APPENDIX I: Evidence for midazolam buccal vs diazepam rectal for seizures in children

Study (year)	Study design	Participants (studies) Follow up	Study comparators	Summary of findings				
				Study event rates (%)		Absolute risk reduction(95% CI)	NNT/NNH: midazolam versus diazepam	Relative risk: midazolam versus diazepam
				Diazepam	Midazolam			
McIntyre J *et al.Lancet* 2005; 366: 205-210[i]	Multi-centre open-label, controlled study, pseudo randomized (treatment allocation by calendar weeks) - acute seizures: generalized, partial/focal (protocol violation) - Seizure cessation within 10 minutes and no recurrence within 1 hour	- children > 6 months of age (n=177;219 episodes - 42 patients recruited more than once). - median age: 3 yrs, IQR 1–5 yrs; range 7 months–15yrs.	rectal diazepam (iv preparation administered rectally), approx 0.5 mg/kg (episodes=110) vs buccal midazolam (iv preparation administered buccally), approx 0.5 mg/kg (episodes=109) Weight-band dose: 6 –12 months:2.5mg; 1– 4 yrs: 5 mg; 5– 9 yrs: 7.5 mg; > 10 yrs: 10mg	***Primary outcome:*Therapeutic success- cessation of visible signs of seizure activity within 10 minutes of administration of the study treatment and without respiratory depression or another seizure recurrence within 1 hr.**				
				27%(30/110)	56%(61/109)	% difference 29 (16 to 41)	NNT=4 (3 to 7)	
				Seizures stopped within 10 minutes.				
				41%(45/110)	65%(71/109)	% difference 24 (11 to 37)	NNT=5 (3 to 10)	%
				Rate of respiratory depression, all episodes				
				6% (7/110)	5% (5/109)	% difference 2(-4 to 8), NS	No significant difference	
Scott RC *et al.*Lancet 1999; 353: 623-626[ii].	Randomized, open-label, controlled study - prolonged seizures: generalised - tonic clonic, tonic, atonic, myoclonic ; absence; complex ; partial - Seizure cessation within 10 minutes.	- students, age 5–22 yrs (n=18; 79 episodes), previously treated with rectal diazepam for seizures -BP and oxygen saturation monitored continuously for 30 minutes	rectal diazepam, 10 mg (episodes=39) vs buccal midazolam (iv preparation administered buccally), 10 mg (episodes=40)	***Primary outcome*: Cessation of visible signs of seizure activity within 10 minutes of administration of study treatment.**				
				59% (23/39)	75%(30/40)	% difference 16	No significant difference	
				p=0.16				
Mpimbaza A *et al. Pediatrics* 2008; 121: e58-64[iii]	Single-centre, randomised, single-blind controlled study conducted in Uganda. - prolonged seizure, febrile, generalized tonic clonic, tonic, myoclonic, focal - Seizure cessation within 10 minutes and no recurrence within 1 hour	- patients, 3 months to 12 yrs presenting to the acute care unit with a seizure lasting at least 5 min.	rectal diazepam (iv preparation administered rectally), approx 0.5 mg/kg (n=165) vs buccal midazolam (iv preparation administered buccally), approx 0.5 mg/kg (n=165) Weight-band dose: 3 –11months:2.5mg; 1– 4 yrs: 5 mg; 5– 9 yrs: 7.5 mg; 10–12 yrs: 10mg.	***Primary outcome:* Cessation of visible seizure activity within 10 minutes, without recurrence in the subsequent hr; measured treatment failure defined as - if convulsion persisted beyond 10 minutes or recurred within 1 hr.**				
				43% (71/165)	30.3% (50/165)	% difference 12.7	NNT=8	RR 1.42 (1.06 to 1.90); p=0.016
				Sub-group analysis of treatment failure in patients without malaria.				
				55.9% (33/59)	26.5% (13/49)	% difference 29.4	NNT=4	RR 2.11 (1.26 to 3.54); p=0.002
				Cessation of seizures within 10 minutes				
				69.1% (114/165)	75.8%(125/165)	% difference 6.7	NNT=15	RR 0.91 (0.80 to 1.04); p=0.175
Baysun S *et al. Clin Pediatr (Phila).* 2005; 44:771–6.	Prospective, open-label, pseudo-randomised (odd or even days of the month) -Generalised: tonic clonic; tonic; Non—generalised: simple partial seizures; complex partial seizures	- children: 2 months to 12 yrs (n=43; 43 episodes) with convulsive symptoms regardless of type and aetiology, assumed prolonged	rectal diazepam, ≤5 yrs= 0.5 mg/kg; (≥6 yrs=0.3 mg/kg (n=20; 20 episodes) vs buccal midazolam (iv preparation administered buccally), 0.25mg/kg (n=23; 23 episodes)	**Seizure cessation within 10 minutes.**				
				85%(17/20)	78%(18/23)	% difference 7; p>0.05	NNT=15	
				Adverse effects				
				1 patient had bradypnea and oxygen saturation of 84% at 5 minutes; resolved spontaneously.	1 patient coughed non paroxysmally for 1–2 minutes, resolved spontaneously	No statistically significant difference between the 2 groups in adverse effects (p=0.09)		
McMullan J *et al. Acad Emerg Med* 2010; 17: 575-582[iv]	Meta-analysis (n=774; 6 studies: all administration routes) (n=628; 3 studies: rectal diazepam vs buccal midazolam) - Seizure cessation within 10 minutes and/or no recurrence - Case definition of seizure cessationwas clinically based and varied based on time until convulsion stoppage and ⁄ or absence of seizure recurrence. - Included: prolonged, simple, partial or focal convulsions. - Despite clinical and methodologic differences - no significant statistical heterogeneity in pooled analysis of all studies (I2 = 0%).	Children, young adults <22 yrs	diazepam (IV and rectal) vs midazolam (buccal, intranasal, IM). Dosing of medications varied: - diazepam: 0.2–0.3 mg/kg IV,approx. 0.5 mg/kg per rectum, 10 mg per rectum - midazolam: 0.2 mg⁄ kg IM, intranasal or approx.0.5 mg⁄ kg buccal, 10 mg buccal.	**Seizure cessation of rectal diazepam compared to buccal midazolam (3 studies – primary outcomes differed slightly).**				
				[data not provided]	*[data not provided]*	-	NNT = 6	RR 1.54 (1.29 to 1.85); i^2=0
				Respiratory complications requiring intervention, regardless of administration route.				
				0.8% (3/375)	0.53% (2/375)	% difference 0.27%	No significant difference	RR 1.49 (0.25 to 8.72)
European Medicines Agency[v]	Meta-analysis (Pooled data from by Mpimbaza, McIntyre, Scott)[vi] (n=618; 3 studies: rectal diazepam vs buccal midazolam - acute prolonged seizures: generalized – tonic clonic, myoclonic, atonic, tonic ; non-generalised: simple partial, focal, febrile - **Seizure cessation within 10 minutes** - Heterogeneity in pooled data (I^2≥ 70%), but	Children, young adults <22 yrs	diazepam (IV and rectal) (episodes=314) vs midazolam (buccal, intranasal, IM). (eposides=314)	Cessation of visible seizure activity within 10 minutes				
				58%(182/314)	72% (226/314)	% difference 14%	NNT=8	RR 1.24 (1.11 to 1.39), p=0.002

	this disappeared when patients with malaria were excluded (I^2=0%).							

Efficacy:

Case definition of the primary outcome varied slightly between studies. Cessation of seizures was clinically based on time until convulsion stoppage and/or absence of seizure recurrence. Furthermore, some studies included non-generalized seizures (focal, partial, febrile). However, despite these methodological and clinical variances, the meta-analysis by McMullan *et al* (2010) showed no statistical significant heterogeneity in pooled data (I^2= 0%).

As cessation of seizure activity within 10 minutes was a common endpoint in the studies, a further meta-analysis performed by the European Medicine Agency (EMA) suggested that buccal midazolam was superior to rectal diazepam for controlling seizures in children. However, only one (Mcintyre *et al*, 2005) of the three studies showed statistically significant outcomes with a non-significant trend supporting midazolam rather than diazepam in the other two studies. Study methodologies had flaws (no double-blinding, inadequate randomization). And, the EMA considered that probable under dosing of rectal diazepam in older children was a confounder that may have inflated the effect of midazolam. The EMA considered that a claim of superiority of buccal midazolam over rectal diazepam was not justified and that a conclusion of non-inferiority was probably more plausible.

Safety:

McMullan *et al* (2005) reported that there was no apparent difference between safety of rectal diazepam and buccal midazolam with regards to respiratory depression (requiring intervention- assisted ventilations, endotracheal intubation) and change in oxygen saturations. In the study by McIntyre et al (2005) 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.

Midazolam is not available as an oromucosal preparation in South Africa. It is registered in the United Kingdom and the European Union. The Summary of Product characteristics recommend that infants between 3-6 months of age should be treated in a hospital setting where monitoring is possible andresuscitation equipment is available. This recommendation is based on limited data: population pharmacokinetic analysis of data from MID001 submitted to the EMA for registration of oromucosal midazolam (not published as yet) - showing the highest concentration of active metabolite to parent drug ratio in children 3–6 months (in 3 children)[vii].

Evidence supports buccal midazolam as an alternative to rectal diazepam to treat prolonged, acute, convulsive seizures in infants and children from 6 months of age in a pre-hospital, emergency setting. The ease of administration and more socially acceptable mode of administration are additional benefits.

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[i] McIntyre J, Robertson S, Norris E, et al. Safety and efficacy of buccal midazolam versus rectal diazepamfor emergency treatment of seizures in children: a randomised controlled trial. Lancet.2005; 366:205–10.

[ii] 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.

[iii] 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.

[iv] 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.

[v] 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.

[vi] 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

[vii] 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