5.12 NALOXONE

Nasal spray containing naloxone hydrochloride dihydrate, 1.8 mg per actuation (single use), 2, Nyxoid®, Mundipharma Pty Ltd

1 Purpose of Application

1.1 The minor submission sought to list an intranasal (IN) presentation of naloxone as an unrestricted benefit for use in opioid overdose.

2 Requested listing

2.1 The submission requested an unrestricted, General Schedule listing of naloxone. The submission also indicated a willingness for a dual General Schedule and Section 100 listing if considered appropriate by the PBAC.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NALOXONE Nasal spray containing naloxone hydrochloride dihydrate 1.8mg, 2	1	0	Nyxoid Mundipharma Pty Ltd

Category / Program:	General Schedule
Prescriber type:	☒Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	-
PBS Indication:	-
Restriction:	☒Unrestricted ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined

2.2 The requested unrestricted listing is consistent with PBS listings of other naloxone formulations.

2.3 The current naloxone listings include dental, nurse and medical practitioner prescriber types. This has been proposed for the new formulation.

2.4 The submission proposed a maximum quantity of one pack containing two single use nasal sprays. The pharmacokinetic study demonstrates the average maximum plasma concentration is achievable with two sprays and therefore the requested maximum quantity was reasonable.

2.5 The submission did not request a prescriber bag listing, which is consistent with the current listing of the prefilled syringe form of naloxone.

2.6 Naloxone should be exempt from the Early Supply Rule as it is used for short term or episodic use, there is a clinical imperative for use, and the dosage regimen is not standard. Other formulations of naloxone are currently exempt from the PBS Early Supply Rule.

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

3 Background

3.1 IN naloxone is TGA registered with the following indication:
Nyxoid is intended as part of the emergency treatment for known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression in:

- the home or other non-medical setting, or
- a health facility setting.

For this reason, Nyxoid should be carried by persons at risk of, or likely to witness, such events.

3.2 IN naloxone is easy to administer with minimal training, does not carry risk of needle stick injury, and shows similar early-uptake pharmacokinetics to intramuscular administration.

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

4 Current Situation

4.1 In 2016, there was an estimated 12,602 opioid overdoses and 1,359 opioids related deaths in Australia (Penington Institute, 2018).

4.2 Naloxone is the only approved antidote to opioid overdoses. It is demonstrated to be effective and safe to use with very low abuse potential and has an established history of use.

4.3 Currently-listed naloxone presentations include ampoules (400 microgram/mL injection, 5 x 1 mL ampoules or 10 x 1 mL ampoules) and prefilled syringes (1 mg/mL injection, 2 mL syringe) for either intramuscular (IM) or intravenous (IV) administration.

4.4 Naloxone was recently rescheduled from Schedule 4 (Prescription Only Medicine) to Schedule 3 (Pharmacist Only Medicine) under the TGA *Poisons Standard*, enabling easier access in the community (take-home) setting. This was expected to reduce harm and fatalities due to overdoses in the community.

4.5 Table 1 shows the PBS items processed for all non-prescriber bag items showing relatively low uptake of both ampoules (currently 675 per year) and prefilled syringes (currently 565 per year).

Table 1: PBS and PRB data 2016 to 2018 non-prescriber bag naloxone items processed.

Item Code	Schedule	Year			Total
		2016	2017	2018	
10783M (400 mcg/mL injection, 5 x 1 mL ampoules)	**PBS + RPBS**	221	691	684	1,596
	PBS	220	673	675	1,568
	RPBS	1	18	9	28
11078C (1 mg/mL injection, 2 mL syringe)	**PBS + RPBS**		144	565	709
	PBS		143	562	705
	RPBS		1	3	4
Total	**Total**	**220**	**817**	**1240**	**2277**

4.6 The submission noted injectable presentations may pose several issues including: the person administering the drug requires training; some pharmacists may be reluctant to supply over the counter; and there have been recent supply availability issues with the IM formulation.

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

5 Comparator

5.1 The minor submission nominated naloxone 400 microgram/mL injection, 5 x 1 mL ampoules as the primary comparator.

5.2 The PBAC considered that naloxone 2 mg in 2 mL pre-filled syringe was more appropriate, as this presentation syringe was intended for bystander administration and was therefore most likely to be replaced in practice

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 as it was a minor submission.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (4), health care professionals (38) and organisations (9) via the Consumer Comments facility on the PBS website. The comments described a range of benefits associated with IN naloxone use in acute opioid overdose including ease of administration, increased accessibility and availability, all of which aim to reduce deaths from opioid overdose.

Clinical trials

6.3 The submission did not include any direct clinical trials. Efficacy has been inferred based on pharmacokinetic studies. The submission presented one study (Table 2) to demonstrate comparative pharmacokinetics of IN naloxone (1mg, 2mg and 4mg), IM (0.4mg) and IV (0.4mg) routes using healthy volunteers (n=38).

Table 2: Trials and associated reports presented in the submission

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Direct randomised study		
EudraCT: 2015–004493-15 McDonald et al. 2017	Pharmacokinetics of concentrated naloxone nasal spray for opioid overdose reversal: Phase I healthy volunteer study	Addiction vol. 113, 3 (2017): 484-493.
Indirect randomised study		
Kelly et al. 2005	Randomised trial of IN versus IM naloxone in prehospital treatment for suspected opioid overdose.	Med J Aust 2005; 182 (1): 24-27
Kerr et al. 2009	Randomized controlled trial comparing the effectiveness and safety of IN and IM naloxone for the treatment of suspected heroin overdose	Addiction. 2009 Dec;104(12):2067-74

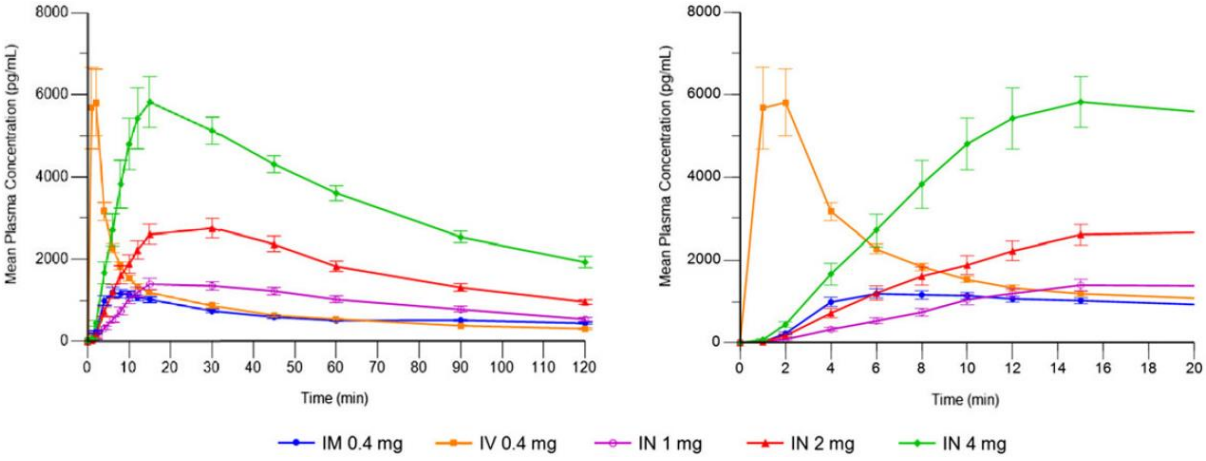
Comparative effectiveness

6.4 The mean plasma concentrations over time plots for naloxone in IM, IV and IN administration routes from the pharmacokinetic of McDonald et al (2017) are shown in Figure 1.

6.5 The 2mg IN dose achieved concentrations equivalent to 50% of maximum concentration ($C_{50\%}$) of the IM reference at 6 minutes, i.e. within 2 minutes of the IM reference, suggesting that early IN and IM naloxone plasma concentrations do not differ greatly. The 2mg IN treatment reached twice the naloxone plasma concentration of the 0.4mg IM treatment at 15 minutes then maintained more than twice this concentration over the remainder of the 120 minutes.

6.6 A meta-analysis by WHO (2014) was provided in the submission. This collated data from two randomised trials in Victoria (Kerr et al, 2009 and Kelly et al, 2005), and found no significant difference between 2mg IN and 2mg IM naloxone in terms of time to opioid overdose reversal and adverse events (minor, major, and acute withdrawal reactions). However, the analysis indicated that rescue doses were required more often after IN administration (81 per 1000 for IM, 213 per 1000 for IN).

Figure 1: Mean plasma naloxone concentrations (observed values): dosing to 120 minutes (left) and dosing to 20 minutes (right)



Source: McDonald et al 2017, p488.

Clinical claim

6.7 The submission claimed non-inferior comparative effectiveness and superior comparative safety of IN naloxone (2 x 1.8mg) compared with naloxone ampules (5 x 400mcg). While no comparative safety data was provided in the submission, the claimed safety benefits relate to the manner of administration, such as reduced time to administer versus injectable naloxone, eliminated risk of needle-stick injuries, and reduced risk of acute withdrawal-related risks to responders.

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

Economic analysis

6.8 The submission proposed an ex-manufacturer price equal to the approved ex-manufacture price of naloxone hydrochloride 400 microgram/mL injection, 5 x 1 mL ampoules (PBS item 10783M) and the cost of administering IM naloxone, based on contents of the NSW Users and AIDS Association (NUAA), Naloxone Kit. The cost-analysis is presented in Table 3.

6.9 Ancillary equipment is not a cost to the PBS for IM administration of naloxone. The Pre-PBAC response highlighted that this approach was consistent with the Manual of Resource Items and Associated Unit Costs 2016 (Section 4.4), which states that economic evaluation 'uses a price equivalent to the average price charged to the consumer'.

6.10 The comparator, naloxone vials, include five vials per pack and not all vials in the pack will be used per treatment. This may impact the equi-effective dose in the economic analysis.

Table 3. Cost-analysis summary for IM naloxone administration.

NUAA Kit:	Purchasing Costs			Per kit	
	Cost per pack	Qty	Item cost	Qty	Total cost
Swabs	$[redacted]	200	$[redacted]	2	$[redacted]
Disposable gloves	$[redacted]	100	$[redacted]	2	$[redacted]
Sharps container	$[redacted]	1	$[redacted]	1	$[redacted]
Syringes	$[redacted]	100	$[redacted]	2	$[redacted]
Face shield	$[redacted]	1	$[redacted]	1	$[redacted]
Sub-Total					**$[redacted]**
Naloxone (5 vials) PBS item 10783M- ex manufacturer price					$48.89
Total cost of administering naloxone IM					**$[redacted]**

Source: 'Nyxoid - 2 - PBAC submission - 14 Dec 2018', p15.

Cost/patient/treatment: $[redacted] (DPMQ).

6.11 Applying the relevant mark-ups and dispensing fees for a General Schedule item, the proposed dispensed price for maximum quantity (DPMQ) for one pack of two naloxone nasal sprays would be $[redacted].

6.12 Naloxone prefilled syringes (Prenoxad®, 1 mg/mL injection, 2 mL prefilled syringe, providing 5 doses) is currently approved under section 19a of the *Therapeutic Goods Act 1989*, and is PBS listed with a DPMQ of $57.69 per syringe, reducing to $48.27 on 1 April 2019, following a price disclosure price reduction.

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

Estimated PBS usage & financial implications

6.13 The minor submission estimated a net cost to the PBS of less than $10 million in Year 6 of listing, with a total net cost to the PBS of less than $10 million over the first 6 years of listing. This is summarised in Table 4.

6.14 The net cost to the PBS includes reduced costs from other naloxone presentations being displaced as well as IN naloxone market growth. The submission assumes the following to derive the data:

- A 35% growth in naloxone ampoules is assumed for 2019 based on past PBS Services data (from 2016/17 to 2018/19) and 25%, 15% and 10% thereafter is assumed for subsequent years where the decline in growth is anticipated based on the recent withdrawal of the prefilled syringe Naloxone presentation, Minijet.
- Nyxoid is assumed to displace 10% of naloxone ampoule prescriptions in the first year, rising to 45% in years 5 and 6, and 5%, of prefilled syringe prescriptions in the first year, rising to 22.5% in years 5 and 6.

6.15 The submission has not provided data to substantiate the growth and displacement estimates of naloxone ampules and IN naloxone respectively.

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 scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of Nyxoid						
Cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Cost to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Estimated financial implications for other naloxone presentations						
Savings to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Savings to PBS/RPBS less co-payments	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS/RPBS	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Source: Adapted from Table 6 of minor submission, page 20.

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

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

7 PBAC Outcome

7.1 The PBAC recommended the dual General Schedule and Section 100 listing of intranasal naloxone on a cost-minimisation basis to injectable naloxone, at equivalent cost per treatment. The PBAC considered that there was a public health need to increase use of naloxone, as outlined in the consumer comments received, and considered that while the clinical benefits of IN naloxone were similar to injectable naloxone, availability of the IN formulation could contribute to increasing use due to ease of administration.

7.2 The PBAC agreed with the submission that IN naloxone was likely to be easier to administer than injectable forms in some scenarios, did not carry any risk of needle

stick injury, and may contribute to improved uptake as the person administering the drug in an emergency does not require specific training.

7.3 The PBAC considered that an unrestricted benefit listing was appropriate as this is consistent with PBS listings of other naloxone formulations. The PBAC acknowledged IN naloxone exhibited different maximum plasma concentrations per dose compared with injectable forms, however it considered two naloxone nasal sprays to be sufficient in the take-home setting, and therefore that the maximum quantity of one pack with no repeats was appropriate. The PBAC considered that naloxone nasal spray would be suitable for continued dispensing to further improve subsidised medicine access for some patients.

7.4 The PBAC considered that, while the nominated comparator 400 mcg/mL injection ampoules would be replaced to some extent in practice, this is predominantly administered by health professionals and is less appropriate as a comparator in the "take home" setting. As such, the PBAC considered that the more appropriate comparator was naloxone 1mg/mL prefilled syringe as this presentation syringe was intended for bystander administration and was therefore most likely to be replaced in practice.

7.5 The PBAC were satisfied that, despite slight pharmacokinetic differences, the clinical benefit of IN naloxone was comparable to the clinical benefit of injectable naloxone. While the clinical claim of superior safety is not quantifiable, the PBAC considered it reasonable that there were likely to be safety benefits of IN naloxone including a reduction in needle stick injury and a potential reduction in withdrawal-related harms.

7.6 The PBAC did not consider it appropriate to include the costs of ancillary equipment cost in the cost-minimisation, as these are not PBS costs. As naloxone pre-filled syringe was considered the most appropriate comparator, the PBAC considered that the cost-minimisation should be based on the equivalence of one pack of IN naloxone (containing 2 x 1.8mg doses) to one pre-filled syringe (containing up to 5 x 0.4mg doses).

7.7 The PBAC noted that the estimated PBS usage and financial implications presented in the submission were uncertain, but agreed with the submission that the introduction of IN naloxone was likely to result in increased uptake of naloxone in the community setting and displace some existing use of naloxone pre-filled syringes. The PBAC considered that any such increased use of naloxone would contribute to reducing the current high rates of harm from opioid overdose.

7.8 The PBAC recommended that naloxone should not be treated as interchangeable with any other drugs.

7.9 The PBAC advised that IN naloxone is suitable for prescribing by nurse practitioners and dental practitioners.

7.10 The PBAC recommended that the Early Supply Rule should apply.

7.11 The PBAC noted that this submission is not eligible for an Independent Review as it

received a positive recommendation.

Outcome:

Recommended

8 Recommended Listings

8.1 Add new item:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NALOXONE			
Nasal spray containing naloxone hydrochloride dihydrate 1.8mg, 2	1	0	Nyxoid Mundipharma Pty Ltd

Category/Program	General Schedule
Prescriber type:	☒Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
PBS Indication:	-
Restriction:	☒ Unrestricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required – Emergency ☐Authority Required - Electronic ☐Streamlined

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

The sponsor had no comment.