Application for Inclusion of Buccal Midazolam in the WHO List of Essential Medicines

Submitted by

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To:
Expert Committee on the Selection and Use of Essential Medicines
1. Summary statement of the proposal for inclusion, change or deletion

Parenteral midazolam is proposed for buccal administration for the treatment of acute repetitive convulsive seizures and prolonged convulsive seizures, including status epilepticus where an intravenous access is unavailable, in both children and adults.

2. Name of the focal point in WHO supporting the application

Dr Tarun Dua, Department of Mental Health and Substance Abuse  
Dr Wilson Were, Department of Maternal, Newborn, Child and Adolescent Health

3. Name of the organizations consulted and supporting the application

WHO Collaborating Centre for Research and Training in Mental Health and Service Evaluation, Department of Public Health and Community Medicine, Section of Psychiatry, University of Verona, Verona, Italy  
WHO Collaborating Centre for Research and Training in Child and Neonatal Health, Centre for International Child Health, University of Melbourne, Australia

4. International non-proprietary name of the medicine

Midazolam

5. Formulation proposed for inclusion

The EML already contains intravenous preparations of midazolam as a preoperative/sedative medication and as a medicine for use in palliative care. This application is for the additional inclusion of use of parenteral formulation for buccal use for the control of acute convulsive seizures.

6. Information supporting the public health relevance

Seizures are common presentation in emergency room settings. The treatment for acute convulsive seizures is aimed at earliest cessation of seizures in order to prevent progression to status epilepticus, cardiorespiratory compromise and cerebral damage. Absence of timely intervention may lead to a protracted seizure episode that is more difficult to control with significant subsequent neurological morbidity and mortality.

Dispensing antiepileptic drugs intravenously is the fastest route of administration, however, achieving peripheral venous access may be difficult in a convulsing person, especially children. This situation is compounded by resource constraints, lack of trained personnel and pre-hospital settings resulting in the frequent use of non-intravenous routes as the first line for
administration of anticonvulsant medications in resource limited settings. Similarly, IV access is not possible in home settings by parents/caregivers.

The treatment most commonly used around the world to abort prolonged or rapidly recurring seizures is rectal diazepam, partly because in some countries it is the only treatment option or the only licensed medication for this indication. In 2004, the evidence-based guidelines of the Royal College of General Practitioners, London, already recognized that “for many individuals and in many circumstances, buccal midazolam is more acceptable than rectal diazepam and is easier to administer”. Since then, further evidence has accumulated indicating that buccal midazolam to be more effective than rectal diazepam (the most appropriate comparator in this indication) in the emergency management of convulsive seizures when an intravenous line is not available, e.g., in the absence of medical personnel, or difficult to access, e.g., in a convulsing small child.

7. Treatment details

7.1 Indications

Buccal midazolam is indicated for the treatment of acute repetitive convulsive seizures and prolonged convulsive seizures, including status epilepticus where an intravenous access is unavailable, in both children and adults.

7.2 Dose

For buccal administration of midazolam, the parenteral injection formulation licensed for intravenous and intramuscular use may be employed. The recommended doses is usually about 0.3-0.5 mg/kg in children and 10 mg in adults.

If the midazolam injection formulation is used, to administer the prescribed amount the appropriate volume is drawn up from the ampoule through a filter straw attached to a syringe, and the syringe is then placed into the side of the patient’s mouth, between the gums and the teeth. Preferably, the dose is given half into one cheek and half into the other cheek. Written instructions on how and when to administer should be given to patient and caregivers.

Midazolam preparation specifically indicated for buccal administration are available, for example:

- Buccolam® - contains Midazolam Hydrochloride 5mg in 1ml in pre-filled oral syringes of 2.5mg, 5mg, 7.5mg and 10mg.
- Epistatus® - contains Midazolam Maleate 10mg in 1ml. It is a preparation in a 5ml bottle with four oral syringes in the packaging. Epistatus® is also available as pre-filled oral syringes of 2.5mg, 5mg, 7.5mg and 10mg. This is an unlicensed product, available as a ‘special’.

7.3 Monitoring

Patients with seizures who receive buccal midazolam will need monitoring of vital signs, oxygenation and respiratory efforts.
8. Summary of comparative effectiveness in a variety of clinical settings

The Department of Mental Health and Substance Abuse (MSD) and the Maternal, Newborn, Child and Adolescent Health Department (MCA) recently commissioned review of evidence on management of acute convulsive seizures in adults and children, when no IV access is available, as part of the update of Mental Health Gap Action Programme (mhGAP) Guidelines for management of mental, neurological and substance use disorders including epilepsy (http://www.who.int/mental_health/mhgap/evidence/en/) and Paediatric Emergency Triage Assessment and Treatment (ETAT) Guidelines on Fluids, Oxygen therapy and Seizures http://www.who.int/maternal_child_adolescent/documents/9241546875/en/.

These evidence profiles included the evidence on comparative effectiveness of buccal midazolam. Both the guidelines are currently in the process of finalisation to be approved by WHO Guideline Review Committee. The recommendations for the management of acute convulsive seizures in adults and children, when no IV access is available have been ratified by the respective Guideline Development Groups.

8.1 Systematic search for evidence

In order to identify relevant systematic reviews the following databases were searched: Medline, Embase, The Cochrane Library, BMJ Clinical Evidence and Psychinfo up to September 2014. The following search strategy, developed by the McMaster University for systematic reviews was used to identify existing meta analyses: (meta analysis [Publication Type] OR meta analysis [Title/Abstract] OR meta analysis [MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]). The following additional terms were used: (status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR paraldehyde).

In order to identify additional primary studies, the search strategy developed by the McMaster University for Randomised controlled trials was used:

(randomized controlled trial [Publication Type] OR randomized [Title/Abstract] OR placebo [Title/Abstract]). The following additional terms were used: (status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR paraldehyde) and the search included studies from 2008 to October 2014.

8.2 Inclusion and exclusion criteria

Having found primary studies from recent years and there being no systematic review published in the last two years including non IV treatment of acute seizures, a new systematic review and meta-analysis was completed. The inclusion and exclusion criteria for this review were as follows:

Study type and design: Randomized controlled trials, quasi-randomized controlled trials, irrespective of blinding.

Population: Children and adults or children presenting with an acute seizure (hospital or community setting) and who received treatment with an anticonvulsant medication,
irrespective of the duration of the presenting convulsion. Children including those presenting
de novo with a first convulsion and those with an established diagnosis of epilepsy. Any and
all causes of the convulsion (including convulsive status epilepticus) were included in the
review.

Interventions: In adults or children presenting with an acute seizure including status
epilepticus, trials were included if they compared one treatment with another. Specific
medicines included the benzodiazepines (diazepam, lorazepam and midazolam), and
paraldehyde. Different routes of medication administration were also included, these included
intra-venous, intra-nasal, buccal, sub-lingual, rectal and intra-muscular administration.

Outcome measures:

1. Efficacy (Cessation of seizure within 10 minutes of medication administration)
2. Safety (Incidence of respiratory depression requiring intubation/ventilation)

8.3 Data collection and analysis methodology

Two members of the research team independently assessed trials for inclusion. The research
team extracted the outcome data according to the inclusion and exclusion criteria specified
above and a preliminary assessment of the quality of the evidence. Data were independently
extracted by two review authors and cross-checked. Any disagreements were resolved by
team discussion.

The preliminary methodological quality assessment of each trial was carried out using the
following criteria: randomisation method; baseline comparability of the trial arms; allocation
concealment; method of double-blinding; and full reporting of analysis exclusions. If the
evidence was deemed of satisfactory quality, it was included.

The primary meta-analysis analysis was by ‘intention-to-treat’ and included all randomized
participants, analysed in the treatment group to which they were allocated, irrespective of
which treatment they actually received. Clinical heterogeneity was assessed by reviewing the
differences across trials in characteristics of recruited participants and treatment protocols as
well as being assessed statistically using a chi squared test and I² for heterogeneity.
Dichotomous outcomes were expressed as relative risks (RR) with 95% confidence intervals
(CIs).

8.4 Details of included studies in GRADE tables and footnotes

Systematic reviews

convulsions including convulsive status epilepticus in children. Cochrane Database of
Systematic Reviews, (3):CD001905.13

This was a systematic review of randomized and quasi-randomized controlled trials
comparing any anticonvulsant drugs used for the treatment of an acute tonic-clonic
convulsion including convulsive status epilepticus in children were reviewed. Four trials
(Appleton 1995, Lahat 2000, McIntyre 2005, Ahmad 2006) involving 383 participants were included.


This was a systematic review of randomized and quasi-randomized controlled trials comparing non-IV midazolam to IV or non-IV diazepam for treatment of status epilepticus in pediatric and adult patients were included. Six trials (Chamberlain 1997, Lahat 2000, Mahmoudian 2004, McIntyre 2005, Mpimbaza 2008, Scott 1999) involving 774 participants were included.


This was a systematic review of randomised controlled trials of participants with premonitory, early, established or refractory status epilepticus using a truly random or quasi-random allocation of treatments were included. Eleven studies (including Chamberlain 1997) with 2017 participants were included.


This was an update of the Prasad 2005 systematic review of randomised controlled trials of participants with premonitory, early, established or refractory status epilepticus using a truly random or quasi-random allocation of treatments for inclusion. Eighteen studies (including Silbergleit 2012) with 2755 participants were pooled and presented in this systematic review.

Additional Individual Studies


8.6 GRADE tables

1. Comparative efficacy of buccal midazolam and intravenous diazepam: The RCT by Talukdar et al compared buccal midazolam (IV formulation administered through the buccal route) with intravenous diazepam (N=120) in children. Children aged up to 12 years presenting with acute seizures (generalised, focal seizures) in the pediatric emergency department were included. 120 children were randomized into buccal midazolam (0.2 mg/kg midazolam IV solution [1 mg/ml] squirted into the buccal mucosa by syringe) and
intravenous diazepam (0.3 mg/kg) groups. Seizure cessation within 10 minutes was seen in 51/60 (85%) children in midazolam group and 56/60 (93.3%) children in diazepam group [RR 0.91 (0.8 to 1.03)]. The evidence has been graded as below:

**Author(s): Puneet Jain**  
**Settings: Emergency Department**  

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Buccal Midazolam</th>
<th>Intravenous Diazepam</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure cessation within 10 minutes (assessed with: Clinical Observation)</td>
<td>1 randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>serious&lt;sup&gt;2&lt;/sup&gt;</td>
<td>none</td>
<td>51/60 (85%)</td>
<td>56/60 (93.3%)</td>
<td>RR 0.91 (0.8 to 1.03)</td>
<td>84 fewer per 1000 (from 187 fewer to 28 more)</td>
<td>LOW</td>
<td>CRITICAL</td>
</tr>
<tr>
<td>Respiratory Depression requiring intubation (assessed with: Clinical observation)</td>
<td>1 randomised trials</td>
<td>none</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0/60 (0%)</td>
<td>0/60 (0%)</td>
<td>-</td>
<td>-</td>
<td>CRITICAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> No mention of allocation concealment  
<sup>2</sup> CI crossing line of no effect  

2. Comparative efficacy of buccal midazolam and rectal diazepam: Following relevant studies were identified:


Five studies compared buccal midazolam with rectal diazepam for management of acute convulsive seizures. Three studies were pediatric studies. Nakken 2011 and Scott 1999 also included adults. Two studies used the buccal solution, Epistatus. Other three studies used IV preparation for the buccal use.

The meta-analysis methodology is reported in section 8.3

Outcome 1: Seizure cessation within 10 minutes

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buccal Midazolam</th>
<th>Rectal Diazepam</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott 1999</td>
<td>30/40 23/39</td>
<td></td>
<td>1.27 [0.93, 1.75]</td>
</tr>
<tr>
<td>McIntyre 2005</td>
<td>71/109 45/110</td>
<td></td>
<td>1.59 [1.22, 2.07]</td>
</tr>
<tr>
<td>Mpimbaza 2008</td>
<td>125/165 114/165</td>
<td></td>
<td>1.10 [0.96, 1.25]</td>
</tr>
<tr>
<td>Ashrafi 2010</td>
<td>49/49 49/49</td>
<td></td>
<td>1.00 [0.96, 1.04]</td>
</tr>
<tr>
<td>Nakken 2011</td>
<td>32/37 37/43</td>
<td></td>
<td>1.01 [0.84, 1.20]</td>
</tr>
</tbody>
</table>

Total (95% CI): 400/406 100.0% 1.16 [0.89, 1.51]

Outcome 2: Respiratory Depression requiring intubation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Buccal Midazolam</th>
<th>Rectal Diazepam</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashrafi 2010</td>
<td>0/49 0/49</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>McIntyre 2005</td>
<td>2/109 3/110</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Mpimbaza 2008</td>
<td>0/165 0/165</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Nakken 2011</td>
<td>0/37 0/43</td>
<td></td>
<td>Not estimable</td>
</tr>
<tr>
<td>Scott 1999</td>
<td>0/40 0/39</td>
<td></td>
<td>Not estimable</td>
</tr>
</tbody>
</table>

Total (95% CI): 400/406 100.0% 0.67 [0.11, 3.95]
The second GRADE table assesses the quality of the new meta-analysis of five primary studies:

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Buccal Midazolam</th>
<th>Rectal Diazepam</th>
<th>Relative (95% CI)</th>
<th>Absolute</th>
<th>Quality</th>
<th>Importance</th>
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<tbody>
<tr>
<td>Seizure cessation within 10 minutes (assessed with: Clinical observation)</td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>randomised trials</td>
<td>serious</td>
<td>Very serious</td>
<td>no serious indirectness</td>
<td>serious</td>
<td>none</td>
<td>307/400 (76.8%)</td>
<td>268/406 (66%)</td>
<td>RR 1.16 (0.89 to 1.51)</td>
<td>106 more per 1000 (from 73 fewer to 337 more)</td>
<td>☀️ đo</td>
<td></td>
</tr>
<tr>
<td>Respiratory depression requiring intubation (assessed with: Clinical observation)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5</td>
<td>randomised trials</td>
<td>serious</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>very serious</td>
<td>none</td>
<td>2/400 (0.5%)</td>
<td>3/406 (0.74%)</td>
<td>RR 0.67 (0.11 to 3.95)</td>
<td>2 fewer per 1000 (from 7 fewer to 22 more)</td>
<td>☀️ đo</td>
<td></td>
</tr>
</tbody>
</table>

1 Nakken 2011 was a quasi-randomized (groups were assigned alternatively) study; All studies were open label; Allocation concealment only mentioned in Mpimbaza 2008.
2 High heterogeneity, I²=94%
3 Nakken 2011 was done in adults
4 Wide confidence interval crossing line of no effect
5 Nakken 2011 was a quasi-randomized (groups were assigned alternatively) study; All studies were open label; Allocation concealment only mentioned in Mpimbaza 2008.
6 Small number of events; Wide CI crossing line of no effect

**Summary of results**

Talukdar et al study\(^2\) demonstrates that the overall frequency of response in both the groups (buccal midazolam and IV diazepam) was similar and this suggests that buccal midazolam might be equally effective in controlling acute convulsions of the types of generalized tonic, tonic–clonic and complex partial within a short time irrespective of their duration and resulting from diverse etiology. The drug effect was faster with IV diazepam and this is obviously due to the drug being pushed directly into blood, while with buccal midazolam some more time is needed for absorption of the drug from buccal mucosa. The treatment initiation time was shorter with buccal midazolam as the solution could be quickly instilled into the buccal mucosa, whereas with IV Diazepam more time was needed as it involved transferring the solution into the syringe, starting an intravenous line and pushing the drug slowly and carefully. In some cases, especially infants, one might struggle for quite some time to have an intravenous line in place. The total controlling time was significantly shorter with buccal midazolam, obviously due to shorter treatment initiation time.
The result of meta-analysis demonstrate that buccal midazolam is at least as effective as rectal diazepam in the acute treatment of seizures. Administration via the mouth is more socially acceptable and convenient and may become the preferred treatment for seizures that occur outside hospital.

9. Summary of comparative evidence on safety

The impact of not having buccal midazolam for the treatment of active convulsive seizures where an intravenous access is unavailable, would be lack of early seizure control, prolonged seizures, resulting in more cases of established and refractory status epilepticus and, consequently, increased mortality and sequelae from brain damage and systemic complications. Increased numbers of patients will require admission to medical facilities, including intensive care units in centres lacking such facilities, and medical centres will be unable to cope with the higher load of patients due to lack of safe transport systems and bed space.

The most common serious adverse effect of midazolam is respiratory depression, although the risk is primarily associated with intravenous use, particularly in combination with other central nervous system depressants. The tolerability of buccal midazolam is generally favorable and complications occur no more frequently with buccal midazolam than with other anticonvulsants used in the same setting. This is reflected by the studies included in the meta-analysis above: Talukdar\textsuperscript{21}, which did not report any neurologic or cardiorespiratory depression; McIntyre\textsuperscript{16}, in which less than 2\% of the (n=109) children who had received buccal midazolam required intubation; and the rest of the adverse events studies did not report any serious adverse effect with use of buccal midazolam\textsuperscript{22-25}.

Less common adverse effects include hypotension, cardiac arrhythmias, and hypersensitivity reactions such as angioedema and bronchoconstriction. Overall, the most common adverse effects of midazolam consist on sedation and, less frequently, hiccups, cough, nausea and vomiting. Other adverse effects include altered coordination, dyskinesias, and paradoxical reactions such as agitation, restlessness, disorientation, hostility, aggression and rage.

10. Summary of available data on comparative cost and cost-effectiveness within the pharmacological class or therapeutic group:

In a recent European cost effectiveness analysis including data from five countries\textsuperscript{26} was undertaken for children with seizures receiving buccal midazolam in the community setting. The model assessed the likelihood of medication being administered successfully, seizure cessation, ambulance call-outs, hospitalisations and patient quality of life. Despite differences in current therapy, treatment patterns and healthcare costs in all countries assessed, Buccolam was shown to be cost saving and offered increased health-related benefits for patients in the treatment of prolonged acute convulsive seizures compared with the current local standard of care.

In a further cost effectiveness analysis from Spain\textsuperscript{27} and not included in the aforementioned European analysis, results showed that buccal midazolam use in the community setting is more cost-effective than rectal diazepam (reduction in the need to call out ambulances and for stays in hospital, as well as an improved health-related quality of life).
According to the International Drug Price Indicator Guide 2013, the median price of midazolam 5 mg/mL is 0.26 U.S. $./ml

11. Summary of regulatory status of medicine.
Midazolam injection is widely available. The specific buccal preparation may not be widely available, however, various human studies have used intravenous preparation for buccal use.

The EML already contains intravenous preparations of midazolam as a preoperative/sedative medication and as a medicine for use in palliative care.

Buccal midazolam is suitable for administration by non-medical personnel. Although adverse effects may occur, including respiratory depression, its safety is adequate for use in the community setting.

Some examples of midazolam preparation specifically indicated for buccal administration are:

- **Buccolam®** - contains Midazolam Hydrochloride 5mg in 1ml in pre-filled oral syringes of 2.5mg, 5mg, 7.5mg and 10mg.
- **Epistatus®** - contains Midazolam Maleate 10mg in 1ml. It is a preparation in a 5ml bottle with four oral syringes in the packaging. Epistatus® is also available as pre-filled oral syringes of 2.5mg, 5mg, 7.5mg and 10mg. This is an unlicensed product, available as a ‘special’.

12. Availability of pharmacopoieal standard
Parenteral midazolam is listed in various drug catalogues, including the British and the Australian formularies.

13. Proposed text for the WHO Model Formulary
Listing is requested as an individual medicine and formulation (parenteral formulation, for use by the buccal route).

**Buccal Midazolam**

*Injection, (solution for injection)* 5 mg/ml, 1 mg/ml (administered into the buccal cavity between the gum and cheeks by syringe)

**Uses:**
treatment of acute repetitive convulsive seizures and prolonged convulsive seizures, including status epilepticus where an intravenous access is unavailable, in both children and adults.

**Dosage:**
- Child (6 months and older): 0.2-0.5 mg/kg (maximum single dose 10 mg) by the buccal route
- Adult: 10 mg by the buccal route

Repeat doses:
- If seizures persist after 10 min in small children at the lower end of the age range (<5 years), and ambulance should be called and a further single dose may be given while en route to the emergency department. A third dose must not be administered sooner than 6 h after the second dose.
- If seizures persist after 10 min in children at the upper end of the age range and the child is breathing normally, give a second dose. If the child is breathing shallowly, call an ambulance and do not give a second dose. If no effect is seen after the second dose, call an ambulance. A third dose must not be administered sooner than 6 h in children under 40 kg and sooner than 12 h in adults.

Higher initial doses: An initial dose of 0.5 mg/kg (maximum single dose 10 mg) may be given if the patient is at an emergency department with facilities for mechanical ventilation.

**Adverse effects:**

**Common**
Dizziness, vertigo, ataxia, disorientation, irritability

**Serious**
Cardiorespiratory depression

The most common serious adverse effect of midazolam is respiratory depression, although the risk is primarily associated with intravenous use, particularly in combination with opiates during anesthesiology practice\(^{28,29}\). Less common serious adverse effects include hypotension, cardiac arrhythmias, and hypersensitivity reactions such as angioedema and bronchoconstriction\(^{28,29}\). Overall, the most common adverse effects of midazolam consist in sedation and, less frequently, hiccups, cough, nausea and vomiting. Other adverse effects include altered coordination, dyskinesias, and paradoxical reactions such as agitation, restlessness, disorientation, hostility, aggression and rage\(^{66}\). As with all benzodiazepine drugs, withdrawal symptoms, including insomnia, anxiety, agitation, convulsions and psychotic reactions, may occur when midazolam treatment is stopped after prolonged administration.
References:


