

## 5.08 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® ,**

**Clinect Pty Ltd.**

### 1 Purpose of submission

- 1.1 The category 2 submission requested a Section 85, Authority Required (telephone) listing of midazolam maleate oromucosal solution (pre-filled syringes), for the treatment of generalised convulsive status epilepticus (GCSE) in patients with epilepsy aged over 6 months and a high risk of status epilepticus.
- 1.2 The listing was requested on the basis of a cost-consequences analysis comparing the costs associated with midazolam oromucosal solution with midazolam hydrochloride for intravenous/intramuscular injection.

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

Component	Description
Population	Patients from 6 months of age where a medical practitioner has diagnosed epilepsy with a high risk of status epilepticus
Intervention	Midazolam maleate oromucosal solution in pre-filled single use syringe for buccal administration - midazolam 2.5 mg in 0.25 mL, 5 mg in 0.5 mL, 7.5 mg in 0.75 mL, 10 mg in 1.0 mL oromucosal solution
Comparator	Midazolam hydrochloride for intravenous/intramuscular injection 5 mg/mL, by buccal or intranasal administration
Outcomes	Seizure cessation within ten minutes of treatment
Clinical claim	Noninferior effectiveness and safety compared to midazolam hydrochloride. In addition, midazolam oromucosal solution provides significantly superior and important pragmatic and practical improvements to the accurate and timely administration of midazolam during an acute health emergency.

Source: Table 1-1, p28 of the submission

- 1.3 The clinical claim was inconsistent between the main body of the submission (noninferior efficacy versus the main comparator) and some sections of the executive summary (superior efficacy versus the main comparator). Given the main body of the submission and the economic analysis was based on the claim of noninferior efficacy

and safety, and no evidence supporting a claim of superior effectiveness was presented in the submission, the evaluation was conducted on this basis.

- 1.4 In addition, the submission claimed that midazolam oromucosal solution provides significantly superior and important pragmatic and practical improvements to the accurate and timely administration of midazolam during an acute health emergency. The submission stated that midazolam oromucosal solution is likely to provide a qualitatively (but unquantifiable) improvement in efficacy and safety when administered by parents and carers in a non-hospital setting, compared to the main comparator, off-label use of midazolam ampoules. The submission stated that expectations of more accurate dosing and easier administration were supported by local expert advice, but did not present evidence to support this claim.

## **2 Background**

### ***Registration status***

- 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 The TGA clinical evaluation noted that the bioequivalence of midazolam oromucosal solution and midazolam hydrochloride, administered buccally, was demonstrated in healthy adults (pharmacokinetic study SPL002), but no evidence was presented supporting bioequivalence in children (Delegate’s Overview, 2020). In addition, it was noted that results for simulated paediatric exposures compared to the adult population were well below the acceptable bioequivalence limits (Delegate’s Overview 2020).
- 2.3 The Advisory Committee on Medicines (ACM, August 2021) recommended approval of midazolam oromucosal solution (ZYAMIS®), on the basis of a literature-based submission. The clinical evaluation report stated that the efficacy and safety of midazolam administered via intravenous, intramuscular, intranasal, or buccal route for the treatment of seizures in children and adults have been demonstrated in a body of clinical studies and have been confirmed by extensive use in clinical practice (Glauser et al. 2016; McTague et al. 2018; Trinko et al. 2016). The ACM (ACM, August 2021, p5) also noted that several efficacy studies were submitted, but these were not specific to this proposed buccal midazolam formulation. The ACM were of the view that the two most relevant studies were Talukdar et al. (2009) and Tonekaboni et al. (2012) and noted that both studies demonstrated that buccal midazolam was comparable to intravenous diazepam for seizure control.
- 2.4 The submission stated that midazolam oromucosal solution was bioequivalent to midazolam parenteral solution administered via the oromucosal route based on a

study in healthy adult subjects, that was cited in the ACM minutes (SPL002 BE; n = 51), but no further details were provided in the submission.

2.5 Midazolam oromucosal solution has not previously been considered by the PBAC.

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

### 3 Requested listing

3.1 The requested listing and suggested wording for the restriction as proposed by the Secretariat (additions are in italics, deletions in strikethrough) is presented below.

Name, Restriction, Manner of administration and form	Maximum amount (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	1	1	<del>\$\$\$</del>	Zyamis®
5 mg in 0.5 mL solution	1	1	<del>\$\$\$</del>	Clinect Pty Ltd
7.5 mg in 0.75 mL solution	1	1	<del>\$\$\$</del>	
10 mg in 1.0 mL solution	1	1	<del>\$\$\$</del>	

Restriction Summary [new] / Treatment of Concept: [new]
<b>Category / Program:</b> GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b> <input checked="" type="checkbox"/> Medical 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>
Patient must have epilepsy;
<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>
<i>Patient must have been assessed to be at significant risk of status epilepticus</i>
<b>Population criteria:</b>
Patient must be over six months of age
<b>Treatment criteria:</b>
<i>Treatment must be initiated by a specialist physician experienced in the treatment of epilepsy.</i>
<b>Administrative Advice:</b>
No increase in the maximum quantity or number of units may be authorised.
No increase in the maximum number of repeats may be authorised.
<i>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.</i>

<b>Treatment Phase:</b> <i>Continuing treatment</i>
<b>Clinical criteria:</b> <i>Patient must have previously received PBS-subsidised treatment with this drug for this condition</i>
<b>Administrative Advice:</b> <i>No increase in the maximum quantity or number of units may be authorised.</i> <i>No increase in the maximum number of repeats may be authorised.</i>  <i>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.</i>

- 3.2 The submission requested listing for a maximum quantity of one prefilled syringe and one repeat. The submission also suggested inclusion of administrative advice that “No increase in the maximum quantity or number of units may be authorised” and “No increase in the maximum number of repeats may be authorised”.
- 3.3 The Pre-Sub-Committee Response (PSCR) stated that the maximum quantity of one pack and one repeat would reflect the likely utilisation patterns for the majority of patients, based on a UK Delphi study (Ludwig and Fisher 2020<sup>1</sup>) that estimated more than half of patients would experience zero to one prolonged acute convulsive seizure per 6-month period. However, the ESC considered that a maximum quantity of two syringes per script may be appropriate, to cater for patients requiring a second dose. In the clinical evidence, between 2.7% and 12.5% of patients experienced seizure recurrence within 1-2 hours of an initial dose of midazolam oromucosal solution (see paragraph 6.19). In addition, the ESC suggested it may be reasonable to allow a higher maximum quantity for patients at risk of frequent attacks, noting that a proportion of the affected population is living in group homes and that timely administration of midazolam would likely reduce hospitalisations in this patient group.
- 3.4 The requested restriction is narrower than the TGA approved indication, limiting eligibility to patients with epilepsy, and at least one prolonged seizure of >5 minutes duration requiring emergency medical attention, within the previous 5 years.
- 3.5 The requested restriction did not specify the minimum duration of seizure prior to administration of midazolam oromucosal solution, while the treatment regimen described in the proposed clinical management algorithm, Australian clinical guidelines for pre-hospital intervention for GCSE, and the treatment regimen used in the included clinical trials, required a seizure duration of >5 minutes prior to administration of buccal midazolam. The submission proposed a relatively broad listing that would replace off label use of midazolam solution for injection, which is

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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.

commonly recommended for buccal administration for acute treatment of status epilepticus in both adults and children (see paragraph 3.8).

- 3.6 The requested restriction omits a requirement that the initial prescription of midazolam oromucosal solution must be initiated by a specialist physician experienced in the treatment of epilepsy, as recommended in the Product Information. The sponsor supported the addition of this criterion in the PSCR. The ESC considered it would be appropriate to require that the treatment is initially prescribed by physician experienced in treatment of epilepsy.
- 3.7 The submission stated that listing was requested for patients with epilepsy aged over 6 months and a high risk of status epilepticus, however the proposed restriction did not reference the risk profile of the patient, other than to say that the patient must have experienced at least one prolonged seizure (>5 minutes duration) requiring emergency medical attention within the previous 5 years. It is unclear whether a further criterion should be added to assess that the patient has a specific need for the product due to significant risk of status epilepticus, akin to the risk assessment applying to adrenaline pens on the PBS. The sponsor supported the addition of this criterion in the PSCR. The PBAC considered it would be appropriate to include a clinical criterion stating that the patient has been assessed to be at significant risk of status epilepticus.
- 3.8 The use of buccal midazolam is widely recognised as the appropriate first line therapy for GCSE in the out-of-hospital emergency setting (Royal Children’s Hospital Clinical Practice Guidelines for Afebrile Seizures - Midazolam for seizures 2020; NICE Epilepsies: diagnosis and management guidelines 2012). In addition, it has been noted that early treatment with buccal midazolam improves outcomes and avoids complications, and that when used in the community, can reduce hospital admissions for children with complex epilepsy (Smith and Brown, 2017). An Australian review recommended that supply of midazolam solution to a parent or carer should be considered for children (and dependent adults) who have convulsive seizures which frequently last more than five minutes (Smith and Brown, 2017).
- 3.9 The ESC did not support the inclusion of a requirement that the medicine be limited to patients with an established history of discharge from hospital or emergency department after acute treatment with benzodiazepine for GCSE (similar to the criteria applying to adrenaline pens). The ESC considered this would inappropriately exclude patients that would benefit from the proposed listing, including patients that are currently prescribed off-label midazolam despite not having a history of discharge from hospital or emergency department.
- 3.10 The sponsor modified the requested maximum quantity in the pre-PBAC response, to reflect a maximum quantity of two prefilled syringes and stated that this change could support some flexibility in the pricing per unit. The PBAC considered that expert clinical advice is required with regard to the maximum quantity and whether exceptions should be allowed on request (see paragraph 7.3).

- 3.11 The PBAC noted that the sponsor’s requested restriction was not consistent with the proposed treatment algorithm presented in the submission, which indicated that one dose of midazolam should be administered after 5 minutes from onset of seizure and that a second dose could be administered after a further 5 minutes if the seizure continued and in accordance with the patient’s individual epilepsy management plan. The PBAC considered that expert clinical advice is required with regard to defining the restriction (see paragraph 7.3).
- 3.12 The PBAC considered that training will be essential for medication givers (family members or carers) with respect to seizure recognition and midazolam administration. The sponsor may refer to the Epilepsy Nurses Association (ESNA) guideline which was produced in collaboration with the International League against Epilepsy (ILAE) as an example<sup>2</sup>.

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

## **4 Population and disease**

- 4.1 Epilepsy is a brain disorder characterised by repeated seizures (i.e. abnormal excessive electrical activity in the brain resulting in sensory disturbances, abnormal movements, or abnormal behaviours), of varied or unknown aetiology. A diagnosis of epilepsy is difficult and should be made by a specialist paediatrician or physician based on a detailed patient survey, a reliable history of seizure events, and additional investigations, e.g., electroencephalogram, neuroimaging, neuropsychological assessment (NICE 2012).
- 4.2 Status epilepticus (SE) is defined as continuous seizure activity of more than 30 minutes duration, or two or more sequential seizures spanning 30 minutes without full recovery (International League Against Epilepsy (ILAE) 1993; NICE Clinical Guidelines No 137, Epilepsies: diagnosis and management, 2012; Prasad et al. 2014), and may be categorised as focal or generalised. Generalised convulsive status epilepticus (GCSE) is characterised by bilateral tonic and/or clonic motor activity (seizure/convulsion) and loss of consciousness, and is considered a medical emergency requiring urgent effective treatment to reduce the risk of associated neuronal damage, systemic complications, morbidity, and mortality (NICE 2012).
- 4.3 Given seizures become more refractory to treatment with increased duration, timely reduction of seizure duration may decrease seizure related morbidity and mortality (Scott et al. 1999; Glauser et al. 2016). Therefore, the operational definition of a GCSE event is  $\geq 5$  minutes of continuous seizures, or two or more discrete seizures between which there is incomplete recovery of consciousness.

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<sup>2</sup>Tittensor P, Tittensor S, Chisanga E, Bagary M, Jory C, Shankar R. UK framework for basic epilepsy training and oromucosal midazolam administration. *Epilepsy Behav.* 2021 Sep;122:108180. Epub 2021 Jul 9.

- 4.4 Adverse outcomes after GCSE include death, cognitive impairment, permanent neurological deficits and subsequent epilepsy (Novorol et al. 2007). GCSE related mortality accounts for 12.5% of epilepsy related deaths (Gaitatzis and Sander 2004). Mortality attributed to status epilepticus is less common in children (3%) than in adults (26%; DeLorenzo et al. 1996). Morbidity secondary to childhood GCSE is widely reported (e.g. Gurcharran & Grinspan 2019; Novorol et al. 2007, NSW Health 2016, Sillanpaa 2002).
- 4.5 An Epilepsy Australia commissioned report (Deloitte 2020), applying ABS National Health Survey age and gender specific epilepsy prevalence rates to Australian population data, estimated the prevalence of epilepsy in Australia in 2019-2020 at 142,740 (19,196 aged 0-14; 93,987 aged 15-64; 29,557 aged over 65 years).
- 4.6 The proportions of patients with epilepsy experiencing GCSE events are poorly reported for the Australian population, but older international studies have suggested that 27% of children and 15% of adults with epilepsy will experience a GCSE event during their lifetime (Sillanpaa 2002; Trinkka 2012).
- 4.7 Midazolam maleate oromucosal solution is formulated for buccal administration only, and is available in four standard dose strengths in pre-filled oral syringes. Table 2 summarises the formulations of midazolam oromucosal solution, and the dosing regimens recommended in the Product Information.

**Table 2: Midazolam oromucosal solution recommended dose strengths**

Age range	Weight range	Recommended dose strength
>6 months to <1 year	7 kg to <12 kg	midazolam 2.5 mg in 0.25 mL oromucosal solution
1 year to <5 years	12 kg to <21 kg	midazolam 5 mg in 0.5 mL oromucosal solution
5 years to <10 years	21 kg to <29 kg	midazolam 7.5 mg in 0.75 mL oromucosal solution
>10 years and adults	≥29 kg	midazolam 10 mg in 1.0 mL oromucosal solution

Source: Table 1-2, pp37-38 of the submission; Table 1, p2 of the proposed Product Information

- 4.8 Administration is expected to be in the pre-hospital setting by healthcare professionals or appropriately trained parents/carers. A second dose of midazolam oromucosal solution may be given in accordance with either the patient’s individual written care plan or as authorised by a medical practitioner.
- 4.9 The submission described the importance of timely and effective management of status epilepticus, and stated that midazolam oromucosal solution was specifically developed for ease of use in the pre-hospital setting (where IV access is unavailable), to satisfy the needs of parents and carers. The submission discussed that strategies for improvement of formulation, dose, packaging, and presentation could help minimise errors and improve ease of administration.
- 4.10 The submission argued that there is no clinical or pharmacological difference between midazolam maleate oromucosal solution and midazolam hydrochloride (the comparator), when administered via the buccal mucosa. However, the submission claimed that the maleate salt was selected for the development of the new formulation due to its better taste profile, solubility and pH characteristics. The proposed clinical management algorithm places midazolam oromucosal solution as a

replacement for buccal and intranasal administration of midazolam hydrochloride (solution for injection). The submission stated that the proposed PBS listing of midazolam oromucosal solution as prefilled syringes would provide an improved vehicle from which the midazolam can be accurately and easily administered via the buccal route, providing improved quality use of medicines.

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

## **5 Comparator**

- 5.1 The submission nominated midazolam hydrochloride solution for intravenous or intramuscular injection, administered buccally or intranasally, as the main comparator.
- 5.2 The submission acknowledged that this use of midazolam hydrochloride is outside the ARTG listed indication and route of administration, but noted that midazolam hydrochloride is the most used medicine for GCSE in the pre-hospital setting, and is widely recommended for the treatment GCSE in the pre-hospital setting in Australian clinical practice guidelines (Royal Children's Hospital, Melbourne. Afebrile Seizures August 2020).
- 5.3 The submission noted that rectal diazepam was the commonly recommended pre-hospital emergency treatment of prolonged epileptic seizures in Australian clinical practice prior to the adoption of midazolam hydrochloride. However, as intranasal or buccal midazolam has a more rapid onset of action and is generally preferred to rectal diazepam (McKee & Abou-Khalil 2015), rectal diazepam was not nominated as a comparator. This was appropriate. However, rectal diazepam is the active comparator in all clinical trials presented in the submission, given the lack of comparative data for midazolam oromucosal solution versus midazolam hydrochloride. Neither midazolam hydrochloride nor rectal diazepam (prepared by compounding pharmacies) are listed on the ARTG for the treatment of GCSE.
- 5.4 As midazolam hydrochloride is not listed on the PBS for emergency treatment of prolonged epileptic seizures, a cost-effective price of midazolam hydrochloride for the treatment of GCSE has not been established. As the cost of midazolam hydrochloride to parents/carers could not be determined, the submission used the price of midazolam hydrochloride supplied via the PBS Prescriber Bag program as a proxy for non-subsidised midazolam use in the economic evaluation.
- 5.5 The ESC noted that the TGA evaluation was based on a literature-based submission (see paragraph 2.3), and that despite extensive use of midazolam in clinical practice, there was limited evidence available to inform the clinical and economic evaluations of the PBAC submission.

*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 and welcomed the input from health care professionals (3), a medical organisation (1) and health consumer organisations (2) via the Consumer Comments facility on the PBS website. The PBAC acknowledged the advice received from Epilepsy Australia and Epilepsy Action Australia, which supported the proposed listing. The input included a consumer survey with 48 responses. Main themes described in the comments included ease of use and the quality use of medicines. 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, and there was less risk of harm from incorrect dosing. 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.
- 6.3 The PBAC noted the advice received from the National Paediatric Medicines Forum clarifying the likely use of midazolam oromucosal solution in clinical practice. The advice supported the proposed listing, and noted potential for less dose confusion, improved safety and reduced risk of midazolam loss/abuse. The input also noted that midazolam has been used extensively in paediatrics for numerous years to successfully terminate seizures and reported utilisation statistics from a selection of Australian children's hospitals. 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, in which it was reported that approximately 13,200 ampoules were dispensed by one metropolitan hospital alone in the last 12 months (see paragraph 6.57).

### ***Clinical trials***

- 6.4 No studies were identified directly comparing midazolam oromucosal solution with midazolam hydrochloride (the main comparator), or that were suitable for an indirect comparison. The submission acknowledged that a comparison of clinical outcomes between midazolam oromucosal solution and the main comparator (buccal administration of midazolam hydrochloride) could not be presented.
- 6.5 The submission argued that because the bioequivalence between midazolam oromucosal solution and buccal administration of midazolam for injection had been demonstrated in healthy adults (pharmacokinetic study SPL002), that similar efficacy in the pre-hospital setting could be assumed, and therefore, studies comparing

midazolam administered buccally versus any benzodiazepine administered by routes other than intravenous or intramuscular, may be informative.

- 6.6 The submission presented seven head-to-head prospective studies comparing buccal administration of midazolam with rectal administration of diazepam (Ashrafi 2010, Baysun 2005, McIntyre 2005, Mpimbaza 2008, Nakken 2011, Scott 1999, Trajano 2009).
- 6.7 In addition, the submission presented the results of three real world studies of the prescribing and utilisation of buccal midazolam to control seizures in adults (IQVIA Report, 2019; pH Associates study, 2016; Special Products Ltd Report, 2010), the results of a meta-analysis of the included studies, conducted for the submission, and five published meta-analyses including studies presented in the submission (Arya et al. 2015; Brigo et al. 2015; Jain et al. 2016; McMullan et al. 2010; McTague et al. 2018) as supporting evidence.
- 6.8 The included studies do not provide a comparison of clinical outcomes between midazolam oromucosal solution and the main comparator (buccal administration of midazolam hydrochloride).
- 6.9 Details of the studies included in the submission are presented in Table 3.

**Table 3: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Clinical trials (buccal midazolam versus rectal diazepam)</b>		
Ashrafi et al. 2010	Ashrafi MR, Khosroshahi N, Karimi P, Malamiri RA, Bavarian B, Zarch AV, Mirzaei M, Kompani F. Efficacy and usability of buccal midazolam in controlling acute prolonged convulsive seizures in children.	<i>European Journal of Paediatric Neurology</i> , 2010; 14(5):434-438.
Baysun et al. 2005	Baysun Ş, Aydın ÖF, Atmaca E, Güler YKY. A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures.	<i>Clinical Pediatrics (Phila)</i> , 2005; 44(9):771-776.
McIntyre et al. 2005	McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier, J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial.	<i>Lancet</i> , 2005; 366(9481):205-210.
Mpimbaza et al. 2008	Mpimbaza A, Ndeezi G, Staedke S, Rosenthal PJ, Byarugaba J. Comparison of buccal midazolam with rectal diazepam in the treatment of prolonged seizures in Ugandan children: a randomized clinical trial.	<i>Pediatrics</i> , 2008; 121(1): e58-64.
Nakken et al. 2011	Nakken KO, Lossius MI. Buccal midazolam or rectal diazepam for treatment of residential adult patients with serial seizures or status epilepticus.	<i>Acta Neurologica Scandinavica</i> , 2011; 124:99–103.
Scott et al. 1999	Scott RC, Besag FMC, Neville BGR. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: A randomised trial.	<i>Lancet</i> , 1999; 353(9153):623-626.
Trajano et al. 2009	Trajano ML, Sanchez BC, Lukban MB, Salonga AM. Buccal midazolam compared to rectal diazepam and intravenous midazolam as emergent treatment of acute seizures in children: preliminary study.	<i>Journal of the Neurological Sciences</i> , 2009; 285:S254-255.

Source: Table 2-2, p68 of the submission.

- 6.10 Key features of the included trials are summarised in Table 4.

Table 4: Key features of the included trials

Trial	N/ events	Design	Patient population	Interventions	Primary outcome	Risk of bias
Ashrafi 2010	N=98	Prospective R, AC, OL, MC. Apr 2007 - Apr 2008.	<ul style="list-style-type: none"> <li>Children aged <math>\geq 3</math> months, with no IV access, admitted to 2 major referral hospitals (Iran)</li> <li>Prolonged convulsive seizure &gt;5 minutes, or convulsing on admission.</li> <li>Any aetiology. 86% with generalised convulsive seizures.</li> </ul>	Buccal midazolam (Epistatus or midazolam maleate solution) 0.3-0.5 mg/kg <sup>a</sup> vs Rectal diazepam for injection 0.5 mg/kg <sup>a</sup>	Cessation of convulsions within <5 minutes, without respiratory depression, or recurrence within 1 hour.	High
Baysun 2005	N=43	Prospective AC, OL, SC. Trial period not reported.	<ul style="list-style-type: none"> <li>Children aged 2 months to 12 years, admitted to a hospital emergency unit (Turkey).</li> <li>Convulsing on admission.</li> <li>Any aetiology. 42% with seizures possibly related to epilepsy.</li> </ul>	Buccal midazolam for injection 0.25 mg/kg vs Diazepam rectal solution 0.3-0.6 mg/kg <sup>b</sup>	Cessation of convulsions in <10 minutes.	High
McIntyre 2005	N=177 219 events	Prospective R, AC, OL, MC. Oct 2000 - Feb 2004.	<ul style="list-style-type: none"> <li>Children aged <math>\geq 6</math> months with no IV access, admitted to 4 hospital emergency units (UK).</li> <li>Convulsing on admission.</li> <li>Included patients receiving pre-hospital interventions.</li> <li>Any aetiology.</li> <li>Patients contributed multiple episodes.</li> </ul>	Buccal midazolam for injection $\sim 0.5$ mg/kg <sup>a</sup> vs Rectal diazepam $\sim 0.5$ mg/kg <sup>a</sup> (formulation not reported)	Cessation of convulsions in <10 mins, without respiratory depression requiring intervention, or recurrence within 1 hour.	High
Mpimbaza 2008	N=330	Prospective R, SB, AC, SC. Nov 2005 - Jun 2006.	<ul style="list-style-type: none"> <li>Children aged 3 months to 12 years, admitted to hospital acute care unit (Uganda).</li> <li>Prolonged convulsive seizure &gt;5 minutes, or convulsing on admission.</li> <li>Any aetiology. 70% with malaria, febrile convulsions. &lt;4% with epilepsy.</li> </ul>	Buccal midazolam $\sim 0.5$ mg/kg <sup>a</sup> vs Rectal diazepam $\sim 0.5$ mg/kg <sup>a</sup> (formulations not reported)	Cessation of convulsions in <10 minutes, without recurrence within 1 hour.	High
Nakken 2011	N=22 80 events	Prospective AC, OL, SC. Trial period not reported.	<ul style="list-style-type: none"> <li>Adults in residential care (Norway).</li> <li>Convulsive or non-convulsive status epilepticus or prolonged convulsive seizure &gt;5 minutes.</li> <li>Difficult to treat epilepsy. 91% with history of focal seizures.</li> <li>Patients contributed multiple episodes.</li> </ul>	Buccal midazolam (Epistatus) vs Diazepam rectal solution (doses not reported) <sup>c</sup>	Cessation of seizure activity in <10 minutes, without recurrence within 2 hours.	High
Scott 1999	N=18 79 events	Prospective R, AC, OL, SC. Trial period not reported.	<ul style="list-style-type: none"> <li>Students aged 5 to 22 years in residential centre for severe epilepsy (Surrey, UK).</li> <li>Prolonged convulsive seizure &gt;3 minutes.</li> <li>Severe epilepsy.</li> <li>Patients contributed multiple episodes.</li> </ul>	Buccal midazolam (formulation not reported) vs Diazepam rectal solution (doses not reported) <sup>d</sup>	Cessation of seizure activity in <10 minutes.	High

Trial	N/ events	Design	Patient population	Interventions	Primary outcome	Risk of bias
Trajano 2009	N=34	Prospective R, AC, OL, SC. May 2006 - Apr 2007.	<ul style="list-style-type: none"> <li>Children aged 1 month to 15 years admitted to emergency unit (Philippines).</li> <li>Convulsing on admission.</li> <li>Any aetiology. 35% with epilepsy.</li> </ul>	Buccal or intravenous midazolam 0.5 mg/kg vs Rectal diazepam 0.5 mg/kg (formulations not reported)	Cessation of seizure activity in <10 minutes.	High

Source: Section 2.4, pp74-88 of the submission.

Abbreviations: AC, active control; IV, intravenous; MC, multi-centre; OL, open label; R, randomised; SC, single centre; UK, United Kingdom.  
 Note: Shaded rows correspond to studies that used buccal midazolam maleate (Epistatus, the previous brand name of Zyamis)

<sup>a</sup> Age-based doses: ≤12 months - 2.5mg; 1-4 years - 5mg; 5-9 years - 7.5mg; >10 years - 10mg.

<sup>b</sup> Age-based doses: ≤5 years - 0.5 mg/kg; ≥6 years - 0.3 mg/kg.

<sup>c</sup> Individualised dosing based on prior experiences.

<sup>d</sup> Midazolam 10 mg and diazepam 10 mg preparations were used, but dose administered was not reported.

- 6.11 Allocation/randomisation in the included studies was poor. Six studies were open label with an easily identified active comparator arm (rectal diazepam). Mpimbaza 2008 was a single-blind placebo controlled study. Overall, given the methods of randomisation, identification of treatment allocation, and the limited recording of results, the risk of bias in all studies was high.
- 6.12 All studies recruited patients on presentation to hospital emergency or acute care units with prolonged seizures (Ashrafi 2010, Baysun 2005, McIntyre 2005, Mpimbaza 2008, Trajano 2009), or on experiencing prolonged seizures in residential care (Nakken 2011, Scott 1999).
- 6.13 Study design and methodology varied substantially between studies in terms of patient recruitment, location, randomisation and treatment allocation, aetiology and presentation of seizure activity, index seizure duration, intervention (formulation, dose, method of administration), and outcome definition.

### **Comparative effectiveness**

- 6.14 The key outcome presented in the submission (cessation of seizure activity) varied substantially between studies, with three studies requiring cessation of seizure activity within 10 minutes of treatment (Baysun 2005, McIntyre 2005, Mpimbaza 2008, Scott 1999 and Trajano 2009), Ashrafi 2010 applying a shorter period of 5 minutes, and four studies using composite endpoints of seizure cessation and respiratory depression and/or recurrence of seizure activity within 1 or 2 hours (Ashrafi 2010, McIntyre 2005, Mpimbaza 2008; Nakken 2011).
- 6.15 Table 5 summarises the key outcome of cessation of seizure or convulsion activity within 5 or 10 minutes of administration of buccal midazolam or rectal diazepam.

**Table 5: Patients achieving treatment success (cessation of seizures)**

Trial ID	Buccal midazolam	Rectal diazepam	Difference
<b>Cessation of seizure in &lt;5 minutes without respiratory depression or recurrence within 1 hour</b>			
Ashrafi 2010	49/49 (100%)	40/49 (82%)	p < 0.001
<b>Cessation of seizure in &lt;10 minutes</b>			
Baysun 2005	18/23 (78%)	17/20 (85%)	p > 0.05
Scott 1999 (episodes)	30/40 (75%)	23/39 (59%)	p = 0.16
Trajano 2009	12/13 (92%)	6/6 (100%)	NR
<b>Cessation of seizure in &lt;10 minutes, without recurrence within 1 hour</b>			
Mpimbaza 2008 <sup>a</sup>	115/165 (70%)	94/165 (57%)	NR
<b>Cessation of seizure in &lt;10 minutes, without recurrence within 2 hours</b>			
Nakken 2011 (episodes)	30/37 (81%)	32/43 (74%)	NR
<b>Cessation of seizure in &lt;10 minutes, without respiratory depression or recurrence within 1 hour</b>			
McIntyre 2005 (initial)	49/92 (53%)	24/85 (28%)	25% (95% CI 11, 39)
McIntyre 2005 (episodes)	61/109 (56%)	30/110 (27%)	29% (95% CI 16, 41)

Source: Table 2-12, p91 of the submission.

Abbreviations: CI, confidence interval.

<sup>a</sup> Study analysed treatment failures. Treatment success calculated post-hoc for the submission.

- 6.16 Larger proportions of patients administered buccal midazolam achieved cessation of seizures within 5 or 10 minutes of administration, compared to rectal diazepam in five studies (Ashrafi 2010, McIntyre 2005, Mpimbaza 2008, Nakken 2011, Scott 1999), while larger proportions of patients administered rectal diazepam achieved cessation of seizures within 5 or 10 minutes of administration, compared to buccal midazolam in two studies (Baysun 2005, Trajano 2009). The proportions of patients achieving treatment success varied widely between studies for both buccal midazolam (53-100%) and rectal diazepam (27-100%).
- 6.17 The submission presented the results of a post hoc analysis of seizure cessation within 10 minutes for the studies that used a composite endpoint to define treatment success. The results were generally consistent with the primary outcome results.
- 6.18 Median time to seizure cessation was generally shorter for patients treated with buccal midazolam, but varied widely between studies (2.8-10 minutes for buccal midazolam; 4.35-15 minutes for rectal diazepam).
- 6.19 In Nakken 2011 larger proportions of patients achieving treatment success experienced seizure recurrence within 2 hours in the buccal midazolam treatment arm (9.3%) compared to rectal diazepam (2.7%). However, in McIntyre 2005 and Mpimbaza 2008, smaller proportions of patients achieving treatment success experienced seizure recurrence within 1 hour, in the buccal midazolam treatment arm (12.5% versus 8% respectively), compared to rectal midazolam (38.7% versus 17.5% respectively). Ashrafi 2010 reported no recurrence of seizure activity within 1 hour, in both treatment arms.
- 6.20 Quality of life outcomes were not collected in the included studies.
- 6.21 The submission presented the results of a meta-analysis of the included studies. Given the substantial clinical and statistical heterogeneity across the included studies in terms of study methodology and study design, location, randomisation and treatment

allocation, patient characteristics, intervention (formulation, dose, method of administration), and outcome definition, and the high risk of bias in the included studies, the results of the meta-analyses are not reliable.

- 6.22 The submission also identified five published meta-analyses of the studies included in the submission. The results of the published meta-analyses are similar to the meta-analyses conducted for the submission discussed above, reported similar substantial clinical and statistical heterogeneity, and offer no additional reliable evidence.
- 6.23 The ESC noted that the submission had presented seven studies of rectal diazepam vs buccal midazolam (Table 4), and that all of the studies had a high risk of bias. As the comparator was rectal diazepam, the clinical evidence could not be used in the economic analysis, and the evidence had limited applicability to Australian clinical practice due to the widespread use of (off-label) buccal midazolam. The ESC noted that the submission had also presented a meta-analysis of the studies, and described five published meta-analyses (see paragraphs 6.21 to 6.22), however differences between the included studies made the results difficult to interpret. Overall the ESC considered it was reasonable to conclude that the clinical efficacy of buccal midazolam is similar to rectal diazepam.

### **Comparative harms**

- 6.24 Adverse events were not reported, or poorly reported in the included studies. Adverse events were not reported in the Ashrafi 2010 and Trajano 2009 studies, but Ashrafi 2010 noted that respiratory depression requiring mechanical intervention occurred infrequently in both treatment groups. Nakken 2011 and Scott 1999 reported no respiratory depression and no other observed important adverse events.
- 6.25 Baysun 2005 reported one 5 minute episode of bradypnea with oxygen desaturation (84%) in a patient treated with rectal diazepam, and one 2 minute episode of non-paroxysmal coughing in a patient treated with buccal midazolam, with both episodes resolved spontaneously.
- 6.26 McIntyre 2005 reported a low frequency of respiratory depression in children treated with buccal midazolam (5/109 episodes) and rectal diazepam (7/110 episodes), with five children requiring intubation (buccal midazolam 2/5 episodes; rectal diazepam 3/7 episodes).
- 6.27 Mpimbaza 2008 reported four patients with respiratory depression, two in each treatment arm, three of whom recovered and one (treated with rectal diazepam) who died after seizure cessation (possibly related to cerebral malaria). Twenty deaths during the study were attributed to underlying illness; i.e. malaria 10, malnutrition 3, sepsis 3, pneumonia (HIV related) 2, meningitis 2. One child experienced intense pruritus that resolved with oral antihistamines, and was possibly related to buccal midazolam.
- 6.28 Overall, there were few adverse events reported in the included studies and treatment related respiratory depression was infrequent.

- 6.29 The submission also presented the results of Connolly et al. 2015, an Australian telephone survey of 63 carers exploring carer perceptions of training for out-of-hospital use of buccal midazolam for seizures. Twenty-one carers (33%) gave buccal midazolam after appropriate training. Ten carers reported problems administering midazolam including excessive buccal secretions (N=7), difficulties in drawing up the solution (N=2) and difficulty in placing the syringe in the buccal space (N=1). Most carers reported no adverse effects when using buccal midazolam, with some carers reporting sleepiness (N=7), post-ictal irritability (N=1) and hiccups (N=1). Respiratory depression was reported by two carers, one related to a child receiving palliative care management and typically receiving multiple doses. Four children were admitted to intensive care with status epilepticus requiring intubation.
- 6.30 The most recent Periodic Benefit Risk Evaluation Report (PBRER), for the period 10 September 2016 to 09 September 2019, reported important identified risks including shallow or slow breathing (respiratory depression), sedation (CNS depression), interactions with other drugs which act on the brain (including alcohol), apnoea, respiratory arrest, cardiac arrest, memory loss (anterograde amnesia), paradoxical reactions, nausea and vomiting, and pruritis, and important potential risks including physical dependence, off label use, asphyxiation/aspiration, abuse potential/diversion, buccal irritation, oral/facial trauma, and drug-facilitated sexual assault. However, post-marketing data suggest serious adverse events are rare.
- 6.31 The ESC considered that the potential harms associated with midazolam are well recognised by prescribers.

### **Benefits/harms**

- 6.32 A benefit/harms summary was not presented due to the claim of noninferiority.

### **Clinical claim**

- 6.33 The submission described midazolam oromucosal solution as non-inferior in terms of effectiveness and safety compared to buccal or intranasal midazolam hydrochloride. The therapeutic conclusion presented in the submission was not supported by the evidence presented in the submission, given the included studies do not inform the comparison between midazolam oromucosal solution and the main comparator, buccal or intranasal midazolam hydrochloride (off-label). However, the clinical evidence presented in the submission suggests the efficacy of buccal administration of midazolam is similar to rectal diazepam.
- 6.34 In addition to the clinical claim, the submission claimed that midazolam oromucosal solution provides significantly superior and important pragmatic and practical improvements to the accurate and timely administration of midazolam during an acute health emergency. This claim was not supported by clinical evidence presented in the submission.
- 6.35 The ESC noted that the submission's claim was supported by expert advice and considered it plausible that the prefilled syringe could be beneficial as compared with

off-label use of midazolam ampoules which require carers to either draw up liquid into a syringe before administration (syringe method) or to squeeze a plastic ampoule to administer the drug to the buccal cavity (ampoule method), noting that GCSE is a stressful situation for parents and carers. The ESC also noted that some paediatric hospitals have ceased dispensing off-label midazolam for this purpose due to legal reasons or hospital policies.

- 6.36 The ESC considered that process benefits associated with the pre-filled syringe could provide benefits to patients and carers, e.g. associated with relative ease of use of the device (compared with ampoules) and due to improvements in product labelling and instructions for use which could support its appropriate use in the community (compared with ampoules). The submission acknowledged that parents and carers can be anxious about giving midazolam, and that training is needed.
- 6.37 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.
- 6.38 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***

- 6.39 The submission presented a cost-consequences analysis of the use of midazolam oromucosal solution for the treatment of GCSE events in adults and children over 6 months of age with a diagnosis of epilepsy, compared to buccal midazolam hydrochloride, based on the claim of noninferior effectiveness and safety. The economic analysis was not supported by the clinical evidence presented in the submission, but may be reasonable if the formulations are assumed to provide equivalent doses of midazolam.
- 6.40 The cost consequences analysis presented in the submission compared the costs of medicines for the treatment of GCSE, the costs of epilepsy management, and the claimed benefits of improved accuracy and timely administration of midazolam during an acute health emergency for midazolam oromucosal solution versus midazolam hydrochloride. The inclusion of the costs of epilepsy management, based on the Deloitte 2020 Economic Burden of Epilepsy in Australia 2019-2020 report, was not

justified given the results were not directly applicable to the use of midazolam in the emergency treatment of GCSE and no differences between treatments were assumed.

- 6.41 The submission assumed that the doses of midazolam administered are equi-effective at a ratio of 1 mg:1 mg, based on the assumed bioequivalence of midazolam oromucosal solution and midazolam hydrochloride administered buccally. However, the submission assumed that the drawing-up of midazolam hydrochloride from ampoules will result in substantial wastage, as up to 10 ampoules may be dispensed on each occasion. The submission assumed that remaining ampoules would not be used, either due to spillage or expiration<sup>3</sup>. Given the maximum recommended dose of midazolam hydrochloride 10 mg can be obtained from 2 ampoules of this formulation, the assumption that each episode of buccal midazolam hydrochloride would require 10 × 1 mL ampoules (50 mg) of this formulation was not adequately justified.
- 6.42 The cost of midazolam oromucosal solution was based on the proposed DPMQ of \$1 for each of the dose strengths (2.5 mg in 0.25 mL, 5 mg in 0.5 mL, 7.5 mg in 0.75 mL, 10 mg in 1.0 mL). The submission used the listed price of midazolam hydrochloride (5 mg/mL, 10 x 1mL ampoules) for the PBS Prescribers Bag (\$39.85 DPMQ; PBS item 10178Q), as a proxy for the cost of this formulation to patients. The cost of midazolam hydrochloride to patients could not be determined during the evaluation.
- 6.43 Table 6 summarises the results of the cost consequences analysis. The cost of treating one episode of GCSE with midazolam oromucosal solution or midazolam hydrochloride was combined with the annual cost of epilepsy management. No justification was provided for the assumption of one GCSE episode requiring one midazolam treatment per patient per year. It may be more appropriate to compare the drug costs of treating GCSE alone, given the assumption of no difference in epilepsy management costs.

**Table 6: Cost consequences analysis: midazolam oromucosal solution versus midazolam hydrochloride**

Service	Midazolam oromucosal solution	Midazolam hydrochloride	Increment
<b>Costs</b>			
Drug costs (based on 1 GCSE episode per person per year)	\$1	\$39.85	\$1 (1% increase)
Annual costs of epilepsy management	\$1	\$2,802.07	\$0
<b>Total costs</b>	<b>\$1</b>	<b>\$2,841.92</b>	<b>\$1</b> <b>(1% increase)<sup>a</sup></b>
<b>Benefits</b>	Midazolam oromucosal solution is associated with improved accuracy and timely administration of midazolam during an acute health emergency compared to midazolam hydrochloride		Not quantified.

Source: Table 3-6, p177 of the submission.

Abbreviations: GCSE, generalised convulsive status epilepticus.

<sup>3</sup> The submission (p182) stated that the shelf-life of midazolam oromucosal solution is currently 14 months, although this is expected to be extended to 18 months as stability data allow.

<sup>a</sup> Corrected during the evaluation. The submission inappropriately estimated the difference between treatments as a proportion of the costs associated with midazolam oromucosal solution, instead of the comparator.

- 6.44 Based on the submission's cost consequences analysis, midazolam oromucosal solution is associated with additional drug costs of \$1 compared with midazolam hydrochloride, with no difference in epilepsy management costs, and improved accuracy and timely administration of midazolam during an acute health emergency. No justification was provided for the assumption of one GCSE episode requiring one midazolam treatment per patient per year. The drug costs of midazolam hydrochloride were based on the listed price of midazolam hydrochloride on the PBS Prescriber Bag listing, as a proxy for the cost to patients. The ESC noted that based on the PBS price for the Prescriber Bag listing, midazolam hydrochloride injection ampoules, while not specifically indicated for the proposed population, are available for a substantially lower price than was requested for midazolam oromucosal solution.
- 6.45 During the evaluation, it was noted that a guideline covering diagnosis and management of epilepsy was recently published by the UK National Institute for Health and Care Excellence (NICE), including guidance for treating status epilepticus (NG217, published 27 April 2022)<sup>4</sup>. It was noted that the proposed price per dose of midazolam oromucosal solution for Australia was higher than the prices described in the corresponding evidence review underpinning NICE guideline NG217<sup>5</sup> (price per dose of £45.76 for Epistatus (the previous brand name of Zyamis) and £22.88 for Buccolam (brand not registered in Australia). The ESC noted that the proposed price per dose in Australia appears significantly higher than international prices. The pre-PBAC response noted differences between the UK setting and Australian setting including the smaller market size in Australia, and reiterated the sponsor's intention to list four different dosages of midazolam oromucosal solution to cater for all age groups, while in comparison there is only one strength of Epistatus marketed in the UK. The response also described additional costs associated with supplying the product in Australia such as costs for secure transport of goods to Australia, import permits, and costs associated with damage or wastage in the distribution channel.
- 6.46 The ESC noted that a cost-consequences analysis was provided in the base case which was not consistent with PBAC guidelines. The ESC noted that a cost-minimisation analysis is usually required where there is a claim of non-inferior efficacy and safety however the submission claimed that the proposed PBS listing would provide quality use of medicines benefits.
- 6.47 The ESC 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. The ESC considered it

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<sup>4</sup> <https://www.nice.org.uk/guidance/ng217/chapter/7-Treating-status-epilepticus-repeated-or-cluster-seizures-and-prolonged-seizures#repeated-seizures-or-cluster-seizures>, accessed 4 May 2022.

<sup>5</sup> <https://www.nice.org.uk/guidance/ng217/evidence/9-antiseizure-medication-status-epilepticus-pdf-398366282772> (see Table 11: UK costs of drugs used for Status Epilepticus), accessed 4 May 2022.

plausible that the prefilled syringe would be beneficial as compared with off-label use of midazolam ampoules and noted that a number of benefits were described in the PSCR, such as:

- 1) Enabling midazolam to be administered by carers who previously were not allowed to draw up/measure medications as part of their organisational medication policy;
- 2) Making it easier to access the buccal cavity and give the full dose (and less risk of the dose being dribbled out);
- 3) Reduced time and stress associated with drawing up midazolam.
- 4) Reduced potential complications associated with drawing up medication into a syringe such as air bubbles, inaccurate dose and spillage;
- 5) Removed the need to measure small volumes to meet dosing requirements
- 6) Reduced spillage out of the mouth due to smaller medication volumes;
- 7) Reduced bitterness compared with the IV solution, providing a significant benefit for people who require midazolam and have awareness during their seizure; and
- 8) Single doses are packaged separately, thereby reducing wastage.

6.48 The ESC noted the claim regarding improvements in accurate and timely administration and considered that the submission could have done more to map out potential consequences of the proposed listing based on published literature, even if it was unable to quantify these. The sponsor could have mapped out the causal chain of expected effects that may feasibly result from the proposed listing, especially in relation to risks or benefits that may impact survival and/or quality of life. The ESC also noted that process benefits could have been described, and potential for cost savings (reduced waste and hospitalisations). The proposed mapping may also be informed by input from experienced clinicians and patients/carers with knowledge of the treatment of GCSE, such as the benefits described by the Epilepsy Foundation in the PSCR (see paragraph 6.47). The ESC considered that a consolidated list of potential effects would be valuable to the PBAC to assist understanding of the potential value of quality use of medicines benefits. The PBAC noted that a summary table was provided in the pre-PBAC response which listed potential beneficial impacts such as 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.

### **Drug cost per GCSE event**

6.49 The cost of treating one GCSE event with midazolam oromucosal solution is \$ [REDACTED] (DPMQ), for all dose strengths based on the price proposed in the submission and assuming that a single dose is used.

### Estimated PBS usage & financial implications

- 6.50 This submission was not considered by DUSC. The submission used an epidemiological approach to estimate the utilisation and financial impact associated with the PBS listing of midazolam oromucosal solution for the treatment of GCSE in patients over the age of 6 months with epilepsy, using an incidence/prevalence model.
- 6.51 The key inputs used in the financial estimates are presented in Table 7.
- 6.52 The submission estimated the prevalent pool of patients based on separate incident cohorts of patients diagnosed with epilepsy and GCSE in each of the 6 years prior to listing. However, the submission incorrectly estimated the size of the eligible population by treating the prevalent population in each year of each cohort as unique patients rather than the same patients over time. For example, for patients diagnosed six years ago (in 2016), the patients eligible in Year 1 of listing are assumed to be distinct from the patients eligible from the 2016 cohort in Year 2, Year 3, and up to Year 6 of listing; and their persistence to treatment over the six years of listing subsequently calculated. This significantly overestimated the number of eligible patients in the prevalent population. The submission’s estimates of financial implications to the PBS were corrected during the evaluation and presented below in Table 8.

**Table 7: Key inputs for financial estimates**

Parameter	Value applied and source	Comment
<b>Eligible population</b>		
Prevalence of epilepsy in the Australian population	Adults >18 years = 0.7% Children 0-17 years = 0.5% (ABS National Health Survey 2017-2018).	This is appropriate.
Annual incidence of epilepsy	Adults >18 years: 0.072% Children 0-17 years: 0.051%	Incidence to prevalence ratio (0.1023 per 1,000 persons) derived from Deloitte 2020, applied to the ABS National Health Survey prevalence data to transform prevalence to incidence.
Proportion of population with epilepsy likely to experience ≥ 1 prolonged seizure in a lifetime	Adults: 15% (Trinka 2012)  Children: 27% (Sillanpaa 2002)	Proportions of adults likely to experience a GCSE during their lifetime derived from Trinka (2012), included all SE including non-convulsive and focal seizures. This is most likely an overestimate. Proportions of children likely to experience a GCSE event during their lifetime were derived from Sillanpaa 2002, a prospective cohort study of 150 children <16 years with new onset epilepsy between 1961 and 1964 (Finland) observed from 1972 to 1997 (data were 50-25 years old). As a simplifying assumption, the submission assumed that the index GCSE event occurred in the year of diagnosis. Given the advances in epilepsy management and diagnosis over time, these data do not reflect the contemporary Australian setting.

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Parameter	Value applied and source	Comment
Persistence	100% Years 1-5 (assumption) 51% from Year 6 onwards (Sillanpaa 2002)	The assumption of 100% persistence for Years 1-5 is not plausible. The submission assumed that patients not experiencing a recurrent event within 5 years of their index event cease using midazolam in Year 6, and reduced the population by 49% in Year 6 (1.0 - 0.51; Sillanpaa 2002), but not in subsequent years. As above, these data do not reflect the contemporary Australian setting. Given prescribed midazolam oromucosal solution may be a core component of Epilepsy Management Plans (particularly in children), the cessation of treatment after five years may not be reasonable.
Uptake of midazolam oromucosal solution	Adults: █% - █% over 6 years Children: █% - █% over 6 years	Assumed. Uptake of midazolam oromucosal solution is highly uncertain.
Average number of scripts/patient/index event and recurrent events	Index event: 1 script in Year 1 Recurrent events: 1.73 scripts/year (Sillanpaa 2002)	The submission assumed one additional script for all patients in Year 1 for the index event. Based on the proportions of patients experiencing 2-3 (34%) or ≥4 (22%) GCSE events in a year, reported in Sillanpaa 2002. Calculated: $[2.5 \times 0.34] + [4 \times 0.22] = 1.73$ . As noted above, older data may not reflect the contemporary Australian setting.
Average number of scripts/patient/year adjusted for used and expired medicines	1.00173 scripts/patient/year Based on the proportion of patients experiencing a GCSE event per year and requiring replacement scripts (based on cumulative incidence data from Sillanpaa 2002); and the assumption that patients without an event will require 1 script per year due to expiry (14 month shelf-life with an effective dispensed expiry of 12 months).	The sum of scripts for each year (replacement scripts and expiry scripts) was ≤1 for all years other than Year 1. <sup>a</sup> This estimate is not plausible, given most patients would require at least one replacement script every 12 months, and additional scripts for recurrent GCSE events.
Average patient copayment	PBS: \$4.75 RPBS: \$4.98	Based on the average patient copayment for clonazepam 1 mg/mL ampoules for injection (PBS item 1807D), restricted benefit for slow intravenous infusion; 2020. The average patient copayment was low and may underestimate the patient copayment associated with midazolam oromucosal solution.

Source: Table 4-1, p183 and Table 4-2, p184 of the submission.

Abbreviations: ABS, Australia Bureau of Statistics; GCSE, generalised convulsive status epilepticus.

<sup>a</sup> Total scripts (adjusted for used and expired scripts) for Year 1 = 1.54; Year 2 = 0.6540; Year 3 = 0.8847; Years 4 & 5 = 1.0; Year 6 = 0.9527.

6.53 Table 8 summarises the financial impact of listing midazolam oromucosal solution on the PBS.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Total Australian population (ABS)	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 (ABS)	5,969,108	6,064,728	6,150,343	6,225,933	6,299,095	6,372,633
Incident epilepsy patients (0.051%)	1	1	1	1	1	1
Experiencing GCSE (27%)	1	1	1	1	1	1
Treatment uptake	%	%	%	%	%	%
Incident patients	2	1	1	1	1	1
Total incident/persistent treated	2	1	1	1	1	1
<b>Children aged 0-17 years with historic diagnosis up to 6 years prior to Year 1<sup>a</sup></b>						
Historic persistent children treated	1	1	1	1	1	1
<b>Total children treated</b>	1	1	1	3	3	3
<b>Adults aged 18-100 years diagnosed in Years 1-6</b>						
Australian population (ABS)	20,757,917	21,082,471	21,411,852	21,744,502	22,073,220	22,393,101
Incident epilepsy patients (0.072%)	4	4	4	4	4	4
Experiencing GCSE (15%)	1	1	1	1	1	1
Treatment uptake	%	%	%	%	%	%
Incident patients	1	1	1	1	1	1
Total incident/persistent treated	1	1	1	1	3	3
<b>Adults aged 18-100 years with historic diagnosis up to 6 years prior to Year 1<sup>a</sup></b>						
Historic persistent adults treated	3	3	3	3	3	3
<b>Total adults treated</b>	3	3	4	4	4	4
<b>Total patients treated</b>	3	4	4	4	4	4
Total patients treated (submission)	3	5	6	7	8	9
<b>Estimated cost of midazolam oromucosal solution to the PBS/RPBS</b>						
Number of scripts (1.00173/pt/year)	3	4	4	4	4	4
Cost to the PBS/RPBS (\$ /script)	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
Patient copayments (\$4.76/script)	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
<b>Net cost to the PBS</b>	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
Cost to the PBS/RPBS (\$ /script)	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
Patient copayments (\$4.85/script)	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10	\$ 10
<b>Net cost to the RPBS</b>	10	10	10	10	10	10
<b>Net cost to the PBS/RPBS</b>	10	10	10	10	10	10

Source: Constructed during the evaluation using the Attachment 14 of the submission- Section 4 model.

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

<sup>a</sup> Incident and prevalent cohorts calculated using the same methods as applied for patients with index events in Years 1-6.

The redacted values correspond to the following ranges:

<sup>1</sup> 500 < 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> 20,000 to < 30,000

<sup>6</sup> 30,000 to < 40,000

<sup>7</sup> 40,000 to < 50,000

<sup>8</sup> 50,000 to < 60,000

<sup>9</sup> 60,000 to < 70,000

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

6.54 The estimated net cost to the PBS/RPBS was \$0 to < \$10 million in Year 1, increasing to \$0 to < \$10 million in Year 6, and a total of \$10 million to < \$20 million over 6 years (corrected during the evaluation). The submission estimated a net cost to the

PBS/RPBS of \$0 to < \$10 million in Year 1, increasing to \$10 million to < \$20 million in Year 6, and a total of \$30 million to < \$40 million over 6 years (uncorrected).

- 6.55 The estimated cost of midazolam oromucosal solution to the PBS/RPBS is highly uncertain, and may not be reliable:
- Many of the assumptions underpinning the estimated eligible population were derived from observational data from 1972-1997 (Sillanpaa 2002), which do not reflect contemporary Australian clinical practice.
  - The uptake of midazolam oromucosal solution was assumed, and highly uncertain.
  - The estimated numbers of scripts required to replace used and expired supply was most likely underestimated, and the likelihood of a second dose of midazolam being used was not adequately considered in the submission.
  - The prevalent cohort only included patients diagnosed with epilepsy in the 6 years prior to listing. This excluded patients diagnosed with epilepsy more than 6 years ago who may have experienced a recent GCSE event, and would be eligible for treatment under the proposed restriction.
- 6.56 The ESC considered that the corrections made by the commentary were appropriate, and noted the uncertainties in the financial estimates as described in paragraph 6.55. The ESC considered that the corrected estimates remained highly uncertain and possibly underestimated. The ESC noted that the corrected estimates (total of \$12.5 million over 6 years), were considerably lower than the estimates in the submission (total of \$39.8 million over 6 years, see paragraph 6.54). The ESC noted that the estimates assumed a maximum quantity of one pen, and that if the maximum quantity was changed there may be additional costs because of wastage (see paragraph 3.2).
- 6.57 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 was submitted via consumer comments (see paragraph 6.3). 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 noted there may be additional costs due to wastage if higher quantities are dispensed, given that a proportion of patients will not experience any GCSE episodes within the shelf-life of the product and will fill their repeat prescription due to expiry, rather than use of the product.

### ***Quality Use of Medicines***

- 6.58 No quality use of medicines issues were addressed in the submission.
- 6.59 However, the submission acknowledged that parents and carers can be anxious about giving midazolam, so training is needed. It was noted that education is available from specialist epilepsy nurses and can be arranged through patient support organisations such as Epilepsy Action ([www.epilepsy.org.au](http://www.epilepsy.org.au)) and Epilepsy Australia ([www.epilepsyaustralia.net](http://www.epilepsyaustralia.net)). The ACM also acknowledged that caregivers may not be

comfortable administering these treatments in an emergency setting without adequate training, and therefore supported a clear and targeted training plan (ACM August 2021, p6). It is unclear whether existing training programs and resources include sufficient resources targeting the effective prescribing, dispensing and use of midazolam oromucosal solution.

- 6.60 The PSCR provided further information related to proposed training for parents/carers, prescribers, pharmacists and healthcare workers for the safe and effective use of midazolam oromucosal solution, and quality use of medicines initiatives required as part of the Risk Management Program.
- 6.61 The most recent Periodic Benefit Risk Evaluation Report (PBRER), for the period 10 September 2016 to 09 September 2019, identified the potential risk of abuse and diversion of midazolam oromucosal solution. It is unclear whether this risk has been adequately addressed by the sponsor.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend midazolam oromucosal solution for the treatment of generalised convulsive status epilepticus. 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.
- 7.2 The PBAC noted the input from health care professionals and organisations highlighting quality use of medicines benefits associated with midazolam oromucosal solution as compared with off-label use of midazolam ampoules in terms of more effective use of the drug due to correct dosages being given, and less risk of harm from incorrect dosing. The PBAC also noted that the proposed listing would improve access to effective medication during an episode of GCSE, particularly for those living far from hospital settings, or in the context of carers experiencing difficulties using the ampoules.
- 7.3 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 (see paragraph 3.10). 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 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 (see paragraph 6.57).

- 7.4 The PBAC considered that training will be essential for medication givers (family members or carers) with respect to seizure recognition and midazolam administration (see paragraph 3.12).
- 7.5 The PBAC noted that the TGA evaluation was based on a literature-based submission and despite extensive use of midazolam in clinical practice, there was limited evidence available to inform the clinical and economic evaluations of the PBAC submission. The PBAC noted the TGA comments that the bioequivalence of midazolam oromucosal solution and midazolam hydrochloride, administered buccally, was demonstrated in healthy adults in a pharmacokinetic study (SPL002), but no bioequivalence studies were conducted in children (see paragraph 2.2).
- 7.6 The PBAC considered that midazolam hydrochloride was an appropriate comparator as it is widely recognised as appropriate first line therapy for GCSE in the out-of-hospital emergency setting, as documented in clinical guidelines.
- 7.7 The PBAC noted that a comparison of clinical outcomes between midazolam oromucosal solution and the main comparator (midazolam hydrochloride) could not be presented because no clinical studies were identified directly comparing midazolam oromucosal solution with midazolam hydrochloride, or that were suitable for an indirect comparison.
- 7.8 The PBAC noted that the submission presented seven head-to-head prospective studies comparing buccal administration of midazolam with rectal administration of diazepam. Two of the seven trials used the proposed formulation of midazolam oromucosal solution, and all trials had a high risk of bias (see Table 4). The proportions of patients achieving treatment success varied widely between studies for both buccal midazolam (53-100%) and rectal diazepam (27-100%). The PBAC noted that larger proportions of patients administered buccal midazolam achieved cessation of seizures within 5 or 10 minutes of administration, compared to rectal diazepam in five studies (Ashrafi 2010, McIntyre 2005, Mpimbaza 2008, Nakken 2011, Scott 1999), while larger proportions of patients administered rectal diazepam achieved cessation of seizures within 5 or 10 minutes of administration, compared to buccal midazolam in two studies (Baysun 2005, Trajano 2009). The PBAC noted that adverse events were either not reported, or were poorly reported in the included studies. Overall, there were few adverse events reported in the studies and treatment related respiratory depression was infrequent. The PBAC considered that the potential harms associated with midazolam are well recognised by prescribers.

- 7.9 The PBAC noted the submission's claim that midazolam oromucosal solution was 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.
- 7.10 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. 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.
- 7.11 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 (see paragraphs 6.2 and 6.3), the ESC advice (see paragraph 6.35), the PSCR (see paragraph 6.47) and the pre-PBAC response (see paragraph 6.48), 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 \$1 versus \$40) was not justified. 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.
- 7.12 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 (see paragraph 6.3). 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, and that a risk sharing arrangement would be required due to uncertain financial estimates.

7.13 The PBAC considered the outstanding issues could be easily resolved in a simple resubmission for midazolam using the early re-entry pathway. If the sponsor accepts this pathway, the following changes may address these outstanding issues without requiring further re-evaluation.

- Revised PBS criteria as outlined in paragraph 7.3.
- A price reduction to achieve a cost-effective listing as outlined in paragraph 7.11.
- Revised financial estimates incorporating changes to the restriction and price as outlined in paragraph 7.12.
- A risk sharing arrangement as outlined in paragraph 7.12.

The early re-entry resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If the issues cannot be addressed by the sponsor in a simple resubmission and the early re-entry timing is not acceptable, a standard re-entry pathway is available.

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

**Outcome:**

Not recommended

## **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 will continue to work with PBAC to find a path to listing for this important product.