7.11 BUPRENORPHINE WITH NALOXONE,

Tablet (sublingual) 0.7 mg (as hydrochloride) - 0.18 mg (as hydrochloride dihydrate),
Tablet (sublingual) 1.4 mg (as hydrochloride) - 0.36 mg (as hydrochloride dihydrate),
Tablet (sublingual) 2.9 mg (as hydrochloride) - 0.71 mg (as hydrochloride dihydrate),
Tablet (sublingual) 5.7 mg (as hydrochloride) - 1.4 mg (as hydrochloride dihydrate),
Tablet (sublingual) 8.6 mg (as hydrochloride) - 2.1 mg (as hydrochloride dihydrate),
Tablet (sublingual) 11.4 mg (as hydrochloride) - 2.9 mg (as hydrochloride dihydrate),
Zubsolv®,
Mundipharma Pty Ltd.

1 Purpose of Application

1.1 The minor resubmission requested the Section 100 (Opiate Dependence Treatment Program) listing for buprenorphine/naloxone sublingual (SL) tablets (Zubsolv®), for the treatment of patients with opioid dependence.

1.2 The resubmission aimed to address issues raised by the PBAC in its November 2019 rejection of Zubsolv for this indication, and provided a revised price for the drug.

2 Background

Registration status

2.1 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 consideration

2.2 A major submission for Zubsolv was considered by the PBAC at its November 2019 meeting. The PBAC decided not to recommend the listing on the basis that the clinical need for Zubsolv was unclear, non-inferior clinical effectiveness to the nominated comparator (buprenorphine/naloxone SL film) was not demonstrated, and the equi-effective doses were uncertain.

2.3 The PBAC considered 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 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.

2.4 The PBAC also considered there were significant quality use of medicines (QUM) concerns related to switching between Zubsolv and Suboxone due to unclear dose equivalence between products and differences in bioavailability, leading to incorrect dosing of patients.

2.5 A summary of the previous submission and current minor resubmission is provided in the table below.

Table 1: Summary of the previous submissions and current resubmission

	November 2019 submission		**Current resubmission**	
Requested PBS listing	Opiate dependence. The requested restriction is consistent with that for Suboxone film, in terms of the wording of the restriction, maximum quantities and number of repeats [para 2.2]		Unchanged	
Requested price	**Zubsolv** (buprenorphine/naloxone mg)	**Proposed DPMQ**	**Revised DPMQ**	**Reduction (%) from previous submission**
	0.7/0.18	$	$	
	1.4/0.36	$	$	
	2.9/0.71	$	$	
	5.7/1.4	$	$	
	8.6/2.1	$	$	
	11.4/2.9	$	$	
Comparator	Suboxone film The PBAC [para 7.3] also considered methadone, buprenorphine and the individual components (buprenorphine and naloxone were also comparators.		Unchanged	
Clinical evidence	Key results came from the Trial OX219-006, which measured the retention in treatment at Day 3 and Day 15 as the primary clinical outcome. Other trials presented: NCT02038790 OX219-008 (extension study of OX219-006 and OX219-007)		No new clinical trial data.	
Clinical claim	Non-inferior in terms of effectiveness and non-inferior in terms of safety compared with Suboxone film in the treatment of opiate dependence. The PBAC [para 7.4] considered the data presented did not adequately establish non-inferiority between Zubsolv and Suboxone film. The reasons included: - Duration of the key trial (OX219-006) was too short to support the primary outcome of treatment retention. - The risk of bias due to the open label nature of the trial was high. - Equi-effective dose was not adequately established.		Unchanged	
Economic evaluation	The submission presented a cost-minimisation analysis based only on drug costs. The proposed equi-effective doses were 5.7mg buprenorphine in Zubsolv is equal to 8mg buprenorphine in SL Suboxone film, based on the results from Trial OX219-006. The proposed pricing for Zubsolv was based on 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 price per mg extrapolation.		Proposed equi-effective doses unchanged The Sponsor attempted to address PBAC concerns by proposing a % price reduction to the 1.4/0.36 Zubsolv tablet and a % price reduction to the 5.7/1.4 Zubsolv tablet. A price structure was derived from these two price points (Figure 1).	

	Overall, the PBAC [para 7.7] 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.	
Number of patients	The submission used a market share approach, with an epidemiological approach also used to verify patient numbers. Estimated less than 10,000 patients (10,000 – 50,000 scripts) in year 1, increasing to less than 10,000 patients (100,000 – 200,000 scripts) in year 6.	Unchanged.
Estimated net cost to PBS/RPBS	The submission estimated a net save of less than $10 million in year 1, increasing to less than $10 million in year 6, with a total of less than $10 million over the first 6 years of listing. The PBAC [para 7.8] considered that the cost savings estimated by the submission were not likely to be realised because - the claim of non-inferiority of Zubsolv versus Suboxone film was not adequately supported by the data; - buprenorphine of 5.7 mg in Zubsolv is likely to be equi-effective to less than 8 mg buprenorphine in Suboxone film; and - 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 lower price compared with Suboxone film.	The resubmission estimated a net save of less than $10 million in year 1, increasing to less than $10 million in year 6, with a total of less than $10 million over the first 6 years of listing.
QUM	Paragraph 7.10 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.	Proposed measures to address issues: • Product launch roadshow to educate key stakeholders and prescribers on Zubsolv, • Educational evening meetings for accredited prescribers, • Online learning module (for prescribers and pharmacists) with information available through the Sponsor's education platform, • Approaching Primary Health Networks (PHNs) to develop workshops for prescribers; and • Dedicated company representatives to provide information as requested by clinicians.
PBAC decision	Reject. The PBAC did not recommend the listing of buprenorphine/naloxone SL 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.	

Source: Compiled during the overview. Paragraph references for November 2019 refer to the buprenorphine with naloxone (Zubsolv) PBAC Public Summary Document.

For more detail on PBAC's view, see section 6 PBAC outcome.

3 Requested listing

3.1 The requested listing is unchanged from the original November 2019 major submission.

Add new items as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	DPMQ	Proprietary Name and Manufacturer
BUPRENORPHINE WITH NALOXONE buprenorphine 700 microgram + naloxone 180 microgram sublingual tablet buprenorphine 1.4 mg + naloxone 360 microgram sublingual tablet buprenorphine 2.9 mg + naloxone 710 microgram sublingual tablet buprenorphine 5.7 mg + naloxone 1.4 mg sublingual tablet buprenorphine 8.6 mg + naloxone 2.1 mg sublingual tablet buprenorphine 11.4 mg + naloxone 2.9 mg sublingual tablet	28	0	$[redacted] $[redacted] $[redacted] $[redacted] $[redacted] $[redacted]	Zubsolv® Mundipharma Pty Ltd

Category / Program: Section 100 – Opiate Dependence Treatment Program
Prescriber type: ☐Dental ☒Medical Practitioners ☒Nurse practitioners (SCM) ☐Optometrists ☐Midwives
Restriction Level / Method: ☒Restricted benefit
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 sublingual tablets and soluble films may therefore require a dosage adjustment.
Care must be taken to comply with the provisions of State/Territory law when prescribing this drug.
Shared Care Model: 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.
Indication: Opiate dependence
Clinical criteria: The treatment must be within a framework of medical, social and psychological treatment

4 Comparator

4.1 The nominated comparator, buprenorphine/naloxone, SL film (Suboxone®), is unchanged from the previous major submission and was considered appropriate by the PBAC at its November 2019 meeting.

For more detail on PBAC's view, see section 6 PBAC outcome.

5 Consideration of the evidence

Sponsor hearing

5.1 There was no hearing for this item as it was a minor submission

Consumer comments

5.2 The PBAC noted and welcomed the input from health care professionals (10) and organisations (3) via the Consumer Comments facility on the PBS website. The comments outlined the benefits of increasing the range of medications available for patients, including potential palatability improvements. The comments also outlined the reduced risk of diversion due to faster dissolution.

Clinical evidence

5.3 The minor resubmission did not present any new clinical evidence.

5.4 The resubmission presented urine drug screen (UDS) data from studies OX219-006 and OX219-008 to attempt to provide an objective outcome measure of decreased drug use. The resubmission considered that, as the number of patients with opiate-positive UDS was similar between Zubsolv and Suboxone and was maintained in the 24 week extension study OX219-008, the comparative efficacy between the products was supported.

Table 2: Patients with positive opiate* UDS

Trial	Outcomes	Zubsolv	Generic Buprenorphine/ Suboxone Film
OX219-006	**Patients with positive opiate* UDS, n/N (%)**		
	Day 3	[redacted]	[redacted]
	Day 15	[redacted]	[redacted]
	†**Risk difference** (positive drug screen) at Day 15*	[redacted]% (95% CI: [redacted]%, [redacted]%); [redacted]	
	†**Risk Ratio** (positive drug screen) at Day 15*	[redacted] (95% CI: [redacted], [redacted]); p=[redacted]	
OX219-006 patients in extension study OX219-008	**Patients with positive opiate* UDS, n/N (%)**		
	Week 4	[redacted]	Not applicable (all patients received Zubsolv in extension study)
	Week 8	[redacted]	
	Week 12	[redacted]	
	Week 24	[redacted]	
OX219-007 RCT comparing Zubsolv vs. generic BUP over 29 days	**Patients with positive opiate* UDS, n/N (%)**		
	Day 29 / study discontinuation	[redacted]	[redacted]
OX219-007 patients in extension study OX219-008	Week 4	[redacted]	Not applicable (all patients received Zubsolv in extension study)
	Week 8	[redacted]	
	Week 12	[redacted]	
	Week 24	[redacted]	

* Includes non-buprenorphine opiates

†Not included in the November 2019 major submission

Source: Table 2, main body of minor submission. Calculated from results in Zubsolv Major Submission Table 2-34, OX219-008 CSR Table 18 Table 14.2.6.1 provided in Attachment 1, OX219-007 CSR Table 22 provided in Attachment 2.

Economic analysis

5.5 The minor resubmission presented a cost-minimisation analysis of Zubsolv compared with Suboxone Film. The proposed equi-effective dose remained unchanged from the major submission: 5.7mg buprenorphine in Zubsolv is equi-effective to 8 mg buprenorphine in Suboxone.

5.6 At its November 2019 meeting, the PBAC considered the proposed equi-effective doses 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.

5.7 To address the PBAC concern regarding appropriateness of Zubsolv to Suboxone dose relativity used in Trial OX219-006, the resubmission noted that the 10.8mg Zubsolv buprenorphine mean dose dispensed at day 15 of Trial OX219-006 was found to be

consistent with that of extension study OX219-008 at day 1 (11.5mg buprenorphine mean dose) and week 20 (10.9mg buprenorphine mean dose). The resubmission implied that since the same dose relativity used at the day 15 cross-over point of Trial OX219-006 was also used to transition patients from the Suboxone arms of OX219-006 and OX219-007 to the single Zubsolv arm of extension study OX219-008 and, considering titration was allowed in that study, since the mean Zubsolv dose remained consistent, the dose relativity used in these studies was appropriate.

5.8 The sponsor revised its cost-minimisation analysis by applying a [redacted]% price reduction to the 5.7/1.4mg Zubsolv strength and [redacted]% price reduction to the 1.4/0.36mg Zubsolv strength compared to the prices proposed in the original submission. This was based on the [redacted]% lower bioavailability of Zubsolv to Suboxone in the lower strengths and [redacted]% lower bioavailability in the higher strengths (paragraph 6.25 and 6.38, November 2019 PBAC buprenorphine with naloxone Public Summary Document). A [redacted] pricing structure was derived from these two points, as shown in Figure 1 and Table 3.

Figure 1: Comparison between the proposed pricing structure from November 2019 major submission and the revised [redacted] pricing structure in the March 2020 minor resubmission.

[redacted]

Source: Figure 6, main body of minor submission, page 24

Table 3: Proposed Zubsolv Price Derivation

Suboxone Film (buprenorphine/ naloxone mg)			**2/0.5‡**		**8/2‡**		
PBS price (Dec 2019)			$46.20		$132.44		
Original Submission	**Zubsolv** (buprenorphine/ naloxone)(mg)	**0.7/0.18**	**1.4/0.36**	**2.9/0.71**	**5.7/1.4**	**8.6/2.1**	**11.4/2.9**
	November 2019 submission proposed pricing	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Re-Submission	Discount	[redacted]%	[redacted]%†	[redacted]%	[redacted]%†	[redacted]%	[redacted]%
	March 2020 resubmission proposed pricing	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

†Point from which [redacted] model was derived
‡Columns represent equivalent doses as proposed in original submission
Source: Table 5, page 23 of the submission

Drug cost/patient/28 days: $[redacted]

5.9 The resubmission estimated the drug cost/patient/28 days to be $[redacted], based on a 28 day script, and a revised daily dose of 8.6 mg buprenorphine in Zubsolv (equivalent to 12mg buprenorphine in Suboxone Film using the proposed dose relativity ratio of 5.7:8). The submission stated the daily dose was based on data provided by the National Drug and Alcohol Research Centre. However, the mean dose of buprenorphine in Zubsolv used in the financial estimates in the minor resubmission remained as 11.41 mg, as per the previous submission.

Estimated PBS usage & financial implications

5.10 The minor resubmission estimated a net save to the PBS of less than $10 million in Year 6 of listing, with a total net save to the PBS of over the first 6 years of listing.

5.11 The utilisation estimates were unchanged from the November 2019 submission. The ESC previously considered that converting IMS-iQvia sale volumes to predict patient numbers was problematic and the assumption of linear market growth was unsubstantiated.

5.12 The ESC previously noted that the savings estimated by the submission were dependent on the majority of patients being treated with the 11.4/2.9 mg and 8.6/2.1 mg formulations of Zubsolv (as these were the only strengths that offered a lower price compared with Suboxone film). The resubmission sought to address this issue by discounting the price of the four lower strengths by [redacted]%, [redacted]%, [redacted]% and [redacted]% respectively (see table 3).

Table 4: 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 less copayments[c]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for Suboxone						
Cost to PBS/RPBS less copayments[b,c]	$[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
[c] Section 100 Opioid Dependence Program listings do not attract patient co-payments or mark-ups.
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 is less than 10,000 patients, and a net saving to the PBS/RPBS would be less than $10 million.

Quality Use of Medicines

5.13 At the November 2019 meeting, the PBAC considered that listing 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, should patients switch therapies, as well as prescriber confusion over strengths, leading to incorrect dosing of patients. It also noted Zubsolv potentially had a higher abuse potential than Suboxone film.

5.14 The Sponsor reiterated its commitment in providing educational activities, including:

- Product launch roadshow to educate key stakeholders and prescribers on Zubsolv,
- Educational evening meetings for accredited prescribers,
- Online learning module (for prescribers and pharmacists) with information available through the Sponsor's education platform, and
- Approaching Primary Health Networks (PHNs) to develop workshops for prescribers.

5.15 At the November 2019 PBAC meeting, the PBAC considered the proposed listing would require updates to clinical guidelines, and the resubmission would need to present a compelling clinical need for further buprenorphine/naloxone presentations to justify such changes. To address this, the minor resubmission stated the sponsor would engage with relevant regulatory bodies for the updates to the relevant clinical guidelines. The resubmission claimed there is a compelling clinical need, by noting previous interruptions to supply of Suboxone (in May 2016 and June 2019) and implied an additional presentation would ensure continuous supply, and the recent PBAC recommendation of depot presentations indicates there is a clinical need for further presentations. However, as switching between products is challenging, the availability of an alternative product may not contribute significantly to managing future supply shortages.

5.16 The resubmission reiterated that Zubsolv was less likely to be diverted due to its fast dissolution time.

Clinical Pharmacologist Report

5.17 To address the QUM concerns raised by the PBAC, the Sponsor commissioned a clinical pharmacologist report. The report argued that incorrect prescribing and substitution of Zubsolv was not expected to be common due to it only being prescribed by a small, educated and specialised group of prescribers in a supervised clinical setting.

5.18 It noted that Zubsolv is not interchangeable with different buprenorphine products. However, it claimed the risks related to interchangeability were likely to be small in clinical practice due to increased awareness of risks through the PI and other literature, knowledge of products and other opioid replacement therapies and careful monitoring in the prescribing community.

5.19 The report noted there were different bioavailabilities among Zubsolv strengths, and that multiples of the three lower dose presentations should not be used to substitute for any of the three higher doses by the pharmacist without consulting the prescriber.

5.20 The report claimed the range of Zubsolv strengths, compared with Suboxone films, might allow better titration and weaning, increasing the potential for treatment success.

For more detail on PBAC's view, see section 6 PBAC outcome.

6 PBAC Outcome

6.1 The PBAC did not recommend the listing of buprenorphine with naloxone sublingual tablets (Zubsolv®) for the treatment of patients with opioid dependence. The PBAC considered that no further evidence was provided in the resubmission to address the previous concerns raised regarding the uncertain equi-effective dose to Suboxone, unclear clinical need and significant quality use of medicines issues.

6.2 The PBAC noted the single arm extension study (OX219-008) that reported urine drug screen results up to 24 weeks, however considered that the updated data did not provide more certainty of non-inferiority beyond 15 days. Therefore, the PBAC maintained that the data presented did not adequately establish non-inferiority between Zubsolv and Suboxone film.

6.3 The PBAC noted the revised pricing structure proposed in the resubmission, but did not accept that this was sufficient to overcome the uncertainties in relation to dose equivalence between Zubsolv and Suboxone that was outlined in the November 2019 consideration.

6.4 The PBAC considered that, while the resubmission highlighted supply interruptions of Suboxone as a reason to support the listing of Zubsolv, this did not demonstrate a compelling clinical need given the challenges associated with switching between formulations. The PBAC considered the recent recommendations to list weekly and

monthly injection formulations of buprenorphine on the PBS would likely increase alternative treatment options.

6.5 The PBAC considered that overall, the resubmission did not address outstanding QUM concerns in relation to dose equivalence, switching between products, and prescriber confusion between strengths.

6.6 The PBAC considered the claim that the fast dissolution rate of Zubsolv would lead to reduced diversion to be uncertain, as there was no clinical evidence provided in support of this.

6.7 The PBAC noted that this submission is eligible for an Independent review.

Outcome:
Rejected

7 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.

8 Sponsor's Comment

The sponsor had no comment.