

## 7.11 MIDAZOLAM,

**Oromucosal solution in pre-filled syringe 2.5 mg in 0.25 mL,**

**Oromucosal solution in pre-filled syringe 5 mg in 0.5 mL,**

**Oromucosal solution in pre-filled syringe 7.5 mg in 0.75 mL,**

**Oromucosal solution in pre-filled syringe 10 mg in 1 mL,**

**Zyamis<sup>®</sup>,**

**Clinect Pty Ltd**

### 1 Purpose

- 1.1 The early re-entry resubmission requested a Section 85, Authority Required (telephone/online) listing for midazolam oromucosal solution in pre-filled syringes (2.5 mg, 5 mg, 7.5 mg and 10 mg), for the treatment of generalised convulsive status epilepticus (GCSE) in patients with epilepsy aged over 6 months and a high risk of status epilepticus. The resubmission also requested listing in the Prescriber Bag Schedule for the each of the four dose presentations (2.5 mg, 5 mg, 7.5 mg and 10 mg).
- 1.2 The resubmission was based on PBAC advice from the July 2022 meeting (see Table 1).

**Table 1: Summary of key matters to be addressed**

Matter of concern	Resubmission
<p><b>1. Revised PBS criteria (paragraph 7.3).</b>                      The PBAC considered that the restriction criteria required further consultation. The proposed restriction was broad, but other options would include restricting the listing to a highly treatment resistant group of patients (who may use up to 2-4 doses per week). Potential for PBS access for other settings (e.g. Doctors' and Epilepsy Nurse Practitioners' bags, for patients without established diagnosis of epilepsy) should also be considered. Further detail regarding the intended use should be considered, which may include specifying that midazolam should be administered after five minutes from seizure onset.</p> <p>The PBAC advised that the proposed listing should be modified based on expert clinical advice. This should consider revision of the maximum quantity, taking into</p>	<p>The resubmission:</p> <ul style="list-style-type: none"> <li>(i) Requested a Section 85 listing with restrictions very similar to the July 2022 submission.</li> <li>(ii) Requested a Prescriber Bag listing for Medical Practitioners only (proposed that the listing should not apply for Nurse Practitioners).</li> </ul>

Matter of concern	Resubmission
<p>account the likely dose requirements, and frequency of attacks as well as issues of safety, and desirability of minimising wastage from the expiry of dispensed medicines.</p>	
<p><b>2. Price reduction to achieve a cost-effective listing (paragraph 7.11).</b>                      The submission presented a cost-consequences analysis based on the submission's claim that midazolam oromucosal solution improves the accurate and timely administration of midazolam during an acute health emergency. The PBAC noted that a number of benefits were described in the consumer comments, the ESC advice, the Pre-Sub-Committee Response (PSCR) and the pre-PBAC response, including reduced time to administration of the dose, reduced risk of incorrect dosing and ease of administration for carers during the acute stressful situation of a seizure. However, the PBAC agreed with the ESC that the cost-consequences analysis presented by the submission was incomplete and largely uninformative, because it did not model any difference in outcomes between the proposed medicine and comparator. The PBAC considered the benefits associated with the administration were likely clinically meaningful and important for carers, however the proposed price premium over midazolam hydrochloride (DPMQ of \$ [REDACTED] versus \$40) was not justified.</p> <p>The PBAC noted the cost-effective price for midazolam oromucosal solution will depend on the revised population as defined by the restriction, and the maximum quantity and hence likely wastage, however considered that a price that is more than approximately twice the price of midazolam hydrochloride is unlikely to be cost-effective.</p>	<p>The resubmission:</p> <p>(i) Proposed a dispensed price of \$ [REDACTED] for 2 pre-filled syringes of midazolam oromucosal solution, which was [REDACTED]% lower than the dispensed price proposed in July 2022 (\$ [REDACTED] for 2 pre-filled syringes). The proposed price remains considerably higher than the price of midazolam hydrochloride ampoules which are currently used off label for this indication (DPMQ = \$39.91 for midazolam 5 mg/mL injection, 10 x 1 mL ampoules in the Prescriber Bag Schedule for PBS Item 10178Q).</p>
<p><b>3. Revised financial estimates incorporating changes to the restriction and price (paragraph 7.12).</b>                      The PBAC noted that the utilisation estimates provided in the submission appeared low in comparison to the utilisation statistics reported by the National Paediatric Medicines Forum which were submitted via consumer comments. While the submission had assumed a single syringe would be dispensed per script, the PBAC considered this may not meet the needs of a subgroup of the patients with frequent seizures that may require treatment in the range of 2 to 4 doses per week. The PBAC considered that revised financial estimates would be required to incorporate changes to the restriction and price.</p>	<p>The resubmission:</p> <p>(i) Presented revised financial estimates using the proposed price and maximum quantity of 2 units. The estimated number of prescriptions per year is essentially unchanged from the estimates considered by the PBAC in July 2022, however the financial estimates are increased because of the change in maximum quantity per prescription.</p> <p>(ii) The estimated net financial impact to the PBS/RPBS is \$20 million to &lt; \$30 million over six years. This was higher than the estimate from the July 2022 submission \$10 million to &lt; \$20 million (after correction by Evaluators).</p> <p>(iii) The resubmission did not estimate the number of pre-filled syringes to be supplied under the proposed Prescriber Bag item. The proposed price for midazolam oromucosal solution is substantially higher than the price for midazolam ampoules in the Prescriber Bag schedule,</p>

Matter of concern	Resubmission
	therefore any substitution of the existing item will lead to increased costs to the PBS.
<p><b>4. Risk sharing arrangement (paragraph 7.12).</b> The PBAC considered that a risk sharing arrangement would be required due to uncertain financial estimates.</p>	<p>The resubmission:</p> <p>(i) Did not propose a risk sharing arrangement, but acknowledged that the estimates are uncertain, e.g. relating to the proportion of patients likely to experience &gt;1 prolonged seizure in a lifetime, persistence rates, likely uptake of the product within the eligible population, and the proportion of patients with frequent seizures requiring significantly higher rates of treatment.</p>

Source: Midazolam July 2022 Public Summary Document (PSD).

## 2 Background

- 2.1 Midazolam oromucosal solution was listed on the Australian Register of Therapeutic Goods (ARTG) on 22 April 2022. The TGA approved indication for midazolam oromucosal solution is for the treatment of generalised convulsive status epilepticus (GCSE), in those over 6 months old.
- 2.2 This was the second PBAC consideration for midazolam oromucosal solution for the treatment of GCSE.
- 2.3 In July 2022, the PBAC considered that the proposed population was not well defined, and that expert clinical advice would be needed to refine the PBS restriction. The PBAC noted that a number of benefits were described in the consumer comments, the ESC advice and the submission documents, including reduced time to administration of the dose, reduced risk of incorrect dosing and ease of administration for carers during the acute stressful situation of a seizure. However, the PBAC considered that the proposed price was not justified by the submission and that a price reduction would be required to achieve a cost-effective listing. The PBAC considered that revised financial estimates would be required to incorporate changes to the restriction and price, and that a risk sharing arrangement would be required due to uncertain financial estimates (paragraph 7.1, midazolam PBAC Public Summary Document (PSD), July 2022 PBAC meeting).

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## 3 Requested listing

- 3.1 The PBAC Secretariat suggested PBS listing from July 2022 is reproduced below, including updates for this meeting (additions are in italics, deletions in strikethrough).

Public Summary Document – November 2022 PBAC Meeting

MEDICINAL PRODUCT Medicinal Product Pack	Maximum Quantity Packs	Maximum Quantity Units	No. of repeats	Dispensed Price Maximum Quantity	Proprietary Name and Manufacturer
MIDAZOLAM MALEATE Pre-filled oral syringe					
2.5 mg in 0.25 mL solution	2	2	1	\$	Zyamis® Clinect Pty Ltd
5 mg in 0.5 mL solution	2	2	1	\$	
7.5 mg in 0.75 mL solution	2	2	1	\$	
10 mg in 1.0 mL solution	2	2	1	\$	

### General Schedule

<b>Restriction Summary [new] / Treatment of Concept: [new]</b>
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
<b>Condition:</b> Epilepsy
<b>Indication:</b> Generalised Convulsive Status Epilepticus
<b>Treatment Phase:</b> Initial treatment
<b>Clinical criteria:</b>
<i>Patient must have epilepsy;</i>
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have experienced at least one prolonged seizure (>five minutes duration) requiring emergency medical attention within the previous 5 years
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have been assessed to be at significant risk of status epilepticus
<b>Population criteria:</b>
Patient must be over six months of age
<b>Treatment criteria:</b>
<i>For administration once a seizure exceeds five minutes duration.</i>
<b>AND</b>
<b>Treatment criteria:</b>
Treatment must be initiated by a specialist physician experienced in the treatment of epilepsy.
<b>Administrative Advice:</b>
<del>No increase in the maximum quantity or number of units may be authorised.</del> <del>No increase in the maximum number of repeats may be authorised.</del>
Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Treatment Phase:</b> Continuing treatment
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>Administrative Advice:</b>
<del>No increase in the maximum quantity or number of units may be authorised.</del> <del>No increase in the maximum number of repeats may be authorised.</del>

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
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### Prescriber Bag

<b>Restriction Summary [new] / Treatment of Concept: [new]</b>
<b>Category / Program:</b> PRESCRIBER BAG – Prescriber Bag Schedule (Code DB)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse Practitioners
<b>Restriction type:</b> n/a
<b>Condition:</b> Not applicable
<b>Indication:</b> Not applicable
<b>Treatment criteria:</b> Not applicable [It is not possible to specify criteria for Prescriber Bag items]

- 3.2 A maximum quantity of two units per script was proposed, as compared with one unit in the July 2022 submission. The resubmission stated that a maximum quantity of two pre-filled syringes would cater for patients requiring a second dose.
- 3.3 The resubmission requested an ex-manufacturer price of \$ [REDACTED] per pack containing one pre-filled syringe. This represents an [REDACTED]% reduction from the ex-manufacturer price offered in the July 2022 submission (AEMP=\$ [REDACTED] per pre-filled syringe). The requested AEMP corresponds to a dispensed price of \$ [REDACTED] for a maximum quantity (DPMQ) of two pre-filled syringes. This represents a [REDACTED]% reduction from the DPMQ proposed in the July 2022 submission DPMQ=\$ [REDACTED] per pre-filled syringe.
- 3.4 The resubmission requested a Section 85 listing with restrictions very similar to those proposed in the July 2022 submission. One new criterion was added, to indicate that administration should occur after a seizure exceeds five minutes in duration.
- 3.5 The PBAC previously noted that the proposed restriction was broad, but other options would include restricting the listing to a highly treatment resistant group of patients (who may use up to 2-4 doses per week; see paragraph 7.3, July 2022 PSD). The resubmission stated this would deny treatment to patients who could benefit from the treatment, including potential to avoid hospitalisations or deleterious clinical outcomes. The resubmission proposed that the needs of patients requiring frequent doses, could be addressed by removing the administrative advice preventing increased units or repeats. This would allow prescribers to seek approval for higher amounts if required.
- 3.6 In regard to patients with low frequency seizures, the resubmission noted the results of a Delphi survey conducted with health professionals in the UK, which estimated that over half (55%) of patients in the general epilepsy population (as seen in general epilepsy clinics) would experience zero to one prolonged seizure per 6-month period

(Ludwig and Fisher 2020<sup>1</sup>). The publication also reported that over one third (34%) of the total population would experience zero prolonged seizures per 6-month period, and highlighted the risk of wastage associated with provision of higher quantities of midazolam, as the medicine will sometimes need replacement due to product expiry rather than use.

- 3.7 When considering midazolam in July 2022, the PBAC advised that PBS access for other settings (e.g. Doctors' and Epilepsy Nurse Practitioners' bags) should be considered (paragraph 7.3, July 2022 PBAC PSD). The resubmission requested a Prescriber Bag listing for Medical Practitioners.

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## **4 Consideration of the evidence**

### ***Sponsor hearing***

- 4.1 There was no hearing for this item.

### ***Consumer comments***

- 4.2 The PBAC noted and welcomed the input from one individual via the Consumer Comments facility on the PBS website. The comments from the parent of an individual who requires midazolam treatment, described midazolam as an essential emergency medication and expressed concern about affordability if the drug is not PBS listed.
- 4.3 The PBAC also noted that in July 2022 input was received from 3 health care professionals and 3 organisations including Epilepsy Australia, National Paediatric Medicines Forum and Epilepsy Action Australia (paragraphs 6.2-6.3, midazolam PSD, July 2022 PBAC Meeting). The comments indicated support for the proposed listing. Main themes described in the comments included ease of use and the quality use of medicine. Concerns were raised about the current off-label use of ampoules in relation to safety, dosage, storage and the training of carers and non-health professionals to administer midazolam in emergency situations. The comments indicated that compared with the current off-label use of ampoules, pre-filled syringes would lead to more effective use of the drug as correct dosages would be given, there was less risk of harm from incorrect dosing, and there was reduced risk of midazolam loss/abuse. It was reported that midazolam in pre-filled syringes would improve access to effective medication particularly for those living far from hospital settings, or due to parents/carers experiencing difficulties using the ampoules.

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<sup>1</sup> Ludwig C, and Fisher L. 2020. "Buccal Midazolam Solution for the Management of Prolonged Acute Convulsive Seizures: A Cost Analysis." *Pharmacoeconomics* 4:171-9.

### **Clinical claim**

- 4.4 In July 2022, the PBAC noted that the submission described midazolam oromucosal solution as non-inferior in terms of effectiveness and safety compared to buccal or intranasal midazolam hydrochloride. The PBAC considered it was reasonable to consider midazolam oromucosal solution comparable to midazolam parenteral solution given via the oromucosal route, although the TGA had not issued a bioequivalence statement. In addition in July 2022, the PBAC noted the submission's claim that midazolam oromucosal solution provides a significantly superior and important pragmatic and practical improvement to the accurate and timely administration of midazolam during an acute health emergency. The PBAC considered it plausible that the prefilled syringe would be beneficial as compared with off-label use of midazolam ampoules which require carers to either draw up liquid into a syringe before administration or to squeeze a plastic ampoule to administer the drug to the buccal cavity, noting that GCSE is a stressful situation for parents and carers.

### **Economic analysis**

- 4.5 In July 2022, the PBAC considered that in comparison to midazolam ampoules, the benefits of the proposed presentation were likely clinically meaningful and important for carers, however the proposed price premium over midazolam hydrochloride (DPMQ of \$| versus \$40) was not justified. At that time, the PBAC noted the cost-effective price for midazolam oromucosal solution will depend on the revised population as defined by the restriction, and the maximum quantity and hence likely wastage, however considered that a price that is more than approximately twice the price of midazolam hydrochloride is unlikely to be cost-effective (PBAC PSD paragraph 7.11).
- 4.6 The resubmission proposed a dispensed price of \$| for 2 pre-filled syringes of midazolam oromucosal solution, which was |% lower than the dispensed price proposed in July 2022 (\$| for 2 pre-filled syringes). The proposed price remains considerably higher than the price of midazolam hydrochloride ampoules which are currently used off label for this indication (DPMQ = \$39.91 for midazolam 5 mg/mL injection, 10 x 1 mL ampoules, refers to DPMQ for the Prescriber Bag Schedule for PBS Item 10178Q).
- 4.7 As for the July 2022 submission, the resubmission presented a cost-consequences analysis based on the submission's claim that midazolam oromucosal solution improves the accurate and timely administration of midazolam during an acute health emergency. Previously the PBAC considered that the cost-consequences analysis presented by the submission was incomplete and largely uninformative, because it did not model any difference in outcomes between the proposed medicine and comparator (paragraph 7.11, July 2022 PBAC PSD). The analysis presented by the resubmission was unchanged, other than assuming a lower price for midazolam oromucosal solution, specifically \$|, which was not consistent with the proposed DPMQ. If PBS listed, it is likely that most patients will receive the maximum quantity

with each script, therefore the price for midazolam oromucosal solution for one treatment should reflect the proposed DPMQ (\$). The resubmission assumed an effective shelf life of 12 months after dispensing (based on an assumed total shelf life of 14 months<sup>2</sup>).

### **Estimated PBS utilisation and financial implications**

- 4.8 The resubmission accepted the corrections to the estimates proposed during the previous evaluation, and presented new estimates corresponding to the proposed price and maximum quantity of 2 pre-filled syringes. The estimated net financial impact to the PBS/RPBS for listing midazolam oromucosal solution based on the proposed price is \$20 million to < \$30 million over six years (Table 2). This was higher than the estimate from July 2022 of \$10 million to < \$20 million (after correction by Evaluators).
- 4.9 The resubmission applied the same assumptions as the July 2022 submission, corresponding to an average of 1.00173 scripts per patient per year. The resubmission assumed 2 pre-filled syringes per script, corresponding to the proposed maximum quantity.
- 4.10 The resubmission did not estimate the number of supplies for the proposed listing in the Prescriber Bag schedule. In the 2021-2022 financial year, there were 6,951 Prescriber Bag Order Forms for PBS item 10178Q (midazolam 5 mg/mL injection, 10 x 1 mL ampoules, DPMQ \$39.91), and the total benefits paid by the Commonwealth for these orders was \$261,487<sup>3</sup>. The proposed price for midazolam oromucosal solution is substantially higher than the price for midazolam ampoules (listed in the Prescriber Bag schedule), therefore any substitution of the existing item would lead to increased costs to the PBS.

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<sup>2</sup> Source: sheet '3a. Scripts – proposed' in Attachment 1 Section 4 model (cost and utilisation) - resubmission.xlsx)

<sup>3</sup> [http://medicarestatistics.humanservices.gov.au/statistics/pbs\\_item.jsp](http://medicarestatistics.humanservices.gov.au/statistics/pbs_item.jsp) for 10178Q for July 2021 to June 2022, accessed 6/10/2022.

**Table 2: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total Australian population	26,727,025	27,147,199	27,562,195	27,970,435	28,372,315	28,765,734
<b>Children aged 0-17 years diagnosed in Years 1-6</b>						
Australian population	5,969,108	6,064,728	6,150,343	6,225,933	6,299,095	6,372,633
Incident epilepsy patients	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Experiencing GCSE	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Treatment uptake	60.00%	80.00%	90.00%	90.00%	90.00%	90.00%
Incident patients	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Total incident/persistent treated	█ <sup>2</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Children aged 0-17 years with historical diagnosis up to 6 years prior to Year 1</b>						
Historic persistent children treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
<b>Total children treated</b>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Adults aged 18-100 years diagnosed in Years 1-6</b>						
Australian population	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
Incident epilepsy patients	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Experiencing GCSE	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Treatment uptake	30.00%	40.00%	50.00%	55.00%	55.00%	55.00%
Incident patients	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Total incident/persistent treated	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>3</sup>	█ <sup>3</sup>
<b>Adults aged 18-100 years with historic diagnosis up to 6 years prior to Year 1</b>						
Historic persistent adults treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>3</sup>
Total adults treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Total patients treated	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
<b>Estimated cost of midazolam oromucosal solution to the PBS/RPBS</b>						
Number of scripts (1.00173/pt/year)	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Cost to the PBS (\$)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Patient copayments (\$)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
<b>Net cost to the PBS (\$)</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Cost to the RPBS (\$)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Patient copayments (\$)	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>	█ <sup>6</sup>
<b>Net cost to the RPBS</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
<b>Net cost to the PBS/RPBS</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
<b>July 2022 submission estimated utilisation and cost (after correction by Evaluator)</b>						
Total adults treated	█ <sup>3</sup>	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Number of scripts (1.00173/pt/year)	█ <sup>3</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>	█ <sup>4</sup>
Net cost to the PBS (\$)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
Net cost to the RPBS (\$)	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>
<b>Net cost to the PBS/RPBS (\$)</b>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>	█ <sup>5</sup>

Source: Table 9 resubmission, and Table 8 in July 2022 PBAC PSD.

Abbreviations: GCSE, generalised convulsive status epilepticus; PBS, Pharmaceutical Benefits Scheme; RPBS, Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 to < 5,000

<sup>2</sup> < 500

<sup>3</sup> 5,000 to < 10,000

<sup>4</sup> 10,000 to < 20,000

<sup>5</sup> \$0 to < \$10 million

<sup>6</sup> net cost saving

## **Financial Management – Risk Sharing Arrangements**

- 4.11 In July 2022, the PBAC considered that a risk sharing arrangement would be required due to uncertain financial estimates.
- 4.12 The resubmission did not propose a risk sharing arrangement, but acknowledged that the estimates are uncertain, e.g. relating to the proportion of patients likely to experience >1 prolonged seizure in a lifetime, persistence rates, likely uptake of the product within the eligible population, and the proportion of patients with frequent seizures requiring significantly higher rates of treatment.

*For more detail on PBAC's view, see section 5 PBAC outcome.*

## **5 PBAC Outcome**

- 5.1 The PBAC recommended the listing of midazolam oromucosal solution in pre-filled syringes (2.5 mg, 5 mg, 7.5 mg and 10 mg), for the treatment of generalised convulsive status epilepticus (GCSE) in patients aged over 6 months. The PBAC noted that GCSE presents stressful situations for parents and carers, and considered that the proposed listing, incorporating expert clinical advice, offered clinically meaningful benefits by improved quality use of medicines with easier and more accurate administration. This is consistent with stakeholder comments which were received from health professionals, individuals and organisations. The PBAC's recommendation for listing was based on, among other matters, its assessment that the cost-effectiveness of midazolam oromucosal solution in pre-filled syringes would be acceptable if it were cost-minimised against off label use of midazolam ampoules. However, the PBAC recognised there were additional health outcome benefits to this formulation associated with the accurate and timely administration of midazolam during an acute health emergency that justified a significant price premium under the specific circumstances of the restriction. The PBAC considered that the resubmission had partly addressed the concerns raised at the July 2022 PBAC meeting, and the remaining concerns could be addressed with an appropriate risk sharing arrangement.
- 5.2 The PBAC considered there was a clinical need for the proposed listing, especially in children experiencing severe GCSE events, and that it would provide meaningful benefits for families in both metropolitan and regional/remote settings by providing timely access to effective treatment which was not reliant on attendance by ambulance services, which could be subject to delays. The PBAC considered that midazolam is an essential emergency treatment for patients with prolonged seizures and that PBS listing will improve equity of access to the treatment.

- 5.3 The PBAC sought expert clinical advice from paediatric neurologists in relation to the proposed restriction. The advice noted considerable variability in the frequency and duration of seizures across the population. For some patients, a dose may not be used for some time, if at all, before it expires, while others experience frequent seizures, as much as multiple times per day. Access to treatment for parents and carers to administer is essential for patients with prolonged seizures. However, it is not necessary to include the product as a Prescriber Bag item. The proposed restriction text has been updated based on this expert advice as provided in Section 6. The PBAC provided the following additional comments about the requested listing and restriction:
- A General Schedule Authority Required (telephone/online PBS Authorities system) is appropriate.
  - A maximum quantity of 2 pre-filled syringes and 2 repeats is appropriate for most patients. The PBAC considered that the PBS approvals system should be programmed to allow higher requested quantities on request if justified for individual patients requiring more frequent doses, but not more than 10 syringes could be authorised per prescription.
  - The Administrative Advice that “No increase in the maximum quantity or number of units may be authorised” and that “No increase in the maximum number of repeats may be authorised” should both be deleted.
  - The Clinical Criteria that “Patient must have epilepsy” and Treatment Criteria “For administration once a seizure exceeds five minutes duration” should both be deleted, consistent with expert advice.
- 5.4 The PBAC reaffirmed its advice from the July 2022 meeting, that it was plausible that the prefilled syringe would be beneficial as compared with off-label use of midazolam ampoules which require carers to either draw up liquid into a syringe before administration or to squeeze a plastic ampoule to administer the drug to the buccal cavity, noting that GCSE is a stressful situation for parents and carers. The PBAC noted potential beneficial impacts proposed by the sponsor, which may include reduced time to treatment, increased dosing accuracy, less likelihood of diversion for illicit IV administration, reduced administration errors, better patient care, reduced hospitalisations and reduced long-term consequences from extended seizures.
- 5.5 The PBAC noted the sponsor’s proposal for a reduced price compared with the July 2022 submission (see paragraph 4.5). The PBAC considered that the expert advice from paediatric neurologists provided greater certainty with respect to the proposed PBS population (see paragraph 5.3) and that the cost-effectiveness of midazolam oromucosal solution would be acceptable at the price proposed in the resubmission with an appropriate risk sharing arrangement. The PBAC advised that a risk sharing arrangement with 100% rebate above annual cap thresholds should be implemented in order to address its previous concerns about financial uncertainty. The financial caps should be based on the estimates proposed in the resubmission (net cost to

PBS/RPBS ranged from \$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6, see Table 2).

- 5.6 The PBAC advised that midazolam is suitable for prescribing by nurse practitioners for continuing therapy in collaborative practice.
- 5.7 The PBAC recommended that the Early Supply Rule should not apply.
- 5.8 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for midazolam:
- The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over alternative therapies;
  - The treatment is not expected to address a high and urgent unmet clinical need because midazolam ampoules are currently used (off label) for this indication;
  - It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.
- 5.9 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 6 Recommended listing

6.1 To be finalised. Add new medicinal item follows (indicative only):

MEDICINAL PRODUCT Medicinal Product Pack	Maximum Quantity Packs	Maximum Quantity Units	No. of repeats	Proprietary Name and Manufacturer
MIDAZOLAM MALEATE Pre-filled oral syringe				
2.5 mg in 0.25 mL solution	2	2	2	Zyamis®
5 mg in 0.5 mL solution	2	2	2	Clinect Pty Ltd
7.5 mg in 0.75 mL solution	2	2	2	
10 mg in 1.0 mL solution	2	2	2	

### General Schedule

<b>Restriction Summary [new] / Treatment of Concept: [new]</b>
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Restriction type:</b> <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)
<b>Condition:</b> Epilepsy
<b>Indication:</b> Generalised Convulsive Status Epilepticus
<b>Treatment Phase:</b> Initial treatment
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners

<b>Clinical criteria:</b>
Patient must have been assessed to be at significant risk of status epilepticus
<b>AND</b>
<b>Clinical criteria:</b>
<del>Patient must have epilepsy;</del>
<b>AND</b>
<b>Clinical criteria:</b>
Patient must have experienced at least one prolonged seizure (>five minutes duration) requiring emergency medical attention within the previous 5 years
<b>Population criteria:</b>
Patient must be <del>at least over</del> six months of age
<b>Treatment criteria:</b>
<del>For administration once a seizure exceeds five minutes duration.</del>
<b>AND</b>
<b>Treatment criteria:</b>
Treatment must be initiated by a specialist physician experienced in the treatment of epilepsy.
<b>Administrative Advice:</b> <del>No increase in the maximum quantity or number of units may be authorised.</del> <del>No increase in the maximum number of repeats may be authorised.</del>  Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.
<b>Treatment Phase:</b> Continuing treatment
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse Practitioners
<b>Clinical criteria:</b>
Patient must have previously received PBS-subsidised treatment with this drug for this condition
<b>Administrative Advice:</b> <del>No increase in the maximum quantity or number of units may be authorised.</del> <del>No increase in the maximum number of repeats may be authorised.</del>  Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see <a href="http://www.servicesaustralia.gov.au/HPOS">www.servicesaustralia.gov.au/HPOS</a> ) or by telephone by contacting Services Australia on 1800 888 333.

***This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.***

## 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.