5.04 BUPRENORPHINE/NALOXONE,

Tablet (sublingual) containing 0.7 mg buprenorphine hydrochloride with 0.18 mg naloxone hydrochloride, Tablet (sublingual) containing 1.4 mg buprenorphine hydrochloride and 0.36 mg naloxone hydrochloride, Tablet (sublingual) containing 2.9 mg buprenorphine hydrochloride and 0.71 mg naloxone hydrochloride, Tablet (sublingual) containing 5.7 mg buprenorphine hydrochloride and 1.4 mg naloxone hydrochloride, Tablet (sublingual) containing 8.6 mg buprenorphine hydrochloride and 2.1 mg naloxone hydrochloride, Tablet (sublingual) containing 11.4 mg buprenorphine hydrochloride and 2.9 mg naloxone hydrochloride, Zubsolv®,

Mundipharma Pty Ltd.

1 Purpose of Application

1.1 The submission sought Section 100 (Opiate Dependence Treatment Program) listing for buprenorphine/naloxone sublingual (SL) tablets (Zubsolv®), hereafter referred to as Zubsolv, for the treatment of patients with opioid dependence. This is the first submission to the PBAC for Zubsolv.

1.2 The requested basis for listing was a cost-minimisation analysis compared with buprenorphine/naloxone SL film (Suboxone®), hereafter referred to as Suboxone film. Table 1 summarises the key components of the clinical issue addressed by the submission.

Table 1: **Key components of the clinical issue addressed by the submission**

Component	Description
Population	Patients entering opioid substitution treatment
Intervention	Buprenorphine/naloxone sublingual tablets (Zubsolv)
Comparator	Buprenorphine/naloxone sublingual film (Suboxone film)
Outcomes	Primary - Proportion of patients retained in treatment Secondary: Clinical Opiate Withdrawal Scale (COWS); Subjective Opiate Withdrawal Scale (SOWS); Taste acceptability Visual Analogue Scale (VAS); Ease of drug administration; Overall acceptability of formulation VAS; Change from baseline in VAS for craving Key safety outcomes: Adverse events (AEs) and discontinuations due to AEs
Clinical claim	Zubsolv is non-inferior to Suboxone film and offers an alternative treatment option for patients seeking to overcome their opioid dependence.

VAS = visual analogue scale; AE = adverse event
Source: Table 1.4, p9 of the submission.

2 Requested listing

2.1 The proposed restriction is shown below.

Name, Restriction, Manner of administration and form	Max. Qty (units)	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
BUPRENORPHINE/NALOXONE				
Sublingual tablet 0.7/0.18	28	0	$[redacted]	
Sublingual tablet 1.4/0.36	28	0	$[redacted]	
Sublingual tablet 2.9/0.71	28	0	$[redacted]	Zubsolv® Mundipharma
Sublingual tablet 5.7/1.4	28	0	$[redacted]	
Sublingual tablet 8.6/2.1	28	0	$[redacted]	
Sublingual tablet 11.4/2.9	28	0	$[redacted]	

Category/Program:	Section 100 (Opiate Dependence Treatment Program)
PBS indication:	Opiate dependence
Treatment phase:	Initial and Maintenance: detoxification (withdrawal)
Restriction level/method:	Restricted benefit
Clinical criteria:	The treatment must be within a framework of medical, social and psychological treatment.
Prescriber Instructions	For prescribing by nurse practitioners where care of a patient is shared between a nurse practitioner and medical practitioner in a formalised arrangement with an agreed management plan. Further information can be found in the Explanatory Notes for Nurse Practitioners.
Administrative Advice	Buprenorphine with naloxone soluble film and buprenorphine with naloxone sublingual tablet do not meet all the criteria for bioequivalence. Patients being switched between soluble films and sublingual tablets may therefore require a dosage adjustment.
Cautions	Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.

2.2 The requested restriction is consistent with that for Suboxone film, in terms of the wording of the restriction, maximum quantities and number of repeats. The evaluation noted that the other SL tablet formulation (buprenorphine alone; Subutex®) is restricted to a maximum quantity of seven tablets, with zero repeats.

2.3 The Zubsolv 1.4/0.36 mg and 5.7/1.4 mg formulations are priced [redacted] to Suboxone film 2/0.5 mg and 8/2 mg presentations, respectively. Prices for the other doses are based on [redacted] price per mg extrapolation (see paragraph 6.37).

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Background

Registration status

3.1 Zubsolv was TGA registered on 26 March 2019 for the treatment of opioid dependence, within a framework of medical, social and psychological treatment.

Previous PBAC considerations

3.2 In November 2005, the PBAC recommended Suboxone tablets (2/0.5 mg and 8/2 mg) on a cost-minimisation basis to buprenorphine, with the equi-effective doses being determined on a milligram for milligram basis (Suboxone Public Summary Document (PSD), November 2005).

3.3 In March 2011, the PBAC recommended Suboxone film (2/0.5 mg and 8/2 mg) on a cost minimisation basis to Suboxone tablets (March 2011 PBAC outcomes, positive recommendations). Suboxone tablets were subsequently delisted from the PBS.

3.4 In November 2014, the PBAC recommended two additional strengths of Suboxone film (4/1 mg and 12/3 mg) (Suboxone PSD, November 2018), at a price per milligram to be linearly extrapolated from the prices of the currently listed strengths. The PBAC considered there would be a moderate benefit associated with listing additional strengths including a reduced number of films required to be administered to patients, in turn potentially decreasing the risk of diversion, improving pharmacy administration time, and allowing flexibility of dose titration, addressing potential quality use of medicines issues relevant to this product. At the time of PBAC consideration of Zubsolv, the additional strengths of Suboxone film had not been listed on the PBS.

3.5 In March 2019, the PBAC considered two submissions for buprenorphine modified release injection (Buvidal® and Sublocade®). The PBAC recommended Buvidal on a cost-minimisation to Suboxone film with a price premium (Buvidal PSD, March 2018) and deferred its decision on whether to recommend Sublocade, pending provision of a positive TGA Delegate's overview. Buvidal was listed on the PBS on 1 September 2019.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 Opioid substitution therapy (OST) is an approach that assists opioid users to reduce their illicit use of opioids and to thereby improve their health and social wellbeing. The submission highlighted the importance of maintenance of treatment, claiming that illicit opioid use may resume once treatment ceases. Based on an Illicit Drug Reporting System Survey (2017), the submission stated that 38% of persons who regularly inject drugs illicitly had participated in an OST program, with 39% of participants in current treatment reporting that they had been in treatment for 12 months or less.

4.2 Zubsolv is proposed as an alternative to Suboxone film for patients dependent on opioids, as a long-term approach to opioid dependence together with regular clinical reviews and monitoring as well as psychosocial interventions. The recent consideration of buprenorphine modified release injection (Sublocade) at the March 2019 PBAC meeting indicated that '… it was most likely that in Australian clinical practice, patients would be stabilised on daily BUP/NAL SL [Suboxone] film and be responding well to treatment, including being authorised for multiple takeaway doses. It was likely at that point, patients might be considered to be good candidates for transitioning to a modified release injectable formulation. As such Sublocade would be used later in the treatment algorithm' (Sublocade PSD, March 2019, para 4.4). The evaluation expected that patients stabilised on daily Zubsolv doses, responding well and authorised for takeaway doses may also be considered good candidates to transition to buprenorphine modified release injection.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated Suboxone film as the main comparator based on: it is the OST that is most likely to be replaced in clinical practice; it contains the same active drugs as Zubsolv; and the PBS indication is identical to that requested for Zubsolv. Further, both Zubsolv and Suboxone film can be administered as take-away doses. This was considered reasonable, the main comparator was appropriate, and was consistent with the accepted comparators for buprenorphine modified release injection (Buvidal; para 5.4 November 2018 PSD and Sublocade, para 5.2 March 2019 PSD). However, other PBS-listed therapies (methadone and buprenorphine tablets (Subutex)) also represent treatment alternatives.

5.2 For the requested population, the alternative therapies listed on the PBS (methadone, buprenorphine, and the individual components (buprenorphine and naloxone)) are less costly than the requested price for Zubsolv. If treatment with Zubsolv is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of Zubsolv if it is satisfied that Zubsolv provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953*, Section 101(3B)).

5.3 Through the Pre-Sub-Committee Response (PSCR), the Sponsor claimed methadone and buprenorphine should not be considered alternative therapies as they are not intended for take-home treatments and do not include naloxone. The Economics Sub-Committee (ESC) disagreed with the sponsor and considered that these can be used in the take-home setting in Australian clinical practice (e.g. NSW Clinical Guidelines [1],

[1] *NSW Clinical Guidelines: Treatment of Opioid Dependence*, published 30 July 2018, https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2018_019.pdf.

page 37) and are also relevant comparators. In the pre-PBAC response, the Sponsor argued that the NSW Clinical Guidelines, which suggest that methadone can also be take-home (in limited circumstances), actually demonstrates a more stringent risk assessment for methadone than for Suboxone – particularly for patients deemed moderate or low risk.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 *Consideration* of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on one head-to-head trial comparing Zubsolv and Suboxone film (with titration on generic buprenorphine SL tablets) (OX219-006, n =758), with trial NCT02038790 being used as supportive evidence, and Study OX219-008 extension to Trial OX219-006) providing longer-term safety data.

6.4 Details of the trials presented in the submission are provided in Table 2.

Table 2: **Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
OX219-006 (NCT01908842)	Induction, Stabilization, Adherence and Retention Trial (ISTART) - A randomized, non-inferiority, multicenter study to assess early treatment efficacy of OX219 versus Suboxone® Film and to explore switching between treatments.	Clinical study report. 03 October 2014.
	Gunderson E, Hjelmstrom P, Sumner M. Effects of a Higher-bioavailability Buprenorphine/Naloxone Sublingual Tablet Versus Buprenorphine/Naloxone Film for the Treatment of Opioid Dependence during Induction and Stabilization: A Multicenter, Randomized Trial.	Clinical Therapeutics. 2015;37(10):2244-2255
	Gunderson E, et al. Induction, Stabilization, Adherence and Retention Trial (ISTART): Efficacy of Advanced-Formulation Buprenorphine/Naloxone Sublingual Tablet Versus Buprenorphine/Naloxone Film for the Treatment of Opioid Dependence.	25th Annual Meeting and Symposium of the American Academy of Addiction Psychiatry, AAAP 2014.
	Gunderson E. and Sumner M. Efficacy of Buprenorphine/Naloxone Rapidly Dissolving Sublingual Tablets (BNX-RDT) after Switching from BNX Sublingual Film.	Journal of Addiction Medicine. 2016;10(2):124-130.
NCT02038790	Usability of Zubsolv Sublingual Tablets 5.7/1.4 to Suboxone Sublingual Film 8/2 In Buprenorphine/Naloxone Treated Opioid Dependent Population.	ClinTrials.gov. 21 March 2017.
OX219-008 (NCT01903005)	A Multi-Center, Open-Label, 24-Week, Follow-Up Study to Assess Safety, Efficacy, and Treatment Adherence for Maintenance Treatment of Opioid Dependence with OX219.	Clinical study report. 06 March 2014.
	Hoffman K, Peyton M, Sumner M. Safety of a Rapidly Dissolving Buprenorphine/Naloxone Sublingual Tablet (BNX-RDT) for Treatment of Opioid Dependence: A Multicenter, Open-label Extension Study.	Journal of Addiction Medicine. 2017;11(3):217-223.

Source: Table 2-4, pp42-43 of the submission.

6.5 The key features of the direct randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
OX219-006	758	R, MC, initiation blinded then OL, cross-over at Day 15	High	Opioid dependence with at least mild withdrawal symptoms	Retention in treatment at Day 3* and 15 (co-primary outcomes), key secondary outcomes: clinical opiate withdrawal scale and subjective opiate withdrawal scale, taste acceptability, ease of drug administration, change from baseline in Visual Analogue Scale for craving
NCT02038790	33	R, OL, cross-over 2 days	High	Patients on an 8/2 dose of Suboxone film or generic equivalent or on 5.7/1.4 Zubsolv	Patient treatment preference (primary outcome)

*This outcome was added as a protocol amendment, approximately 9 months after the original protocol date
DB=double blind; MC=multi-centre; OL=open label; R=randomised.
Source: Table 2-15, pp69-70 of the submission, Section 2.4 of the submission, and compiled from Section 2 of the submission during the evaluation.

6.6 The ESC noted that Trial OX219-006 may not be directly relevant to Australian clinical practice because: 1) it was conducted in the US, where the OST treatment model

(referred to as opioid agonist treatment (OAT)) is different to Australia. However, the Sponsor argued in its pre-PBAC response, that the differences in treatments between the two countries do not invalidate the comparative trial results; 2) 30% of participants were not OAT naïve, which may introduce bias; and 3) patients were titrated to a maximum of 24 mg buprenorphine for Suboxone film, whereas the maximum daily dose in the Australian setting is 32 mg (NSW Clinical Guidelines, page 30).

6.7 The ESC considered that while the primary outcome of retention in treatment was important, this should ideally have been assessed over a longer time period than 13/15 days and supported by an objective measure of decreased drug use such as 'proportion of patients with urine samples negative for illicit opioids', as presented in the Buvidal (November 2018 PSD) and Sublocade (March 2019 PSD) submissions.

6.8 Dose conversion for patients on Suboxone film who were converted to Zubsolv at Day 15 in Trial OX219-006 occurred using the following conversion table, see Table 4. The PBAC considered the use of pre-assumed dose relativities may introduce bias in any estimation of dose equivalence, with any dose adjustments made only on evidence of under- or over-dosing.

Table 4: Conversion table for doses of Suboxone film to Zubsolv

Suboxone film dose (Buprenorphine/naloxone mg)	**Zubsolv dose** (Buprenorphine/naloxone mg)
8/2	5.7/1.4
10/2.5	7.1/1.8
12/3	8.5/2.1
14/3.5	9.9/2.5
16/4	11.4/2.8
18/4.5	12.8/3.2
20/5	14.2/3.5
22/5.5	15.6/3.9
24/6	17.1/4.2

Source: Table 2-16, p70 of the submission.

6.9 Only a limited number of tablet and film strengths were available for use during the trial. Four additional strengths to the two strengths of Zubsolv that were used in the trial (i.e. 5.7/1.4 mg and 1.4/0.36 mg) are proposed for PBS listing. The conversion table for the tablet and film strengths is detailed in Table 5.

Table 5: Conversion table for dose to tablets/films for Suboxone film and Zubsolv

Zubsolv dose level (Buprenorphine/naloxone mg)		Suboxone film dose level (Buprenorphine/naloxone mg)	
Dose	**Number of tablets**	**Dose**	**Number of films**
5.7/1.4 mg	[redacted]	8/2 mg	[redacted]
7.1/1.8 mg	[redacted]	10/2.5 mg	[redacted]
8.5/2.1 mg	[redacted]	12/3 mg	[redacted]
9.9/2.5 mg	[redacted]	14/3.5 mg	[redacted]
11.4/2.8 mg	[redacted]	16/4 mg	[redacted]
12.8/3.2 mg	[redacted]	18/4.5 mg	[redacted]
14.2/3.5 mg	[redacted]	20/5 mg	[redacted]
15.6/3.9 mg	[redacted]	22/5.5 mg	[redacted]
17.1/4.2 mg	[redacted]	24/6 mg	[redacted]

Source: Table 2-17, p71 of the submission.

6.10 As both trials were open-label (apart from the blinded phase of OX219-006) they had a high risk of outcome bias. This was considered particularly important, given the subjective nature of the outcomes.

6.11 Through the PSCR, the Sponsor maintained the bias in the OX219-006 trial to be low-moderate and that the co-primary outcome 'retention in study at Day 15' is objectively assessed. It stated that due to the differences in the formulation of Zubsolv and Suboxone film (including distinct dissolution and taste), blinding was not feasible. The ESC considered the open label nature of the trial was associated with a high risk of bias.

6.12 In relation to a minimal clinically important difference (MCID), the submission stated that there is little published data on what a clinically relevant MCID is or what difference should be used to support non-inferiority in this therapeutic area. The submission noted that other studies (Beck, Haasen et al 2014, Haemmig 2014) utilised a 10% margin based on a 2-sided test to represent non-inferiority in the area of OST and that ideally, the margin value is chosen to be smaller than the minimum difference between an active therapy and a placebo to indicate clinically relevant results. Other than this margin having being used in other studies, it was unclear how this margin was determined or whether it was appropriate. The evaluation noted the Beck, Haasen et al 2014 publication assessed MCID based on the proportion of heroin-positive urine samples (using a 10% margin), and the Haemmig 2014 reference did not indicate the non-inferiority margin or the assessment outcome.

6.13 In relation to evidence previously considered by the PBAC, the PSD for Buvidal, November 2018 (paragraph 6.7, Buvidal PSD, November 2018) indicated that a pre-defined non-inferiority margin of 11% was used for the outcome of percentage urine samples negative for illicit opioids, without self-reported opioid use (ITT). A non-inferiority margin of 15% was used for the outcome of retention rate at 24 weeks (paragraph 6.18, Buvidal PSD, November 2018).

6.14 The ESC considered that while there was little precedence for a non-inferiority margin in this context, the nominated margin of 10% was adequately justified by the submission.

Comparative effectiveness

6.15 The ESC considered that the results of trial NCT02038790 were not informative given the trial compared only a single dose of Zubsolv and Suboxone film on alternate days.

6.16 Table 6 presents key results from Trial OX219-006.

Table 6: Results of retention in treatment from OX219-006

	Per Protocol Set (PPS)			Full Analysis Set (FAS)		
	Zubsolv	**Generic BUP/ Suboxone film***	**Mean difference (95% CI) (Zubsolv – Generic BUP/Suboxone film)**	**Zubsolv**	**Generic BUP/ Suboxone film***	**Mean difference (Zubsolv – Generic BUP/Suboxone film)**
Retention in treatment at Day 3						
n/N (%)	309/329 (93.9%)	302/326 (92.6%)	1.3% (-2.6%, 5.1%) SE 1.96 p=0.512	357/383 (93.2%)	344/375 (91.7%)	1.5% (-2.3%, 5.2%) SE 1.92 p=0.440
Retention in treatment at Day 15						
n/N (%)	273/329 (83.0%)	269/326 (82.5%)	0.5% (-5.3%, 6.3%) SE 2.95 p=0.875	287/383 (74.9%)	279/375 (74.4%)	0.5% (-5.7%, 6.7%) SE 3.16 p=0.866

BUP = buprenorphine; CI = confidence interval; n = number of participants with event; N = total participants in group
*Patients received generic buprenorphine (BUP) tablets up to day 3, as specified in the protocol, followed by Suboxone Film up to day 15.
Source: Table 2-25, p95 of the submission.

6.17 As the 95% CI for the lower limit of the difference between the two treatments was within the range of -10% to 0% for the Per Protocol Set (PPS) at Day 15 (with the lower limit being -5.3%), the non-inferiority margin in Trial OX219-006 was met. The lower limit of the 95% CI for the difference between the two treatments based on the FAS also met the non-inferiority criteria, with the lower bound being -5.7% at Day 15. The Day 3 outcome results were also similar.

6.18 Overall, as the Day 3 comparison effectively looked at generic buprenorphine versus Zubsolv, the ESC considered that this outcome could not inform the question of whether Zubsolv and Suboxone film are non-inferior.

6.19 The ESC considered that the reliability of the results from the Day 15 endpoint was limited for the following reasons:

- the time of observation was short given the long-term nature of treatment;
- the primary outcome of retention in treatment is not recommended as a standalone end point, without supportive objective measures of decreased drug use, as features of trial design can provide incentives to remain in treatment without accruing clinical benefit; and
- there was potential for outcome bias due to the open-label nature of the trial.

6.20 The pre-PBAC response provided additional results from Trial OX219-006, stating 'there were no statistically significant differences between treatments in the time to first negative urine drug screen (UDS) prior to the switching of treatments at Day 15 (HR [redacted], 95% CI [redacted]), providing an objective measure of the impact of Zubsolv and Suboxone on changes in illicit drug use'. The risk difference presented in the pre-PBAC response for this outcome for Zubsolv compared with generic buprenorphine/Suboxone film was [redacted]% (95% CI: [redacted]%, [redacted]%).

6.21 The ESC noted that there were no statistically significant differences noted for the secondary outcomes for between treatment group preferences, with the exception of acceptability and preference assessments, which favoured Zubsolv treated patients. The ESC noted the key clinical trial only used combinations of two strengths of Zubsolv, which it considered provided a different patient experience to administration with the strengths proposed. The ESC considered the claims that improved taste, mouth feel and ease of administration would result in improved clinical outcomes were not adequately supported by the evidence in the submission.

6.22 The submission reported the mean doses of buprenorphine taken by patients in Trial OX219-006, to be 10.8 mg for Zubsolv treated patients at Day 15 and 15.9 mg for Suboxone film treated patients at Day 15. These doses were not reported in the trial report, but were reported in a publication of the trial (Gunderson et al 2015). The evaluation considered that the data on which this calculation was based was difficult to interpret, as the doses referred to those on Day 15 (after switch of treatments), so it was unclear whether the group reported to be taking Zubsolv (after switch of treatments) referred to those who switched to Zubsolv on Day 15 or those initially randomised to Zubsolv. Should the doses refer to those after switching (which is supported by other information in the trial report), this method was not a reasonable way to estimate the mean dose as the proportion of patients on each dose of the therapies at Day 1 of the switch (Day 15 of the trial) would not represent titrated doses 'that relieved cravings and opioid withdrawal symptoms with minimal side effects'. Rather, this would represent a dose that was based on 'Dose conversion' (see Table 5). In the absence of having doses reported at Day 14 (once titration was presumably complete and steady-state doses achieved), one could assume that the proportion reportedly on 5.7/1.4 mg Zubsolv at Day 15 were on a dose of 8/2 mg Suboxone film on Day 14 (based on the conversions used in the trial) and so on. Assuming this results in mean buprenorphine doses of 11.3 mg for Zubsolv and 15.2 mg for Suboxone film at Day 14. The submission highlighted that the relative amounts of buprenorphine in the therapies used by patients in the trial (10.8 mg versus 15.9 mg) equated to a relativity of 1:1.5. This is similar to the dose relativity of 5.7:8 (1:1.4) that was used to convert doses between the two therapies during the study (and the therapeutic relativity proposed in the submission). This is not surprising given the pre-supposed relativities assumed when patients switched from one therapy to another and the dosing may relate to the day of that switch. Using the above approach estimating

mean buprenorphine doses of 11.3 mg for Zubsolv and 15.2 mg for Suboxone film, the dose relativity would be 1:1.34.

6.23 The PSCR stated 'the primary outcome used to determine non-inferiority and all key secondary outcomes were reported prior to any change in therapy and thus are not impacted by whatever dose conversion was subsequently used'. The ESC agreed that if participants were titrated to effect, pre-assumed knowledge of dose equivalence would not cause significant bias. However, the ESC considered that the PSCR indicated the dose relativity was determined after the conversion had taken place. It considered that since participants were crossed over on Day 15, the doses reported may not have been doses that were titrated to relieve cravings and opioid withdrawal symptoms with minimal side-effects, but doses that were based on the pre-assumed dose conversion table.

6.24 The ESC considered it was also unclear whether the proposed dose relativity of 5.7 mg of buprenorphine in Zubsolv being equivalent to 8 mg of buprenorphine in Suboxone film would be realised in clinical practice. The availability of additional strengths of Zubsolv on the PBS may mean that the dose can be fine-tuned more so than under trial conditions, where only the 5.7/1.4 mg and 1.4/0.36 mg strengths were available in the trial. The ESC considered that if all the Zubsolv strengths which are proposed in this submission had been used in the OX219-006 trial, different dose equivalence to Suboxone may have been reached. Furthermore, the defined initiation dosing for Zubsolv may have been higher than that which would occur in practice, and knowledge of treatment allocation may have influenced the overall dose relativity reported from the trial.

6.25 In relation to bioavailability, the submission did not provide data to show that Zubsolv is bioequivalent to the same strength of Suboxone film. The submission provided data on the biopharmaceutical studies, which it stated established dose proportionality with Suboxone tablets. While the TGA clinical overview concluded that equivalent buprenorphine and naloxone exposure was achieved for the comparisons of Zubsolv and Suboxone tablets, the buprenorphine exposure provided by Zubsolv was numerically less than that provided by Suboxone tablets, with an $AUC_{0\text{-}72h}$ of approximately 88% for buprenorphine in Zubsolv compared to Suboxone tablets (i.e. 12% lower buprenorphine exposure).

6.26 The Suboxone film PI indicates that Suboxone film is not bioequivalent to Suboxone tablets (which are no longer PBS listed) with SL and buccal administration of the film resulting in 20% and 25% higher buprenorphine exposure respectively based on $AUC_{0\text{-}last}$ compared to the equivalent dose given sublingually as Suboxone tablets. Given this, the evaluation and the ESC considered that the proposed dose relativity nominated in the submission of 5.7 mg buprenorphine in Zubsolv equals 8 mg in Suboxone film was not supported by bioavailability data.

6.27 Based on the numerically lower bioavailability of buprenorphine in Zubsolv compared with Suboxone tablets, the evaluation concluded that buprenorphine bioavailability may be: 5.7 mg in Zubsolv < 8 mg in Suboxone tablet < 8 mg in Suboxone film. Alternatively, if the bioavailability of buprenorphine is accepted as being equivalent in Zubsolv and Suboxone tablets, a conclusion regarding buprenorphine bioavailability may be: 5.7 mg in Zubsolv ≡ 8 mg in Suboxone tablet < 8 mg in Suboxone film.

6.28 The bioavailability data also indicated that even if 5.7 mg buprenorphine in Zubsolv was accepted to be equivalent to 8mg buprenorphine in Suboxone tablets, this relativity cannot be assumed at all other relative doses. For example, at one quarter this strength, 1.4 mg buprenorphine in Zubsolv was not shown to be of equivalent bioavailability to 2 mg buprenorphine in Suboxone tablets.

Comparative harms

6.29 Table 7 summarises the adverse events reported in Trial OX219-006.

Table 7: Summary of safety results in Trial OX219-006

	Blinded phase Days 1-2		Open-label phase up to Day 15		Open-label phase by treatment taken at time of onset	
Endpoint	**Zubsolv N=383**	**Generic BUP N=375**	**Zubsolv N=357**	**Suboxone film N=344**	**Zubsolv N=635**	**Generic BUP/Suboxone film N=630**
Treatment-Emergent AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-Related AEs	61 (15.9%)	55 (14.7%)	42 (11.8%)	37 (10.8%)	53 (8.3%)	47 (7.5%)
Severe AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe Treatment-Related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious Treatment-Related AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEs leading to discontinuation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment related AEs reported in 5% or more patients by overall system class						
Gastrointestinal disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nervous system disorders	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

BUP = buprenorphine; AE = adverse event; N = total participants in group.
Source: Tables 2-41, 2-42 and 2-43, pp117-118 of the submission.

Clinical claim

6.30 The submission described Zubsolv as non-inferior in terms of effectiveness and non-inferior in terms of safety compared with Suboxone film in the treatment of opiate dependence.

6.31 The ESC considered that while the results were within the pre-specified non-inferiority margin of 10% for retention in treatment, the clinical claim of non-inferior comparative effectiveness presented in the submission was not adequately supported by the results of Trial OX219-006 for the following reasons:

- Retention rate at Day 15 was a short time-frame for assessment given the long-term nature of treatment.
- There was a high risk of outcomes bias in Trial OX219-006, given the open-label nature of the trial at the Day 15 endpoint and given the subjective nature of the outcome, which was not supported by objective measures of decreased drug use in the submission.
- The comparison at the Day 3 retention in treatment endpoint of OX219-006 was also subjective, and while Days 1 and 2 of the trial were blinded, the analysis involved patients initiated on Zubsolv compared to patients initiated on generic buprenorphine, rather than Suboxone Film. Zubsolv cannot be designated as non-inferior to Suboxone film based on this comparison.
- Suboxone film may also be administered buccally, and this route of administration was not tested in the trials. Therefore, any assertion regarding non-inferiority would not apply to the buccal route.

6.32 The submission's claim of non-inferior safety had the same evidentiary problems as the efficacy claim. However, the evaluation noted that the TGA clinical overview (February 2018) stated that the reported treatment-emergent adverse events with Zubsolv were known events consistent with the current prescribing information for the treatment of opioid dependence. The ESC considered the claim that Zubsolv is non-inferior in terms of safety compared with Suboxone was likely to be reasonable.

6.33 The PBAC considered that the claim of non-inferior comparative effectiveness was not adequately supported by the data.

6.34 The PBAC considered that the claim of non-inferior comparative safety compared with Suboxone film was reasonable.

Economic analysis

6.35 The submission presented a cost-minimisation analysis, however this is only reasonable if the PBAC were to accept the claim that Zubsolv has non-inferior effectiveness and safety compared with Suboxone film.

6.36 The submission estimated that the equi-effective doses were Zubsolv 5.7 mg buprenorphine is equal to 8 mg buprenorphine in Suboxone film (administered sublingually), with the cost-minimisation analysis including drug costs only. As discussed above, this dose relativity was not considered to be supported by the bioavailability data presented and the claim relied on the results from Trial OX219-006. The dose relativity was pre-assumed for dose conversion in Trial OX219-006 and the dosing titration schedule and the conversion of doses used in the trial may have influenced the mean doses that patients were receiving.

6.37 The proposed pricing for Zubsolv was based on [redacted] pricing of Zubsolv 5.7/1.4 mg to Suboxone film 8/2 mg and Zubsolv 1.4/0.36 mg to Suboxone film 2/0.5 mg. The other strengths of Zubsolv were priced based on [redacted] price per mg extrapolation, such that the 11.4/2.9 mg strength is [redacted] the price of the 5.7/1.4 mg strength, and the 2.9/0.71 mg strength is [redacted] the price of the 1.4/0.36 mg strength. The 0.7/0.18 mg strength is priced at [redacted]% of Zubsolv 1.4/0.36 mg and the 8.6/2.1 mg strength is priced [redacted] of the Zubsolv 5.7/1.4 mg and 11.4/2.9 mg strengths (see Figure 1). The PBAC previously considered that it would be appropriate for the price per mg of new strengths of Suboxone film to be linearly extrapolated from the prices of the currently listed strengths (Suboxone film November 2014 PSD, para 7.4).

Figure 1: Zubsolv price derivation overview

[redacted]

Source: Figure 3-1, p144 of the submission

6.38 The evaluation considered that [redacted] pricing for the 1.4/0.36 mg formulation of Zubsolv to the 2/0.5 mg formulation of Suboxone film was (i) not supported by any clinical evidence (other than when both doses were used as 'top-ups'; and (ii) the TGA clinical overview indicated that the lower Zubsolv strength 1.4/0.36 mg does not provide [redacted] exposure to Suboxone tablets 2/0.5 mg, with geometric mean ratios indicating approximately 20% lower buprenorphine exposure and 35% lower naloxone exposure'.

Drug cost/patient/28 days

6.39 The drug cost per patient for Zubsolv and Suboxone estimated in the submission are presented in Table 8. The submission estimated the drug cost for Zubsolv for 28 days based on an average daily dose of [redacted] mg of buprenorphine equivalent. The dose distribution used to calculate this average dose was based on patients' Suboxone film doses on Day 29 in Trial OX219-006, with conversion of the doses to equivalent Zubsolv doses being based on the dose relativity of 8 mg buprenorphine in Suboxone film equals 5.7 mg in Zubsolv. The estimated cost of Zubsolv using this approach for 28 days was $[redacted] (weighted based on assumed use of the different formulations to make up the required doses). This compared to $273 for Suboxone film using the same dose distribution, and based on an estimated average daily dose of 16.01 mg of buprenorphine per day.

Table 8: Drug cost per patient for Zubsolv and Suboxone film

	Zubsolv		Suboxone film	
	Trial (Day 29)	Financial estimates	Trial (Day 29)	Financial estimates
Mean dose buprenorphine	[redacted] mg	[redacted] mg	16.01mg	16.01mg
Cost/patient/month	$[redacted]	$[redacted][b]	$273	$179 – $184[b]
Cost/patient/year	$[redacted][a]	$[redacted][c]	$3,553[a]	$2,145 – $2,203[c]

Source: compiled during the evaluation

[a] estimated as cost/month * 365/28

[b] estimated as cost/patient/year /12

[c] estimated as PBS/RPBS cost per year/number of patients (see Table 9)

Estimated PBS usage & financial implications

6.40 This submission was not considered by DUSC. The submission used a market share approach, with an epidemiological approach also used to verify patient numbers. Uptake was assumed based on sponsor projections based on estimated patient numbers derived from extrapolated curves of IMS-iQvia historical Australian Pharmaceutical Industries (API) and Australian Hospital Industries (AHI) data on buprenorphine/naloxone sales. The ESC considered that converting IMS-iQvia sales volumes to predict patient numbers was problematic and the assumption of linear market growth was unsubstantiated.

6.41 The submission based its analyses on estimating the total mg buprenorphine administered via Suboxone film that would be replaced by Zubsolv using a ratio of 8:5.7 and estimating how the doses would be achieved based on the varying formulations. The submission also estimated that patients would require 1.75 Zubsolv tablets/day versus 2.43 Suboxone films/day based on Day 29 dosing in Trial OX219-006. The ESC considered relative market share was difficult to predict as there would not only be initiators, but also patients switching treatments, and the impact of the recent listing of buprenorphine modified release injection had not been considered in the estimates. However, the ESC considered that market growth as a result of listing Zubsolv would be unlikely. The submission's estimated use and financial implications of listing Zubsolv are presented in Table 9.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Zubsolv						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$0	$0	$0	$0	$0	$0
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for Suboxone film						
Number of scripts dispensed[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Copayments	$0	$0	$0	$0	$0	$0
Cost to PBS/RPBS less copayments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**	**-$[redacted]**

[a] Assuming approximately 14 scripts per year as estimated by the submission

[b] Assuming approximately 19 scripts per year as estimated by the submission

Source: Section 4 Workbook provided with the submission; 4a worksheet, Summary worksheet

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000 and a net saving to the PBS/RPBS would be less than $10 million.

6.42 In converting total mg buprenorphine administered via Suboxone film that would be replaced by Zubsolv, the average number of scripts per patient in Year 1 were underestimated for the proposed less than 10,000 patients assumed to be treated (13.8 Zubsolv and 19.1 Suboxone film scripts, where this would be expected to be 22.8 (1.75/month) and 31.6 (2.43/month) scripts annually, respectively) assuming 100% adherence. Perfect adherence was considered unlikely, but script numbers per patient were still underestimated when assuming 61% would remain on therapy for 12 months and the remainder for 3 months (an assumption made by the submission on estimating patient numbers from Suboxone film units sold). Thus, the estimates provided in the submission were considered to be unreliable.

6.43 Based on the proposed prices, the submission estimated net savings to the Government. All costs and potential cost savings were based on (i) assumed non-inferiority of Zubsolv versus Suboxone film; (ii) assumed dose relativity of buprenorphine of 5.7 mg in Zubsolv versus 8 mg in Suboxone film and (iii) that the doses observed in Trial OX219-006, with two available strengths of Zubsolv, would occur in clinical practice with six available strengths. The ESC considered that each of these issues are unresolved. The savings were also dependent on the assumption that the majority of patients would be treated with the 11.4/2.9 mg formulation of Zubsolv (only this and the 8.6/2.1 mg formulation offer a relative reduced price compared with Suboxone film).

6.44 Sensitivity analysis conducted during the evaluation, assuming 20% additional Zubsolv would be required to get equivalent dosing to Suboxone film (based on the dose relativity discussed above), resulted in a net cost to the PBS each year. The PSCR argued that at worst the 20% reduced bioavailability only applies to the lowest strengths and therefore a net cost to the PBS was not a plausible outcome. The ESC agreed with the PSCR that this assumption should only be applied to the three lowest doses but noted that the predicted cost saving relies on relatively more of the higher strengths being prescribed.

Quality Use of Medicines

6.45 The submission considered that Zubsolv would offer patients an alternate product that might suit them better than Suboxone film, leading to better treatment retention. The submission claimed that the six different strengths of Zubsolv (compared with currently listed two strengths of Suboxone film) provides better scope for titration which would reduce administration times and dosing error, and that the lowest strength would lead to improved cessation of OST for patients. The ESC considered this to be unsubstantiated, particularly since the key clinical trial trials only utilised two strengths of Zubsolv. More rapid dissolution of Zubsolv, compared with Suboxone film could result in reduced supervision burden.

6.46 The evaluation and the ESC noted that the buccal formulation of Suboxone film (compared with the tablet formulation of Zubsolv which could be crushed) can help reduce the possibility of misuse and diversion if dosing is supervised (due to the formation of a gel in the mouth that can be difficult to remove).

6.47 In terms of quality use of medicine harms, the submission noted that there is the possibility of confusion to occur with two types of buprenorphine/naloxone formulations on the market, especially since they are not interchangeable at a patient level. The submission highlighted that the Sponsor is committed to provide ongoing education for Zubsolv and the PSCR stated that switching is discouraged in the PI. The ESC considered that the submission did not provide sufficient details about these education activities. The ESC considered that the possibility of confusion leading to incorrect dosing of patients is a significant quality use of medicines issue, particularly given the number of different strengths of Zubsolv (with the strengths presented with up to two decimal places). The ESC considered that listing Zubsolv would require updates to clinical guidelines and education for prescribers which may not be justified without a compelling clinical need for an additional form of buprenorphine/naloxone.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC did not recommend the listing of buprenorphine with naloxone sublingual tablets (Zubsolv®) for the treatment of patients with opioid dependence on the basis that the clinical need for Zubsolv was unclear, non-inferior clinical effectiveness of

Zubsolv to the nominated comparator (Suboxone film) was not demonstrated and the equi-effective doses were uncertain. The PBAC further considered there were significant quality use of medicines concerns relating to dose titration issues should patients switch therapies, as well as prescriber confusion regarding strengths leading to incorrect dosing of patients.

7.2 The PBAC considered that the clinical need for Zubsolv was low given the availability of other strengths of buprenorphine with naloxone on the PBS, and the recent PBS listing of buprenorphine modified release injection, which a proportion of patients are likely to transition to following stabilisation on daily buprenorphine with naloxone.

7.3 The PBAC considered the nominated main comparator, buprenorphine/naloxone film (Suboxone film) was appropriate as both drugs have the same comparator and patient population. However, it also considered methadone, buprenorphine (Subutex) and the individual components (buprenorphine and naloxone) were also comparators. The cost of methadone, buprenorphine, and the combined cost of the individual components (buprenorphine and naloxone) are all less costly than the requested price for Zubsolv.

7.4 The PBAC considered the data presented did not adequately establish non-inferiority between Zubsolv and Suboxone film. In this regard, the PBAC noted that the duration of the key trial (OX219-006) to be too short to support the primary outcome of treatment retention and the risk of bias of the open label trial was high. The PBAC noted the supplementary data provided in the pre-PBAC response provided an objective measure of the impact of Zubsolv and Suboxone on changes in illicit drug use via the UDS on Day 3 and Day 15, but these data were not considered during the evaluation. The PBAC considered that, while retention in treatment was an important outcome, the clinical evidence from a longer trial supported by objective measures of decreased drug use would have provided greater support to the clinical claim for Zubsolv.

7.5 The PBAC noted the bioavailability comparison presented in the TGA clinical overview and the product information (PI) for Zubsolv only included tablet form of Suboxone, which is no longer PBS listed. It also noted the Suboxone PI states the film and tablet forms are not bioequivalent (buprenorphine exposure of the film is 20% to 25% higher compared to the tablets). Additionally, it noted the TGA clinical overview indicated buprenorphine exposure of Zubsolv was around 12% lower compared to Suboxone tablets. Based on this, the PBAC considered the proposed dose relativity of the submission was unsupported by bioavailability data, as 5.7 mg in Zubsolv was likely to be equi-effective to less than 8 mg Suboxone tablet, and therefore to significantly less than 8 mg Suboxone film.

7.6 The PBAC noted that the key trial, OX219-006, only utilised two of the proposed six doses of Zubsolv, however the PI of Zubsolv indicated that dose equivalence to Suboxone tablet changed across doses. The PBAC considered that even if 5.7 mg

buprenorphine in Zubsolv was accepted to be equivalent to 8 mg buprenorphine in Suboxone tablets, this relativity could not be assumed at across all doses. Both of the PBAC and the ESC considered that pre-assumed dose relativity (5.7:8 or 1:1.4) prior to trial commencement may have also influenced the doses patients were taking, and if all the Zubsolv strengths which are proposed in this submission had been used in the OX219-006 Trial, different dose equivalence to Suboxone may have been reached.

7.7 Overall, the PBAC considered the dose equivalence between Zubsolv and the comparator to be uncertain based on the available bioavailability data to Suboxone tablet, a lack of direct bioavailability evidence between Zubsolv and Suboxone film, and issues with dosing methodology used in the key study.

7.8 The PBAC considered that the cost savings estimated by the submission were not likely to be realised because (i) the claim of non-inferiority of Zubsolv versus Suboxone film was not adequately supported by the data; (ii) buprenorphine of 5.7 mg in Zubsolv is likely to be equi-effective to less than 8 mg buprenorphine in Suboxone film; and (iii) the majority of patients would be treated with six available strengths in clinical practice, but only the 11.4/2.9 mg and the 8.6/2.1 mg formulations of Zubsolv offer a [redacted] price compared with Suboxone film.

7.9 The PBAC recalled at its November 2014 meeting it considered that it was appropriate for price-per-mg of Suboxone film to be linearly extrapolated from currently listed strengths (paragraph 7.4, Suboxone Public Summary Document, November 2014 PBAC meeting). The PBAC considered that the submission did not adequately justify the proposed [redacted] pricing structure for Zubsolv.

7.10 The PBAC noted that the Sponsor committed to provide ongoing education for Zubsolv, however the PBAC considered that the submission did not provide sufficient details about these education activities. The PBAC considered that listing of the new form and strengths of the drug, unclear dose equivalence and the differences in bioavailability between Zubsolv and Suboxone film would have significant quality use of medicines implications relating to dose titration issues should patients switch therapies, as well as prescriber confusion regarding strengths leading to incorrect dosing of patients. It also noted Zubsolv potentially had a higher abuse potential than Suboxone film, which it considered a further QUM issue to be addressed.

7.11 The PBAC noted that listing Zubsolv would require updates to clinical guidelines and education for prescribers and considered that listing on the PBS may therefore not be sufficiently justified without a compelling clinical need for an additional form of buprenorphine/naloxone.

7.12 The PBAC advised that any resubmission for buprenorphine with naloxone (Zubsolv) should consider the following:

- Address the uncertainty with the claim of non-inferior comparative effectiveness discussed in paragraph 7.4, such as with supportive objective

measures of decreased drug use ; and

- Address the uncertainty regarding the dose equivalence to the comparator.
- Demonstrate a compelling clinical need for another form of buprenorphine/naloxone, in the context of the significant updates to clinical guidance and education of prescribers that would be required to mitigate the potential quality use of medicines issues (as identified in paragraph 7.10).

7.13 The PBAC noted that this submission is eligible for an Independent Review.

Outcome:
Rejected

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The Sponsor looks forward to continuing to work with the PBAC and the Department to make Zubsolv available for Australian patients in the near future. For clarification, the Sponsor notes that mention in paragraph 6.8 regarding the dose conversion for patients on Suboxone film who were converted to Zubsolv at Day 15 in Trial OX219-006 occurred according to a fixed conversion factor (5.7 to 8mg) on the basis of the corresponding dose strengths of Zubsolv and Suboxone Film, and using the Table 4 conversions.