# National Essential Drug List Review Process
# Primary Healthcare Medication
# Component: Central nervous system conditions

**Medication Name:** Midazolam (buccal) **Date:** 28 May 2014

**Indication:** Seizures and Status epilepticus in children and young adults

**Evidence:**
A meta-analysis, "*Midazolam Versus Diazepam for the treatment of Status Epilepticus in Children and Young adults: a Meta Analysis*", was retrieved following a literature search.
The objective of the meta-analysis was to determine by systematic review if non-intravenous (non IV) midazolam is as effective as diazepam by any route, in terminating status epilepticus (SE) seizures in children and young adults. Time to seizure cessation and respiratory complications was examined.

*Quality of evidence:*
McMullan *et al.*[1] reviewed the literature, using electronic databases, from 1950 – 2009, as well as hand selected articles from conferences from 2006-2008. Due to their selection criteria they ended up with 6 articles, which compared the two medicines. Routes of medication administration included iv, rectal (PR), diazepam, and buccal, intranasal (IN), and IM midazolam. Dosing of medication varied slightly among studies: diazepam 0.2-0.3mg/kg IV or 0.5mg/kg PR or midazolam 0.2mg/kg IM and IN or 0.5mg/kg buccal midazolam.

An Intravenous preparation of midazolam filtered through a needle or straw was administered into the buccal cavity. The primary outcome measure therapeutic success was the cessation of visible seizure activity within 10min of administration of the randomised drug without respiratory depression

*Clinical efficacy:*
Pooled analysis showed that midazolam, when given by any route was superior to diazepam by any route in achieving seizure cessation (RR 1.52; 95% CI 1.27 to 1.82;n=6; NNT=7).Non-IV midazolam was administered faster than IV diazepam; although times between administration of medication and seizure cessation were comparable. The two studies showed that non IV midazolam was administered 2.46 minutes (95% CI = 1.52 – 3.39 minutes) quicker than iv diazepam to seizing patients
Three studies[2] (n=628) comparing diazepam PR to buccal midazolam found buccal midazolam more successful in achieving seizure cessation(RR 1.54, 95% CI 1.29 to 1.85; $I^2$ = 0%; NNT = 6).Mcintyre *et al.* (2005) showed a median time after treatment until the seizure stooped to be 8 minutes for buccal midazolam and 5 minutes for rectal diazepam (HR 0.7, 95% CI 0.5 to 0.96;p=0.01). The other studies showed buccal midazolam administration terminated seizures within 10 minutes of administration in 75-84% and in 2-20min in 87% of patients in the out-of hospital environment[3]. Baysun *et al.* reported that the seizures of 18/234 (78%) patients terminated in 10 minutes, and that

[1] McMullan J, Sasson C, Pancioli A, Silbergleit R. Midazolam versus diazepam for the treatment of status epilepticus in children and young adults: a meta-analysis. AcadEmerg Med. 2010 Jun;17(6):575-82.
[2] McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet.2005; 366:205–10.
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. Pediatrics. 2008; 121:e58–64.
Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. Lancet.1999; 353:623–6.
Baysun S, Aydin OF, Atmaca E, Gurer YK.A comparison of buccal midazolam and rectal diazepam for the acute treatment of seizures.ClinPediatr (Phila). 2005; 44:771–6.
[3] Scott RC, Besag FM, Neville BG. Buccal midazolam and rectal diazepam for treatment of prolonged seizures in childhood and adolescence: a randomised trial. *Lancet*.1999; 353:623–6.

17/20 (85%) patients also responded in 10 minutes. They found that midazolam was as effective as diazepam and the difference was not statistically significant.

*Safety concerns:*
Respiratory complications: there was no apparent difference between safety of midazolam and diazepam (RR1.49; 95% CI 0.25 to 8.72). The five patients reported to have developed associated respiratory depression with study treatment had been pre-treated with rectal diazepam prior to attendance at the emergency room.
The European Medicines Agency reported that limited data, population pharmacokinetic analysis of data from MID001, submitted by the applicant for registration of oromucosal midazolam (not published as yet), showed the highest concentration of active metabolite to parent drug ratio in children 3–6 months (in 3 children)[4]. The subsequent approved Summary of Product characteristics of Buccolam® recommend that infants between 3-6 months of age should be treated in a hospital setting where monitoring is possible and resuscitation equipment is available.

*Availability of buccal midazolam dosage form:*
Buccal midazolam is currently not registered with the MCC for marketing in South Africa. However, McIntyre et al. (2005) administered 0.5 mg/kg midazolam, IV, filtered through a needle or straw and administered into the buccal cavity (between gum and cheeks).

**Discussion:**
The evidence supports the use of midazolam by non IV routes as a favourable alternative to diazepam in the initial treatment of SE. McMullan et al reported that superior efficacy of non IV midazolam (IN/IM/buccal) to non IV diazepam (PR) is likely due to more favourable pharmacokinetics, higher bio- availability and a short time to peak concentration.
However, only the study by Mcintyre *et al*, 2005 showed statistically significant outcomes. The other studies showed a non-significant trend supporting midazolam rather than diazepam. In addition, study methodologies had flaws (no double-blinding, inadequate randomization) – refer to appendix- and a probable confounder was the under dosing of rectal diazepam in older children (doses by weight-bands) that may have inflated the effect of midazolam.

**Recommendation:**
The available evidence shows that midazolam may be an alternative to rectal diazepam in managing seizures, including SE. Its ease of administration makes it a better option to be considered in the management of SE especially in the pre-hospital setting.

[4] European Medicines Agency – Committee for Medicinal Products for Human Use. Assessment report of Buccolam (midazolam), EMA/662938/2011, September 2011. [Online] [Cited November 2014] Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002267/WC500112312.pdf