Scottish Medicines Consortium
Providing advice about the status
of all newly licensed medicines

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NHS SCOTLAND

midazolam, 5mg/mL, oromucosal solution (Buccolam®)   SMC No. (757/12)
ViroPharma Ltd

13 January 2012

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

midazolam oromucosal solution (Buccolam®) is accepted for use within NHS Scotland.

Indication under review: Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years).

Midazolam given via the buccal route was considered at least non-inferior to rectally administered benzodiazepine in terminating acute prolonged seizures.

The economic case was demonstrated for midazolam oromucosal solution (Buccolam**®)** compared to rectal diazepam.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to <18 years).

Midazolam oromucosal solution (Buccolam®) must only be used by parents/carers where the patient has been diagnosed to have epilepsy.

For infants between three to six months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.

Dosing Information

Buccolam® is presented in pre-filled oral syringes. Dosage is age dependent:
Three to six months (hospital setting only) = 2.5mg
Between six months and < one year = 2.5mg
Between one and < five years = 5mg
Between five and < ten years = 7.5mg
Between ten and < eighteen years = 10mg

Product availability date

October 2011

Summary of evidence on comparative efficacy

Midazolam is a benzodiazepine with anti-convulsant, sedative, anxiolytic and muscle-relaxant effects. It is effective when given by the oromucosal (buccal) route in the management of acute convulsive seizures in children but until recently no licensed preparation was available. Buccolam® is a new formulation of midazolam designed for oromucosal administration in a paediatric population.

Evidence to support the use of Buccolam® for the indication under review is from historical data published in the literature in which midazolam 10mg/2mL injection, administered by the buccal route, was compared with rectal diazepam. Buccolam® has the same formulation as the injection, but is presented in a pre-filled oral syringe.

In a multi-centre open-label, controlled study conducted in four hospitals in the UK, children aged 6 months or older who presented to the emergency room of the participating hospitals with an ongoing seizure and no established intravenous access were recruited. Patients were allocated to receive either buccal midazolam or rectal diazepam at a dose banded to the child's age that would be approximately 0.5mg/kg: 2.5mg for children aged between 6 and 12 months; 5mg for children aged between 1 to 4 years; 7.5mg for children aged between 5 and 9 years; and 10mg for children over 10 years of age. The study utilised a pseudo-randomisation method to allocate treatment: each centre had a weekly block of treatment randomly selected, an approach used to minimise time to treatment. The distribution of the age of children treated was similar between the groups: midazolam (median age = 2, Inter-Quartile Range [IQR] =1 to 5), and diazepam (median age = 3, IQR=1 to 6). For both groups, the distribution of ages treated

was: <12 months = 6%, 1 to 4 years = 62%, 5 to 9 years = 23%, and 10 to 18 years = 9%. There were 219 seizure episodes (involving 177 patients) included in the analysis, of which 109 were treated with buccal midazolam and 110 with rectal diazepam. The primary outcome was therapeutic success, defined as cessation of visible signs of seizure activity within 10 minutes of administration of the study treatment and without respiratory depression or seizure recurrence within 1 hour. A significantly greater proportion of seizure episodes were successfully treated with midazolam (56%, n=61/109) compared to treatment with diazepam (27%, n=30/110), a treatment difference of 29% (95% confidence interval [CI]: 16 to 41%) and an odds ratio of 4.1 (95% CI: 2.2 to 7.6). A greater proportion of seizures stopped within 10 minutes when patients were treated with buccal midazolam compared with rectal diazepam (65% versus 41% respectively, treatment difference 24% [95% CI: 11 to 37]). Significantly fewer patients required intravenous lorazepam (33% versus 57%), or developed a recurrent seizure within the hour (14% versus 33% of responders) in the buccal midazolam group compared with rectal diazepam. There was no difference between the groups in the rate of respiratory depression (5% versus 6% respectively). Similar results were noted when only patients' first seizure episode was included in the analysis.[1]

In a randomised, open-label, controlled study conducted in a residential centre for children and young adults with severe epilepsy and other needs in the UK, patients aged between 5 and 22 years who had previously received rectal diazepam as an emergency treatment for seizures were allocated to receive either midazolam 10mg/2mL administered in the buccal cavity by the on-site nurse, or diazepam given at a dose of 10mg via the rectal route. There was no dose adjustment for bodyweight or age. Only two of the 18 patients, accounting for two seizure episodes, were aged less than 10 years. The primary outcome was the cessation of visible signs of seizure activity within 10 minutes of administration of study treatment. A total of 18 patients with 79 seizure episodes were treated in the study. There was no statistically significant difference in the proportion of seizure episodes successfully treated with either midazolam (75%, n=30/40) or diazepam (59%, n=23/39).[2]

In a single-centre, randomised, single-blind controlled study conducted in Uganda, patients aged between 3 months and 12 years presenting to the acute care unit with a seizure lasting at least 5 minutes were randomised to receive either midazolam via the buccal route with the same age-banded dose described for the first UK study plus a placebo rectal solution, or diazepam via the rectal route at an age-banded dose plus a placebo buccal solution. The majority of children treated in this study had malaria (64% to 70%) and were aged between 3 months and 5 years (95%). The primary outcome was cessation of visible seizure activity within 10 minutes, without recurrence in the subsequent hour. A smaller proportion of patients failed to meet the primary endpoint in the buccal midazolam group compared with the rectal diazepam group (30% [n=50/165] versus 43% [n=71/165] respectively). The relative risk (RR) of treatment failure with rectal diazepam compared with buccal midazolam was 1.42, (95% CI: 1.06 to 1.90). The reason for the difference between the groups for the primary endpoint was seizure recurrence rather than failure to terminate the initial seizure, which was non-significant. In the sub-group of patients without malaria there was a significant difference in the proportion of patients with treatment failure: buccal midazolam (26%, n=13/49), rectal diazepam (56%, n=33/59), RR of treatment failure with rectal diazepam compared with buccal midazolam =2.11 (95% CI: 1.26 to 3.54).[3]

The results of the three controlled studies were pooled and a meta-analysis of the primary endpoints was performed. Using a Mantel-Haenszel fixed-effects model, the estimated relative risk of treatment failure for rectal diazepam compared with buccal midazolam was 1.54 (95% CI: 1.29 to 1.85). Analysis using a random-effects model did not have a meaningful effect on the

results.[4] The primary outcomes were defined slightly differently in each of the three studies. The European Medicines Agency (EMA) pooled the data for the endpoint of cessation of seizure activity within 10 minutes from all three of the studies and the relative risk was in favour of midazolam at 1.24 (95% CI: 1.11 to 1.39).[5]

Evidence supporting the use of buccal midazolam 10mg/2mL administered in the community is from a retrospective telephone survey. The parents of 53 children prescribed buccal midazolam by the children's hospital in Glasgow, were asked about the use and effectiveness of midazolam in comparison with rectal diazepam. Buccal midazolam was used in 74% of patients (n=40/53) and was considered to be effective in 83% of episodes.[6]

Summary of evidence on comparative safety

There was no difference in the incidence of respiratory depression or in the change in oxygen saturations in patients treated with buccal midazolam compared with rectal diazepam in all three studies.[1-3] In the multi-centre UK study, there were 12 episodes in which the child developed respiratory depression (midazolam, n=5/109, and diazepam, n=7/110). Five of these patients had been pre-treated with rectal diazepam prior to attendance at the emergency room.[1]

Summary of clinical effectiveness issues

This medicine is approved under the Paediatric Use Medicine Authorisation process instituted by the European Medicines Agency (EMA) and until now, unlicensed "specials" of midazolam have been used to give buccal doses to patients.

The primary outcome measures were defined slightly differently between the studies supporting the use of buccal midazolam in acute seizures. A common endpoint in the studies was cessation of seizure activity within 10 minutes but only one study demonstrated a statistical and clinically significant benefit with buccal midazolam. Meta-analysis suggested midazolam was superior to diazepam for this endpoint. Two of the studies reported on the endpoint of cessation within 10 minutes plus prevention of recurrence for an hour, and midazolam superiority was demonstrated in both. However, the EMA considered that a claim of superiority of buccal midazolam over rectal diazepam was not justified due to limitations in the methodology of the studies: no double-blinding, and in some of the studies, inadequate randomisation. The EMA also considered that the treatment effect of midazolam may have been magnified as older children within the age-bands may have received doses of rectal diazepam below the dose commonly recommended (2.5mg/kg versus 5mg/kg). A conclusion of non-inferiority was considered to be more plausible. [5]

Rectal diazepam has been superseded by buccal midazolam, a medicine recommended by clinical guidelines published by SIGN and NICE. These guidelines were informed by the second study described above. According to SMC clinical experts, buccal midazolam is considered a first-line option in NHS Scotland. Unlicensed "specials" of midazolam, particularly a 10mg/mL formulation, have been widely used in NHS Scotland to meet this demand. There is no comparative data with the 10mg/mL buccal midazolam formulation.

Strengths of the evidence-base were the generalisability of the data. Two out of the three pivotal studies were conducted in the UK, and patients treated included a broad range of ages

with varying causes of seizure, e.g. febrile, epilepsy. Although in the pivotal studies, treatment was administered by healthcare professionals either in a hospital or residential centre setting, evidence from a retrospective survey supports the use of buccal midazolam in the community.

An advantage of Buccolam® is that the midazolam is presented in a pre-filled syringe, whereas currently unlicensed buccal midazolam preparations dispensed for patients require a more complex procedure in which the dose is drawn from a multiple dose form into an oral syringe before administration. The licensed dose is banded by age, which is in line with the dose advice in the British National Formulary for Children, but SMC clinical experts commonly use doses based on weight when prescribing midazolam and have highlighted that age-related dosing may not be appropriate for underweight children.

SMC clinical experts have indicated that the availability of a licensed preparation of oromucosal midazolam would have benefits to patients and the service. Introduction of this medicine would, however, have implications for the service in terms of patient, parent and carer education since the strength of existing unlicensed preparations of midazolam is different. Training on the administration of the product has been offered by the submitting company.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis comparing Buccolam® with current care for the treatment of prolonged, acute, convulsive seizures in patients <18 years of age. Current care consisted of treatment with unlicensed midazolam, except when treatment is administered by paramedics, where rectal diazepam was used instead. A Markov model was used which consisted of two health states: prolonged seizure and no prolonged seizure. When patients experienced a seizure they entered the decision tree part of the model which determined their treatment pathway. A 6-year time horizon was used on the basis that this is the first time period when the shelf lives of the unlicensed midazolam (2 years) and Buccolam® (18 months) coincide.

Clinical data used in the model were taken from the clinical study comparing midazolam with rectal diazepam. Unlicensed midazolam and Buccolam® were assumed to have equal efficacy, although the model assumed a reduction in the number of failed deliveries with Buccolam®. Additional data relating to frequency, length and outcomes from seizures were collected through a patient survey, a Delphi panel and a Scottish hospital survey. A treatment simulation model was used which combined the results of the surveys and, along with the clinical study data, these results were used to estimate the probability of each outcome in the decision tree part of the model.

Utility values were derived based on EQ-5D data collected from clinicians who participated in the Delphi panel. The clinicians were asked to complete four EQ-5D questionnaires on behalf of patients to proxy the quality of life of patients in different health states. The health states were defined as baseline, during seizure, following seizure (no ambulance called) and following seizure (ambulance called) and also differed according to underlying disease severity. It was estimated that 10% of patients who would be eligible for midazolam have severe disability.

Resource-use estimates included ambulance call-outs, inpatient admissions and high dependency unit admissions and were based on a combination of clinical data and assumption. The company also included some savings from a reduction in drug wastage with licensed

midazolam. The patient simulation model was used to estimate treatment wastage in each arm of the model. The model results indicated that 7.8 doses of unlicensed midazolam will be wasted over the 6-year period versus 0.3 doses of the licensed midazolam. A key assumption in the model is that the pack of four pre-filled syringes allows greater flexibility as the syringes will be distributed between the various locations where the medication is required.

The results of the base case analysis indicated that licensed midazolam would dominate unlicensed midazolam with estimated savings of £2,046 and a quality adjusted life year (QALY) gain of 0.005. Further sensitivity analysis provided by the company equalising the assumptions related to treatment wastage showed licensed midazolam was still the dominant treatment.

The main weakness with the analysis is the choice of comparator. Unlicensed midazolam is current practice in Scotland. However, as SMC policy specifies that only licensed comparators are considered, the base case analysis presented by the company is not appropriate.

The following additional weaknesses were noted:
- The clinical study showed buccal midazolam was superior to rectal diazepam. However, the EMA commented that a conclusion of non-inferiority was considered to be more plausible given the limitations of the data.
- There are a number of uncertainties with the clinical assumptions used in the model, particularly relating to reduced drug wastage and increased flexibility of access to the medicine as a result of midazolam being available in a pre-filled syringe.
- The company were asked to provide a sensitivity analysis which assumed no difference between the treatment arms in terms of efficacy. The results of this analysis indicated that midazolam would still be cost-saving (-£710) as a result of savings from reduced drug wastage and the lower drug acquisition cost. While this analysis is helpful, the savings are likely to be overestimated as the reduction in drug wastage may not be appropriate.
- The cost of unlicensed midazolam is uncertain and there is wide variation in the costs incurred in practice. The base case analysis used a cost of £133 per prescription.

In order to take account of SMC's policy with regard to unlicensed medicines, the company provided additional analyses using a licensed comparator. Two scenarios were presented. The first analysis assumed that current care consisted of all patients being treated with rectal diazepam in all settings. The results of this analysis showed that midazolam oromucosal solution was dominant with estimated savings of £8,516 and a QALY gain of 0.036. The second analysis assumed that no treatment would be administered in the community and therefore an ambulance would have to be called whenever a seizure occurs. The results of this analysis showed that midazolam oromucosal solution was dominant with estimated savings of £17,874 and a QALY gain of 0.068.

The additional analysis provided by the company was helpful as it allowed a comparison with a licensed product and addressed issues relating to efficacy and drug wastage. This indicated that in most scenarios midazolam oromucosal solution remained the dominant treatment option.

The economic case for midazolam oromucosal solution (Buccolam®) was considered to have been demonstrated.

Summary of patient and public involvement

A Patient Interest Group Submission was not made.

Additional information: guidelines and protocols

The Scottish Intercollegiate Guidelines Network published guideline 81 "Diagnosis and management of epilepsies in children and young people" in 2005. Around 80% of children will respond to emergency treatment with benzodiazepines. The guideline recommends that prolonged or serial seizures be treated with either rectal diazepam or nasal or buccal midazolam. Buccal or intranasal midazolam is as effective in treating prolonged seizures as rectal diazepam and in the community setting, parents and carers found it easier to use.

In 2004, the National Institute for Health and Clinical Excellence published "NICE Guideline 20 The diagnosis and management of the epilepsies in adults and children in primary and secondary care". Rectal diazepam is safe and effective in first-line treatment of prolonged seizures and is recommended in the majority of cases. Buccal midazolam has shown similar effectiveness with rectal diazepam, and for many, is a more acceptable and easier to administer treatment option.

Additional information: comparators

The only medicine licensed for use for this indication is rectal diazepam. The use of unlicensed preparations of buccal midazolam is however standard practice in NHS Scotland.

Cost of relevant comparators

Drug	Dose Regimen	Cost per episode (£)
Midazolam oromucosal solution (Buccolam®)	**Dose as per age, administered buccally:** **3 to 6 months (hospital setting only) = 2.5mg** **6 months to 1 year = 2.5mg** **1 to 5 years = 5mg** **5 to 10 years = 7.5mg** **10 to 18 years = 10mg**	**£23**
Diazepam	Dose as per age, administered rectally: Neonate = 1.25 to 2.5mg* 1 month to 2 years = 5mg* 2 to 12 years = 5 to 10mg 12 to 18 years = 10 to 20mg	£1 to £3

Doses are for general comparison and do not imply therapeutic equivalence and assumes one dose per episode. Costs from eVadis on 01 November 2011.
*Diazepam use is unlicensed in children less than one year old.

Additional information: budget impact

The company estimated the population eligible for treatment to be 6,820 patients in year 1 rising to 10,098 patients in year 5. Based on an uptake of 50% in year 1 (3,409 patients) and 100% (10,098 patients) in year 5, the impact on the medicines budget was estimated at £1.1m in year 3 and £3.2m in year 5. Assuming displacement of unlicensed midazolam and rectal diazepam the net medicines budget impact was estimated to result in savings of £377k in year 1 and £1.1m in year 5. The number of patients assumed to receive midazolam seems particularly high in comparison with the numbers estimated by SMC clinical experts, who suggested up to 1,000 patients would receive treatment in Scotland. Using these revised estimates of 500 patients being treated in year 1 rising to 1000 patients treated in year 5, the impact on the medicines budget was estimated at £160k in year one rising to £319k in year 5. Assuming displacement of the existing treatments, the net medicines budget impact was estimated to be a saving of £55k in year 1 rising to £111k in year 5.

References

The undernoted references were supplied with the submission.

1) McIntyre J, Robertson S, Norris E, Appleton R *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:** 205-210. http://dx.doi.org/10.1016/S0140-6736(05)66909-7

2) 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:** 623-626. http://dx.doi.org/10.1016/S0140-6736(98)06425-3

3) 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. http://dx.doi.org/10.1542/peds.2007-0930

4) 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. *Acad Emerg Med* 2010; **17:** 575-582. http://dx.doi.org/10.1111/j.1553-2712.2010.00751.x

5) European Medicines Agency. Buccolam – EPAR. [online] Available from: http://www.ema.europa.eu [Last updated 19 September 2011]

6) Wilson MT, Macleod S, O'Regan ME. Nasal/buccal midazolam use in the community. *Arch Dis Child* 2004; **89:** 50-51. http://dx.doi.org/10.1136/adc.2002.019836

This assessment is based on data submitted by the applicant company up to and including 12 December 2011.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database.   SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.