number of responders contributing to each bar of the histogram.

No attribution of the source of the Figure is given in the Summary of Clinical Efficacy. The same Figure in the Clinical Overview has a label 'According to original response definitions (taken from Module 5.3.5.3\WIS-BUP123).' The Delegate for the Minister has used a variety of techniques to search the report at Module 5.3.5.3. The Delegate for the Minister has been unable to find the same Figure in that report and importantly the Delegate for the Minister has been unable to find any protocol or other description about how this Figure was generated. In these circumstances the Delegate for the Minister places no weight on this Figure or the underlying proposition that responses in non-cancer pain may be extrapolated to cancer pain.

In the Delegate for the Minister's view it is also appropriate to note that the European Committee for Medicinal Products for Human Use (CHMP) published for public consultation on 21 December 2015 a second draft of a guideline titled 'Guideline on the clinical development of medicinal products intended for the treatment of pain, 2nd draft, EMAA/CHMP/970057/2011, Corr 1', dated 17 December 2015. It is to be noted that the Guideline has not been finalised in Europe and has not been adopted by the TGA. It is also to be noted that neither the clinical evaluator nor the Delegate applied the draft Guideline.

None-the- less the Delegate for the Minister is of the view that the text at section 6.3 Cancer Pain is helpful: '*Pain due to malignant diseases is often, but not exclusively, indicative of tissue or organ destruction and frequently features both nociceptive and neuropathic pain components i. e. mixed pain. Although due to its duration and severity arguably a form of chronic pain, cancer pain is still largely an adaptive process to the underlying disease and thus should be regarded separately. Cancer pain can serve as a model to determine analgesic efficacy in long-standing severe pain with a comprehensible underlying pathology. Stratification according to the nature of the pain in terms of bony and/or visceral metastases and neuropathic features may help to characterise the efficacy profile on nociceptive and neuropathic pain components.*' The Delegate for the Minister notes that this draft guideline does not indicate that the results of studies in various types of non-cancer pain may support efficacy in cancer pain.

In summary, the Delegate for the Minister is not satisfied as to the efficacy of Transtec patches for the requested Indication.

Safety

Your company has submitted that:

'For the more limited revised indication proposed, the safety evidence emanating from extensive real world experience over 15 years has demonstrated that the most common systemic ADR's observed are those applicable to the administration of opioid analgesics in general such as nausea, vomiting, constipation, dizziness and somnolence. This evidence as well as the additional warnings and precautions in the PI, CMI and ASA in response to the RMP advice, should be sufficient to satisfy the statutory test for safety.'

In the Delegate for the Minister's view the following matters have not been adequately addressed by the clinical development program:

1. The use of Transtec patches with doses of 20, 30 and 40 mg applied each three days is frequently associated with well documented adverse effects of mu-opioid receptor agonists such as nausea, vomiting, constipation, dizziness and fatigue. The clinical evaluation report notes discontinuation rates of 18 to 46% in post-marketing surveillance studies. Most of these studies involved short term use. In the treatment of moderate to severe cancer pain, it may be anticipated that while some patients will die because of the cancer, others will need adequate analgesia for prolonged periods

(6 months or more). The clinical evaluator's Table 46 (Attachment 1) indicates that of 35,034 subjects in clinical development and post-marketing surveillance studies documented to have been exposed to a patch within the proposed dose range only 238 subjects had an exposure of ≥ 6 months and only 37 subjects had an exposure ≥ 12 months. In the Delegate for the Minister's view this extent of exposure is insufficient to satisfy the safety of Transtec patches in periods of use that may reasonably be expected.

2. In addition to clinical development and post-marketing surveillance studies, the sponsor has reported details of product safety in a series of Periodic Safety Update Reports. Reports 18 and 19 covering the periods 31 July 2011 to 30 July 2014 and 31 July 2014 to 30 July 2015 respectively were included in the Pre- ACPM response and are in Attachment 7 to the appeal documentation. Small numbers of Individual Case Safety Reports describing respiratory depression are noted in each of these two PSURs as having reached the Global Drug Safety Database. The search term used to find these reports in the database was 'Acute central respiratory depression' which is a narrow search term carrying the possibility that other clinically relevant ICSRs will not have been identified. The Delegate for the Minister has noted that the narrative in these PSURs is devoid of a consideration of the strength of the Transtec patch implicated in each report. The Australian submission did not include an up-to-date analysis of post-marketing experience exploring reporting of serious adverse events such as respiratory depression versus the various Transtec strengths implicated in the individual reports. An analysis of other hospitalisations attributable to Transtec patches such as severe nausea and vomiting and acute confusional states versus Transtec strengths has not been provided in the PSURs. The Delegate for the Minister is of the view that the analyses of post-marketing ICSRs have not been sufficiently adequate to support registration.

3. The clinical evaluation has highlighted that instances of unconsciousness attributable to co-administration of other sedating agents including antidepressants has occurred despite clear warnings in the SmPC and in consumer information leaflets.

4. The response by individuals to even the lowest dose Transtec patch is unpredictable. The clinical trials did not include specific actions to investigate the potential for overdose. The submission relies heavily on reference to the existence of a 'ceiling effect' on respiration of buprenorphine. Walsh SL at al[42]described a study involving administration of ascending doses of sub-lingual buprenorphine to four healthy adult males (age range 28 to 41 years). The authors claimed that the study demonstrated a plateau in buprenorphine effects, consistent with its partial agonist classification, and that single doses of buprenorphine up to seventy times the recommended analgesic dose are well tolerated by nondependent humans. Similar reporting of a ceiling effect on respiratory depression but not in analgesia involved intravenous doses of 0.2 mg per 70kg in 10 subjects (5 males) and 0.4 mg per 70 kg buprenorphine in 10 subjects (5 males).[70] All subjects were healthy non-smokers aged between 22 and 35 years. No data are available to support a ceiling effect in older subjects or patients with pre-existing respiratory diseases.

   In contrast to the proposition that patients would be protected by the ceiling effect, the clinical evaluator has noted several reports in the PSURs of respiratory failure occurring at therapeutic doses of buprenorphine or with inadvertent overdoses or in combination with another sedating agents (the details of reports in the PSURs are at page 172 of Attachment 1).

[70] Dahan A at al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth* 2006; 96:627-632

5. The submission does not provide satisfactory guidance for the treatment of overdoses of buprenorphine from Transtec patches. The clinical studies have not specifically investigated this issue. The clinical evaluator (page 36 of Attachment 1) notes that the sponsor has relied on a published review paper concerning the use of naloxone to reverse respiratory depression in healthy volunteers caused by parenterally administered buprenorphine. The proposed Australian PI for Transtec submitted with the Pre-ACPM response (version 8.0) notes that naloxone has a limited impact on the respiratory depressant effect of buprenorphine and that high doses are needed given either as repeat doses or infusion. This version of the PI refers those treating overdose to the naloxone hydrochloride injection PI for further information notwithstanding that the needed bolus doses and infusion rates are not provided for in the naloxone hydrochloride PI.
6. Concerning the proposed maximum dose of two 40 mg patches applied concomitantly, information to support safe use is manifestly inadequate. This dose was not studied in the submitted controlled clinical efficacy studies. The clinical evaluator has estimated that only 131 of 33,673 subjects in Post Market Surveillance studies received a dose greater than 40 mg and up to 80 mg (two patches concomitantly). Of these only two patients received doses in this range for more than 6 months.

The Delegate for the Minister regards the deficiencies set out in 1 to 6 above to be sufficient to refuse registration because the Delegate for the Minister is not able to be satisfied of the safety of the Transtec patches. The Delegate for the Minister notes that a number of other substantial issues, have been identified during the clinical evaluation. The Delegate for the Minister believes that these issues could be dealt with by appropriate warnings in the PI. These include:

- the potential for interactions with CYP3A4 inhibitors and inducers;
- the potential for the patches to cause QT prolongation and consequent Torsades de Pointes, acknowledging that a series of studies have somewhat mitigated this concern;
- the possibility that use of the patches may very uncommonly cause vasospastic angina.

In summary, the Delegate for the Minister is not satisfied as to the safety of the Transtec patches for the proposed Indication.

Other issues

- Your company has submitted that 'The TGA was clearly put on notice as to the age and nature of the studies presented, and on this basis accepted the application for evaluation in accordance with Sub-section 23(2)(b) of the Act that the application contained '*such information, in a form approved in writing, by the Secretory, as will allow the determination of the application.*' In the Delegate for the Minister's view your company would have been or should have been aware that the TGA is required to evaluate the submission and that the Delegate of the Secretary is required to be satisfied as to the quality, efficacy and safety of the goods.
- Your company has submitted that 'Given the acceptance of the application following the Pre-Submission planning/screening process it would be a reasonable interpretation that, in this case, a departure from current guidelines in relation to the design and conduct of the pivotal studies was accepted by the TGA in accepting the application for evaluation under Section 23(2)(b) of the Act'. As stated above, the Secretary is required to evaluate the submission and the Delegate of the Secretary is required to be satisfied as to the quality, efficacy and safety of the goods. There is no provision in the legislation for the Secretary to apply some form of retrospective standard concerning quality, efficacy or safety.

- Your company has submitted that 'In the response to the Delegate's request for ACPM advice, Mundipharma proposed that the indication be modified to limit the administration of Transtec in opioid naive patients and non-cancer pain patients. Consequently, Mundipharma proposed the following revised indication:

  'Use in patients with moderate to severe cancer pain not adequately treated by previous opioids.'

  The Delegate for the Minister notes that the Delegate accepted that proposal and that the Delegate's subsequent decision related to that revised indication.

- Your company has submitted that 'There were no objections to registration based on chemistry (quality) grounds. There were no nonclinical objections to the registration of Transtec patches at the proposed strengths'. The Delegate for the Minister accepts that this is the situation.

- Your company has submitted that 'Whilst Mundipharma agreed to a number of amendments to the PI and CMI following the recommendations of the Second Round RMP evaluation report, it did so in reliance on the TGA undertaking that there would be an opportunity post-ACPM to discuss these recommendations with the TGA. Such an opportunity did not eventuate'. Your company appears to have a misunderstanding of the place of the finalisation of the PI and the RMP in the process of registering a medicine on the Australian Register of Therapeutic Goods.

  Concerning the PI, Section 25AA relevantly provides:

  (1) The Secretary must approve product information in relation to therapeutic goods if:

  (a) the Secretary decides, under subsection 25(3), to register the goods; and

  (b) the goods are:

  (i)restricted medicine; or

  (ii) medicine in respect of which the applicant has been given a notice of the kind referred tom subparagraph 25(1)(da)(ii).

  (1A) However, the Secretary must not approve product information in relation to therapeutic goods under subsection (1) unless the Secretary is satisfied that the product information reflects the basis on which the Secretary decided under subsection 25(3) of the Act to register the goods.

  It is clear that the legislation provides for the PI to be approved after the Delegate has decided to register the goods. The Delegate is then required to ensure that the PI reflects the basis on which the decision to register the goods has been made. It is common for a Delegate to negotiate changes to the PI in order the meet this requirement after having decided to register the goods. In the case of your application, the Delegate of the Secretary decided to refuse registration because safety and efficacy had not been established, and as a consequence there was no requirement to consider further the content of the proposed PI. The wording of the PI was not a reason for the Delegate of the Secretary's refusal.

  Concerning the RMP, section 28(2B) of the Act provides that 'If the Secretary includes therapeutic goods in the Register in relation to a person, the Secretary may, by notice in writing given to the person, impose conditions on the registration or listing of those goods'. Any requirement that a sponsor must adhere to a RMP is imposed by a Delegate as a condition on the inclusion of the goods on the Register. It is common for a Delegate to negotiate changes to the RMP after having become of a mind to register the goods. In the case of your application, the Delegate of the Secretary decided to refuse registration because safety and efficacy had not been established and as a

consequence there was no need to consider further the content of the proposed RMP. The content of the draft RMP was not a reason for the Delegate of the Secretary's refusal.

- Your company has submitted that 'Transtec has been marketed in EU and Switzerland since 2000. The total cumulative post authorisation patient exposure since IBD is estimated at approximately 545.16 million PTD'. I have noted that the licensure of the product in the EU was initially in Germany in 2001; for 'Moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics. Transtec is not suitable for the treatment of acute pain'. Licensure in a further 8 European countries occurred via the Mutual Recognition (MR) process no later than 18 April 2003. The Mutual Recognition process does not involve consideration of the application by the European Committee for Medicinal Products for Human Use (CHMP). It is clear that the scientific basis for the initial licensures in Europe was limited to the three studies WIS-BUP01, WIS-BUP02 and WIS-BUP03. The TGA evaluation makes clear that the results of these three studies are an inadequate basis for approval for the treatment of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics (see pages 53, 68and 83, Attachment 1). The Delegate for the Minister has noted that a post-hoc exploratory analysis of the three clinical trials was undertaken 'upon a request from the UK MHRA (MCA) during the MR procedure performed in 2001'. 'The changes in the main efficacy variables were analysed parametrically and compared to placebo using ANOVA' (see Summary of Clinical Efficacy page 76). The report of this analysis submitted in the application to the TGA is dated 17 November 2004. The second round clinical evaluation report (pages 128 to 130 of Attachment 1) highlights that although the results of the analysis are suggestive of some efficacy compared with placebo the results are unconvincing. Statistically significant efficacy for the combined response of 'Pain relief and rescue medication' was not demonstrated for the 30 mg patch and statistically significant efficacy for the combined response of 'pain intensity and rescue medication' was not demonstrated for the 20 mg and 30 mg patches. It is the Delegate for the Minister's opinion that in this instance the TGA should place little weight on the licensure of the Transtec patches via Mutual Recognition in Europe. Your company may also be seeking to draw reassurance about the safety of the Transtec patches from the extent of use of the Transtec patches in Europe. The Delegate for the Minister has above pointed out that the submitted analyses of post-marketing experience are inadequate for the purpose of assessing the safety of the Transtec patches.

  Your company has submitted that 'The risks identified by the RMP evaluation report in relation to the risk of inadvertent exposure, risk of medication errors for patients switching to/from Transtec and Norspan, and QT prolongation, are not indicated by the global safety database for Transtec'. The Delegate for the Minister has pointed out above that the matters identified in the RMP evaluation report are matters which might be negotiated should the Delegate be of a mind to register the product. In the Delegate for the Minister's view the Delegate (of the Secretary) decided not to register the product for reasons relating to inadequate evidence of efficacy and safety. The Delegate's decision was not significantly influenced by the content of the draft RMP.

  Your company has submitted that 'Some of the recommendations in relation to paediatric use, pregnant or breastfeeding patients, and QT prolongation, require additional monitoring unique to Australia. Mundipharma understands that it has been long standing Government policy that new and unique Australian requirements in the clinical area should only be introduced for uniquely Australian products or in response to unique Australian conditions or in response to a demonstrated public health need. More recently, the former Abbott Government announced that it had adopted the principle that 'if a system, service or product has been approved under a trusted international standard or risk assessment, Australian regulators should not impose

any additional requirements unless it can be demonstrated that there is a good reason to do so.'' Your company's submission reflects a misunderstanding of long standing Government policy. The policy relates to unique Australian 'standards for pharmaceuticals' and has its origins in the adoption of Recommendations 8 and 9 of the 1991 Report on the Future of Drug Evaluation in Australia ("The Baume Report"). That cannot be construed as a restriction on the ability of the Delegate to impose requirements ('conditions') such as additional monitoring under the provisions of s 28 (2B) of the Act where such requirements are justified in order to ensure use that is efficacious and safe. Similarly, an announced Government policy cannot be construed as imposing a restriction on the ability of the Delegate to impose requirements ('conditions') such as additional monitoring under the provisions of s 28 (2B) of the Act.

Conclusion

The Act requires (s25) that the Secretary must evaluate the goods for registration having regard to (amongst other things):

– whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established.

As the Delegate for the Minister noted above, you have applied for the registration of three different strengths of a buprenorphine transdermal drug delivery system (Transtec, Bupatch, Dosbupren, MPL-Buprenorphine BIW) for the following indication:

> '*Management of moderate to severe cancer pain not adequately controlled by previous opioids'.*

As set out above under 'Findings of fact and reasons for my decision', the Delegate for the Minister is of the view that the clinical information currently available to the Delegate for the Minister does not permit the Delegate for the Minister to be satisfied that the efficacy and safety of the goods for the purposes for which they are to be used have been satisfactorily established. For that reason, the Delegate for the Minister has decided to confirm the initial decision to refuse approval of the application.

Outcome from appeal to the Administrative Appeals Tribunal

The sponsor appealed to the Administrative Appeals Tribunal (AAT) for review of the TGA's decision not to register Transtec.

The sponsor later withdrew their application to the AAT.

Attachment 1. Extract from the Clinical Evaluation Report

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