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| | | EMLc | ATC codes: N05CD08 |
| Indication | Status epilepticus | ICD11 code: 8A66.Z | |
| INN | Midazolam | | |
| Medicine type | Chemical agent | | |
| List type | Core Ampoule for buccal administration when solution for oromucosal administration is not available. | | |
| Formulations | Parenteral > General injections > unspecified: 1 mg per mL in ampoule (for buccal administration) ; 10 mg per mL in ampoule (for buccal administration) Local > Buccal > Solution: 5 mg per mL solution for oromucosal administration ; 10 mg per mL solution for oromucosal administration | | |
| EML status history | First added in 2015 (TRS 994) | | |
| Sex | All | | |
| Age | Also recommended for children | | |
| Therapeutic equivalence | The recommendation is for this specific medicine | | |
| Patent information | Patents have expired in most jurisdictions Read more about patents .  | | |
| Wikipedia | Midazolam  | | |
| DrugBank | Midazolam  | | |

Summary of evidence and Expert Committee recommendations

An application was submitted by Drs Satinder Aneja and Suvasini Sharma, Department of Pediatrics, Lady Hardinge Medical College and Kalawati Saran Children’s Hospital, New Delhi, for the inclusion of parenteral midazolam on the EML for buccal administration for the treatment of acute repetitive convulsive seizures and of prolonged convulsive seizures, including status epilepticus, in adults and children when intravenous access is unavailable. The EML already contains intravenous and oral preparations of midazolam as a preoperative/sedative medication and as a medicine for use in palliative care. Expert reviews of the application were prepared by two members of the Expert Committee. Comments on the application were received from Dr Myriam Henkens, International Medical Coordinator, Medecins Sans Frontieres. The Expert Committee noted that correspondence received from the WHO Department of Mental Health and Substance Abuse advised that WHO has included a scoping question on use of buccal midazolam in its latest revision of Emergency Triage Assessment and Treatment (ETAT) guidelines and Mental Health Gap Action Programme (mhGAP) for children and adults respectively. The Guideline Development Group, on review of synthesised evidence following GRADE methodology, has suggested a strong recommendation for use of buccal midazolam. Both sets of guidelines are being finalized for submission to WHO Guidelines Review Committee GRC for approval. The incidence of acute symptomatic seizures (isolated or recurrent) is 29–39 per 100 000 per year (1). The median pooled incidence of epilepsy from published studies is 45.0 (interquartile range (IQR) 30.3–66.7) per 100 000 per year for high-income countries and 81.7 (IQR 28.0–239.5) for low- and middle-income countries (2). Acute symptomatic seizures are more common in the neonatal period than at any other time of life, particularly in premature infants. The second highest incidence and prevalence occur in patients over 65 years of age: reported incidence is 2–13 per 1000 individuals per year over 65 and may be higher as seizures in older patients are frequently underdiagnosed (3–6). Traumatic brain injury, cerebrovascular disease, drug withdrawal, infection and metabolic insults are the commonest causes. Seizures are a common presentation in emergency room settings. Some 12–30% of adults with a new diagnosis of epilepsy present in status epilepticus, a potentially life-threatening condition (7). Treatment for acute convulsive

seizures is aimed at halting seizures as rapidly as possible 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 plus significant subsequent neurological morbidity and mortality. Many drugs have been studied in the management of this condition. Intravenous lorazepam, diazepam or phenytoin is often used for immediate control of status epilepticus. Rectally administered diazepam gel is effective in controlling serially occurring seizures. Buccal midazolam, however, is more effective than rectal diazepam in control of both seizures and frequency of hospitalization or intensive care admissions for community, pre-hospital or ambulatory treatment when intravenous access is not immediately available (8-10). The number needed to treat (NNT) for achieving seizure cessation largely favours buccal midazolam (NNT = 4–6) (10). Moreover, buccal midazolam is significantly more acceptable than rectal diazepam to health professionals and patients (11, 12). The superior efficacy of midazolam compared with diazepam probably reflects more favourable pharmacokinetics of midazolam and erratic absorption of rectal diazepam (13). Evidence suggests that midazolam is as safe as diazepam with regard to respiratory complications, although small differences cannot be excluded. Only very limited differences in the number of patients who experience respiratory depression with rectal diazepam and buccal midazolam, requiring intubation and ventilation, have been reported (8-12, 14). Cost-effectiveness analyses showed that buccal midazolam use in the community setting is more cost-effective than rectal diazepam. It offers health related benefits for patients and health-care systems, including health-related quality of life and reduced need for ambulance call-out and stays in hospital (15, 16). According to the International Drug Price Indicator Guide 2013, the median price of midazolam 5 mg/mL is US\$ 0.26/mL. WHO's Guidelines on the management of acute convulsive seizures in adults and children (when no intravenous access is available) recommend administration of rectal diazepam for control of acute convulsive seizures (17). The evidence profiles include the comparative effectiveness of buccal midazolam, reporting the same efficacy and safety data cited in the sections above but underlining the fact that the buccal formulation is generally not readily available and is not licensed. Midazolam injection, however, is widely available and various human studies have used the intravenous preparation for buccal use. The onset of benzodiazepine effect is faster with IV injection; absorption of buccal midazolam requires more time. Treatment initiation time, however, is shorter with buccal midazolam: IV injection involves transfer of the solution into the syringe, starting an IV line, and pushing the drug slowly and carefully. In some cases establishing an IV line can be challenging, especially in infants and in the emergency management of convulsive seizures when an IV line is not available. The EML already contains intravenous preparations of midazolam for preoperative/sedative medication and for use in palliative care. Buccal midazolam is suitable for administration by non-medical personnel. Although adverse effects may occur, including respiratory depression, the safety of buccal midazolam is adequate for use in community settings to control acute convulsions (generalized tonic, tonic-clonic and complex partial) within a short time, irrespective of their duration or their diverse etiology. Buccal midazolam is considered to be more acceptable, and is easier to administer, than rectal diazepam. The Expert Committee acknowledged that: ■ The fastest route for administering antiepileptic drugs is intravenously; however, peripheral venous access may be difficult to achieve in convulsing patients, especially children. ■ The situation is made more difficult in pre-hospital settings and by resource constraints and a lack of trained personnel, resulting in the frequent first-line use of non-IV routes for administration of anticonvulsant medications in resource-limited settings. ■ IV access is not possible in home settings when treatment is to be administered by parents/caregivers. ■ Treatment for prolonged seizures usually involves giving one dose of diazepam gel into the rectum. The Expert Committee decided that there is sufficient evidence to prioritize buccal midazolam (both the oromucosal solution and the parenteral formulation for buccal administration) as it is more effective and more acceptable than rectal diazepam, the most appropriate comparator included in the EML. The Expert Committee therefore recommended addition to the core list of the EML and EMLc of the oromucosal formulation of midazolam and also the parenteral formulation for buccal administration for the emergency management of convulsive seizures when an intravenous line is not available. It is expected that inclusion of buccal midazolam in the Model List will increase the availability of the commercial product for buccal administration. References: 1. Hauser WA, Beghi E. First seizure definitions and worldwide incidence and mortality. *Epilepsia*. 2008;49(Suppl. 1):8-12. 2. Ngugi AK, Kariuki SM, Bottomley C, Kleinschmidt I, Sander JW, Newton CR. Incidence of epilepsy: a systematic review and meta-analysis. *Neurology*. 2011;77(10):1005-12. 3. Hauser WA, Annegers JF, Kurland LT. Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935-1984. *Epilepsia*. 1993;34(3):453-68. 4. Loiseau J, Loiseau P, Duche B, Guyot M, Dartigues JF, Aublet B. 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