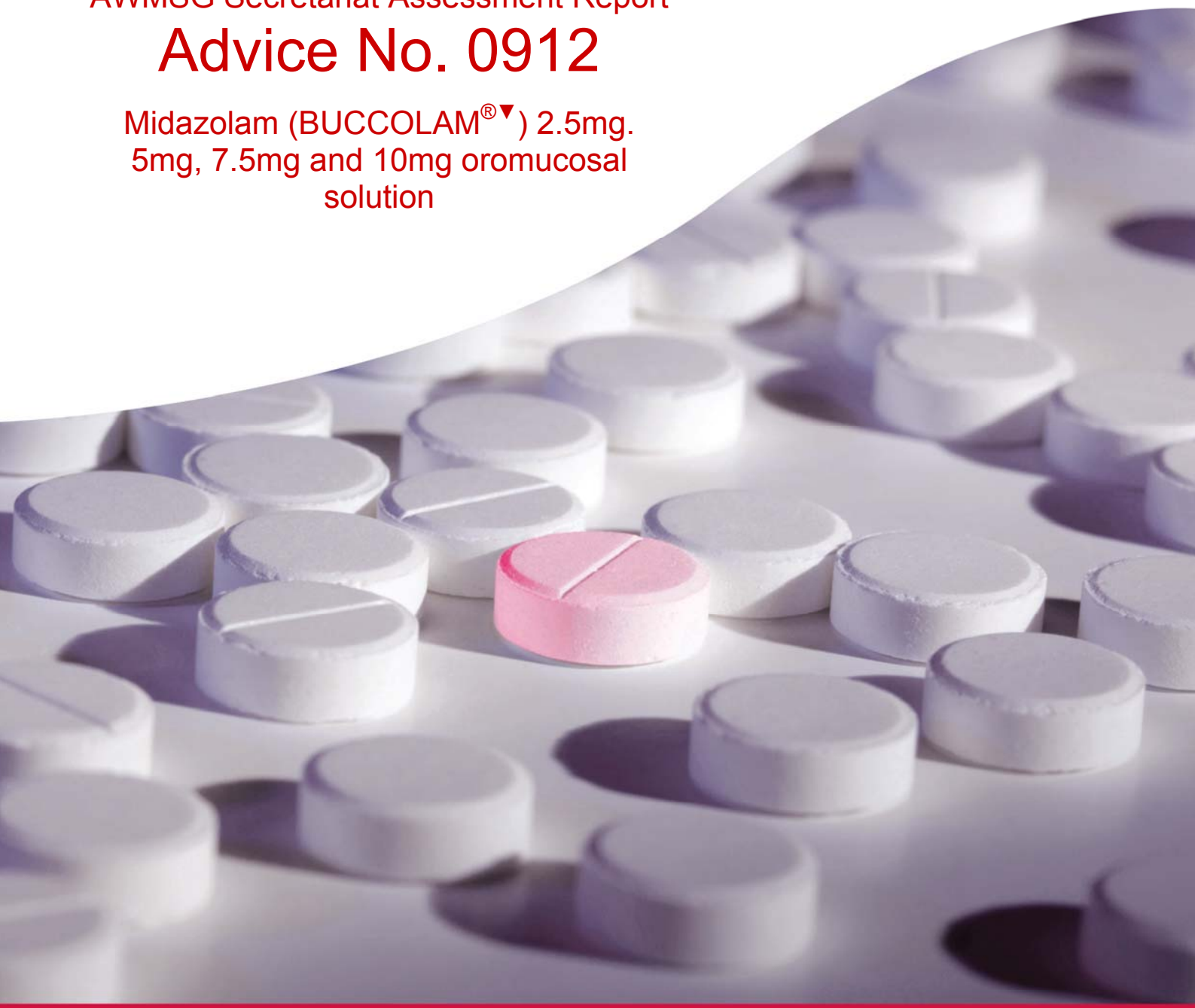
All Wales Therapeutics and Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG Secretariat Assessment Report

Advice No. 0912

Midazolam (BUCCOLAM®▼) 2.5mg. 5mg, 7.5mg and 10mg oromucosal solution



AWMSG Secretariat Assessment Report – Advice no. 0912
Midazolam (BUCCOLAM®▼) 2.5 mg, 5 mg, 7.5 mg and 10 mg oromucosal solution

This assessment report is based on evidence submitted by ViroPharma Ltd on 2 December 2011.

1.0 PRODUCT DETAILS

Licensed indication under consideration	Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years)[1]. BUCCOLAM®▼ must only be used by parents/carers where the patient has been diagnosed to have epilepsy[1].
Dosing	Patients aged: • 3 to 6 months should receive 2.5 mg (hospital setting only); • > 6 months to < 1 year should receive 2.5 mg; • 1 year to < 5 years should receive 5 mg; • 5 years to < 10 years should receive 7.5 mg; • 10 years to < 18 years should receive 10 mg[1].
Marketing authorisation date	5 September 2011[1].

2.0 DECISION CONTEXT

2.1 Background

Prolonged seizure is defined as at least five minutes of continuous seizure activity or fifteen minutes of repetitive seizures; continuous or intermittent convulsive seizure lasting beyond 30 minutes is known as status epilepticus (SE)[2]. SE is a common childhood neurological emergency that can lead to neurocognitive sequelae and death[3]. Acute seizure presents at the first stage of SE. Various drugs are available for the treatment of prolonged, acute, convulsive seizures: first-line treatment recommended by current clinical guidelines is with oromucosal (buccal) midazolam or rectal diazepam[2,4,5].

In September 2011, midazolam (BUCCOLAM®▼ oromucosal solution) was granted marketing authorisation for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents. Midazolam is a derivative of the imidazobenzodiazepine group and acts in a similar way to other benzodiazepines[1]. It exerts an anticonvulsant effect, mediated by enhancement of gamma-aminobutyric (GABA) neurotransmission in limbic, thalamic and hypothalamic regions of the central nervous system[3].

2.2 Comparators

The All Wales Therapeutics and Toxicology Centre (AWTTC) requested rectal diazepam and unlicensed oromucosal midazolam as comparators.

2.3 Guidance and related advice

- National Institute for Health and Clinical Excellence (NICE). Clinical guideline 137. The epilepsies: The diagnosis and management of the epilepsies in adults and children in primary and secondary care (2012)[5].
- Scottish Intercollegiate Guidelines Network (SIGN). Clinical guideline 81. Diagnosis and management of epilepsies in children and young people (2005)[2].

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

BUCCOLAM®▼ has been specifically developed as an oromucosal formulation of midazolam (5 mg/ml as hydrochloride), and its concentration and salt form are the same as those of the licensed intravenous (IV) preparation. The company submission included details of three controlled studies that compared IV midazolam administered via the oromucosal route with rectal diazepam for the treatment of acute seizures in children and young people[6]. Details of the studies performed by McIntyre et al (2005) and Scott et al (1999) are included below[7,8]. The third study described (Mpimbaza et al., 2008) was performed in a Ugandan hospital and recruited a high frequency of patients whose seizures resulted from malaria infection[9]. Though supportive, this study is of limited relevance to Welsh patients and detailed results from this study will not be discussed in this report. However, this study is taken into account in a meta-analysis also described. This meta-analysis was conducted to determine whether midazolam is as effective as diazepam by any route[6,10]; the results are summarised in Section 3.3.

The company submission also included supportive evidence from four uncontrolled studies investigating the use of IV midazolam used oromucosally[6]. Since these did not directly compare oromucosal midazolam to rectal diazepam, these will not be discussed further.

No published studies that compared the use of BUCCOLAM®▼ with unlicensed oromucosal midazolam were included in the company submission. The company stated that there is a paucity of published data regarding the use of unlicensed midazolam; in order to gain consensus on current clinical practice in Wales and the potential impact of a licensed oromucosal midazolam preparation, a Delphi process (a systematic forecasting method which relies on a panel of experts) was conducted[6].

3.1 McIntyre et al (2005)

This multicentre, randomised controlled trial compared IV midazolam administered oromucosally with rectal diazepam in children aged 6 months to 15 years (n = 177) presenting to hospital with acute seizures[3,6,7]. The doses of midazolam and diazepam administered were designed to give approximately 0.5 mg per kg; midazolam was administered as described in the BUCCOLAM®▼ Summary of Product Characteristics (SPC)[1]. The primary endpoint was the cessation of visible signs of seizure activity within ten minutes of treatment administration, without respiratory depression or repeat seizure within one hour. During the study period, treatment was administered for 219 separate episodes (patients may have been recruited on more than one occasion): 109 episodes were treated with oromucosal midazolam and 110 were treated with rectal diazepam. Of the 219 episodes, 14 (6.4%) were in patients aged 6–12 months, 135 (61.6%) were in patients aged 1–4 years, 50 (22.8%) were in patients aged 5–9 years, and 20 (9.1%) were 10 years and older. The primary endpoint was met in 61/109 (56%) episodes treated with oromucosal midazolam, compared with 30/110 (27%) episodes treated with rectal diazepam[6,7]. When centre, age, diagnosis of epilepsy, fever, use of antiepileptic drugs, prior treatment and duration of seizure before treatment were adjusted for, oromucosal midazolam was significantly more effective than rectal diazepam ($p < 0.001$; odds ratio 4.1, 95% confidence interval [CI]: 2.2–7.6)[6].

The rate of respiratory depression was found to be similar in both treatment arms: 5/109 (5%) in the midazolam arm and 7/110 (6%) in the diazepam arm[6,7]. No other safety data were published.

3.2 Scott et al (1999)

This was a randomised controlled trial conducted in a UK residential centre for children and young people (aged 5–19 years, n = 42) with severe epilepsy[3,6,8]. IV midazolam (10 mg in 2 ml) was administered oromucosally for 40 episodes and rectal diazepam (10 mg) was administered for 39 episodes. The primary endpoint was the cessation of visible epileptic phenomena and the return of purposeful response to external stimuli within ten minutes of treatment administration. Of the 40 episodes treated with midazolam, 30 (75%) met the primary endpoint, and of the 39 episodes treated with diazepam, 23 (59%) met the primary endpoint. The difference was not statistically significant ($p = 0.16$)[6,8].

The company reported that no clinically important side effects were identified in either group[6].

3.3 Meta-analysis by McMullan et al (2010)

This meta-analysis was carried out to determine if non-IV midazolam is as effective as diazepam, by any route, in terminating SE seizures in children and adults (patients included were aged up to 22 years)[10]. Six studies were included in the meta-analysis, including the three controlled studies that compared IV midazolam administered via the oromucosal route with rectal diazepam, described above. A subgroup analysis of these three studies (n = 628) showed that buccal midazolam was more successful in achieving seizure cessation than rectal diazepam (risk ratio [RR] = 1.54; 95% CI = 1.29–1.85). Other studies included compared intramuscular or intranasal midazolam with IV diazepam. From a pooled analysis of the six studies it was concluded that midazolam, by any route, was superior to diazepam, by any route, in achieving seizure cessation (RR = 1.52; 95% CI = 1.27–1.82)[10].

3.4

Commercial in confidence data removed[11].

3.5 AWTTC critique

- BUCCOLAM®▼ has been specifically developed as an oromucosal formulation of midazolam, with the concentration and salt the same as the licensed IV preparation[6]. There are no clinical studies which directly compare BUCCOLAM®▼ to rectal diazepam. However, it is accepted that the randomised, controlled studies using IV midazolam used oromucosally, as described in the company submission, are directly supportive of the efficacy and safety of BUCCOLAM®▼. The Committee for Medicinal Products for Human Use (CHMP) concluded that BUCCOLAM®▼ was non-inferior to rectal diazepam and possibly superior[3].
- Other preparations of oromucosal midazolam used in Wales are unlicensed and are of a higher concentration (10 mg/ml) than BUCCOLAM®▼. No studies directly comparing BUCCOLAM®▼ to unlicensed oromucosal midazolam are available. However, appropriate training and increased vigilance may be required to reduce the risk of administering the incorrect product or dose of midazolam.
- As administration of diazepam via the rectal route may be difficult and is considered socially embarrassing or unacceptable by some patients, parents or carers, oromucosal midazolam is considered to be more acceptable[5,12].

- BUCCOLAM®▼ is available as age-specific, colour-coded, pre-filled syringes[1], which may simplify administration[6].
- As noted in the SPC, there is insufficient data to support the safe use of BUCCOLAM®▼ in children aged 3–6 months outside the hospital setting[1]. In addition, CHMP notes that there is a potential risk that adolescents (aged over 12 years and weighing more than 40 kg) might be underdosed[3].
- In the study by Scott et al. (1999) a 10 mg in 2 ml dose of IV midazolam was administered oromucosally. By comparison, the SPC for BUCCOLAM®▼ and the British National Formulary (BNF) for children recommends a 7.5 mg dose for patients aged 5–10 years[1,4]. Similarly, a 10 mg dose of rectal diazepam was administered; however, the BNF for children recommends a dose of 5–10 mg for children aged 2–12, and 10–20 mg for those aged 12–18[4].
- As the study by McIntyre et al was conducted in the hospital setting, the possibility of selection bias cannot be ruled out as patients who received successful emergency treatment in the community setting are excluded. In addition, the possibility of observer bias exists due to a need for unblinded treatment[7]. CHMP noted that overall, the studies had several methodological flaws (i.e. no double-blinding, placebo control or adequate randomisation), however continued that these flaws could not have been avoided given the urgency of treatment and nonetheless remained supportive of the efficacy of buccal midazolam[3].

4.0 SUMMARY OF EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company submission describes a cost-utility analysis of the licensed formulation of midazolam oromucosal solution (BUCCOLAM®▼) compared with "current care" consisting of unlicensed oromucosal midazolam or rectal diazepam[6]. BUCCOLAM®▼ is licensed for the treatment of prolonged, acute, convulsive seizures in children and adolescents aged 3 months to < 18 years; however, the company's economic model reflects its initial use for the treatment of epileptic seizures that occur in the community setting, which would exclude its use in children less than six months of age.

A time-to-event simulation is used to estimate the mean number of seizures (1.2 per month), the location of the seizure, whether emergency medication is present at the location and the extent of medication wastage, based on data from a small survey of Welsh epilepsy patient carers (n = 19) and company-sought medical expert opinion. It is assumed that "current care" involves 95% of seizures being treated with unlicensed oromucosal midazolam and 5% with rectal diazepam. A randomised controlled trial of unlicensed oromucosal midazolam compared with rectal diazepam in the acute hospital setting provides probabilities of seizure resolution and recurrence, which are assumed to be equal for the licensed and unlicensed midazolam formulations[7]. Estimates of utility weights for valuing health states are based on expert opinion, as are the probabilities of subsequent treatment, failed drug delivery, admittance to hospital and admittance to an intensive care/high dependency unit. No deaths are assumed to occur. The model assumes a monthly cycle and a six-year time horizon. See Appendix 1 for further details.

4.1.2. Results

The results of the base case analyses are summarized in Table 1. The model estimates BUCCOLAM®▼ to be both less costly and more effective than "current care" as defined. Small modelled differences in the probabilities of seizure resolution within ten minutes (65% versus 63.1%) and the probabilities of further seizures (14% versus

15%) derived from the trial, and the probabilities of carers being unable to administer treatment (5% versus 6.2%), based on expert opinion and the carers survey, favour BUCCOLAM®▼ and translate into reduced ambulance and inpatient-related costs compared with "current care". Acquisition costs of BUCCOLAM®▼ are modelled to be lower than for the unlicensed product.

Table 1. Company-reported results of cost-effectiveness analysis of BUCCOLAM®▼ compared with "current care".

Base case	BUCCOLAM®▼	Current care	Difference
Drug costs	£1,823	£2,374	-£551
Ambulance costs	£7,299	£7,742	-£443
A&E costs	£1,817	£1,683	£134
Inpatient admission costs	£8,019	£10,163	-£2,144
Intensive care unit admission costs	£414	£524	-£111
Total cost	£19,371	£22,487	-£3,116
Total QALYs	3.763	3.738	0.0248
ICER	BUCCOLAM®▼ dominant*		
** BUCCOLAM®▼ is estimated to be both less costly and more effective than "current care"*			

BUCCOLAM®▼ dominated unlicensed oromucosal midazolam in all the one-way sensitivity analyses presented, except for where the probability of a further seizure upon administration of either preparation is varied. This resulted in an incremental cost-effectiveness ratio (ICER) of around £93,000 per quality-adjusted life-year (QALY) gained, based on an incremental total cost of around £1,000 and very small QALY gains. However, the company notes that it is unlikely that the probabilities of a further seizure upon administration of BUCCOLAM®▼ or unlicensed midazolam would differ to such an extent. The model was next most sensitive to the probability of seizures lasting > 10 minutes, but BUCCOLAM®▼ remains dominant within the range of the 95% confidence interval that was explored.

Ten scenario analyses have been conducted to address the uncertainty of assumptions made in the model, including those surrounding medicine wastage, seizure frequency, proportion of patients receiving oromucosal midazolam or rectal diazepam, length of inpatient and intensive care stay, price for multiple bottles of unlicensed oromucosal midazolam, and re-use of syringes. BUCCOLAM®▼ was dominant compared to "current care" under all proposed scenarios.

Probabilistic sensitivity analysis performed for the base case scenario demonstrated that BUCCOLAM®▼ had 85% probability of being cost-effective at a cost-effectiveness threshold range of £20,000 to £30,000 per QALY; the majority of the 1,000 simulations indicated BUCCOLAM®▼ to be dominant. For other scenarios considered in the company submission, the probability of BUCCOLAM®▼ being cost-effective compared to "current care" varied from 68% to 100% at £20,000 to £30,000 per QALY.

4.1.3 AWTTC critique

Strengths of the economic evidence:

- The company has gone to considerable lengths to consider a wide range of factors that may influence the cost-effectiveness of BUCCOLAM®▼.
- The company has attempted to supplement limited clinical trial data with patient and expert medical opinion where necessary.

Limitations of the economic evidence:

- AWMSG appraises medicines within their whole licensed indication, and the company has provided economic evidence that is limited to a subset of the licensed population with diagnosed epilepsy.
- The clinical trial used to model effectiveness included patients with epilepsy and non-epilepsy related seizures, and there are a number of potential methodological limitations which may have introduced bias into efficacy estimates.
- Utility values to weight health states are proxy values based on health professional opinion, and the uncertainty around these has not been specifically explored in sensitivity analyses. The company suggests these are exploratory weights and the modelled outcomes are not dependent on quality of life due to the modelled total costs savings with BUCCOLAM®▼; however, this would depend on the reliability of assumptions underpinning the modelled costs of treatment.
- The main driver of modelled cost savings with BUCCOLAM®▼ appears to be related to inpatient care costs, which are influenced largely by parameter values, based on expert opinion and a small survey of 19 epilepsy patient carers. This is low-grade evidence and therefore subject to uncertainty.
- Acquisition costs of unlicensed oromucosal midazolam are influenced by the assumptions of no re-use of syringes and wastage, which are subject to uncertainty. However, BUCCOLAM®▼ remained dominant when re-use of syringes was permitted for unlicensed buccal midazolam. For further comments see Appendix 1.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches have not identified any published economic evidence on the cost-effectiveness of midazolam oromucosal solution (BUCCOLAM®▼) compared to rectal diazepam or unlicensed oromucosal midazolam for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents from 3 months to < 18 years of age.

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

NOT FOR NMG TO CONSIDER

5.1 Budget impact evidence

5.1.1 Context and methods

Using data on the prevalence of epilepsy in the UK (reported in NICE guidance) and Welsh population statistics, the company estimated that there are currently 3,326 patients < 18 years with epilepsy in Wales. The company estimates the number of newly diagnosed patients eligible for treatment with BUCCOLAM®▼ would be 201 per year. Assuming a 50% uptake rate in year one and an increase to 100% in year five, the total number of patients treated with BUCCOLAM®▼ is expected to increase from 1,368 to 3,539 over five years. The estimated savings associated with the introduction of BUCCOLAM®▼ in Wales would be £776,202 in year one, rising to £2,007,520 in year five. The estimated numbers of patients and the associated costs over the five-year period are shown in Table 2.

Table 2. Company-reported costs associated with use of BUCCOLAM®▼.

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	2,737	2,938	3,139	3,339	3,540
Uptake	50%	62.5%	75%	87.5%	100%
Number of treated	1,368	1,836	2,354	2,921	3,539

patients					
Primary care costs	-£118,653	-£159,190	-£204,074	-£253,303	-£306,878
Secondary care costs	-£657,548	-£882,193	-£1,130,928	-£1,403,747	-£1,700,643
Overall net costs	-£776,202	-£1,041,383	-£1,335,002	-£1,657,050	-£2,007,520

No sensitivity or scenario analyses of budget impact are presented in the company's submission.

5.1.2 AWTTC critique of the company's budget impact estimates

- The company's budget impact estimates are based only on the use of BUCCOLAM®▼ in patients with epilepsy. Patients with non-epileptic convulsive seizures are not included in these estimates.
- The budget impact model uses costs derived from the cost-utility model; therefore, all the limitations of cost-effectiveness analysis (discussed in detail in Appendix 1) equally apply to the budget impact analysis.
- Collectively, the company-reported cost savings resulting from the use of BUCCOLAM®▼ in NHS Wales are subject to uncertainty.

5.2 Comparative unit costs

Estimation of comparative acquisition costs for unlicensed oromucosal midazolam is complicated, as the number of doses available from the standard 10 mg/ml 5 ml bottle will depend on the age of the child, whether or not the syringes provided are re-used, and the number of doses dispensed from the bottle before discarding. The NHS reimbursement cost includes a sourcing fee for manufacturers, and the overall cost per dose will depend on the number of bottles ordered on prescription. The example cost in Table 3 assumes two 5 ml bottles are ordered on a prescription, which is appropriately endorsed to indicate that the product has been supplied with an integral means of administration. As per the economic model, each bottle is assumed to provide four doses without re-use of syringes.

Table 3. Examples of drug acquisition costs.

Drug	Strength	Cost per package	Regimen	Cost per single treatment*
BUCCOLAM®▼ (midazolam oromucosal solution in prefilled oral syringe)	2.5 mg/0.5 ml	4 = £82.00	• 3 to 6 months (hospital only) and < 6 months to < 1 year: 2.5 mg • 1 to < 5 years: 5 mg • 5 to < 10 years: 7.5 mg • 10 to < 18 years: 10 mg	£20.50–£22.88
	5 mg/1 ml	4 = £85.50		
	7.5 mg/1.5 ml	4 = £89.00		
	10 mg/2 ml	4 = £91.50		
Diazepam rectal solution in tube	2 mg/ml	5 × 2.5 ml = £6.06	0.5 mg/kg	£1.21–£1.88
	4 mg/ml	5 × 2.5 ml = £9.36		
Epistatus® (midazolam oral solution and 4 syringes)	10 mg/ml	2 × 5 ml bottles = 2 × £97.51 (plus £20 specials sourcing fee)	• < 6 months: 0.30 mg/kg • 6 to 12 months: 2.5 mg • 1 to 4 years: 5 mg • 5 to 9 years: 7.5 mg • 10 years and over: 10 mg	£26.87**

** Includes wastage*
*** Assumes that 2 × 5 ml bottles are ordered on a prescription, which is endorsed to indicate that the product is supplied with an integral means of administration, syringes are used once and each bottle provides only four doses. If syringes are re-used and bottles provide more than four doses, the cost per dose will decrease.*
Costs are based on BNF[13] and MIMS[14] list prices with the exception of specials supplied midazolam for oromucosal administration, which is based on NHS eDrug Tariff reimbursement price as of 7 January 2012[15].
This table does not imply therapeutic equivalence of drugs at the stated doses.

6.0 ADDITIONAL INFORMATION

6.1 Shared care arrangements

AWTTC is of the opinion that midazolam oromucosal solution (BUCCOLAM®▼) may be suitable for use within NHS Wales prescribed under specialist recommendation.

AWTTC is of the opinion that midazolam oromucosal solution (BUCCOLAM®▼) should be prescribed by brand name to reduce the risk of medication errors.

6.2 Ongoing studies

The company submission states that there are no studies currently ongoing.

6.3 AWMSG review

This ASAR will be considered for review three years from Ministerial ratification (date will be disclosed on the Final Appraisal Recommendation).

6.4 Evidence search

Date of evidence search: 16 December 2011.
Date range of evidence search: No date limits were applied to database searches.

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14 Haymarket Publications. Monthly Index of Medical Specialities (MIMS). 2011. Available at: http://www.mims.co.uk/.

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Appendix 1. Additional health economic analysis information

Table 1. Health economic analysis detail[6].

	Base case model	Appropriate?
Comparator(s)	"Current care" consisting of rectal diazepam or unlicensed oromucosal midazolam. The analysis assumes that patients are in a community setting, and that 95% of seizures will be treated with unlicensed oromucosal midazolam and 5% with rectal diazepam. In the hospital setting, rectal diazepam is assumed to be used in 38% of cases, and unlicensed oromucosal midazolam in 62% of cases. Ambulance staff will use rectal diazepam in 100% of cases.	Yes: AWTTC requested comparison against unlicensed oromucosal midazolam and rectal diazepam. The proportions of use of each assumed in the base case model are derived from a Delphi panel (low grade of evidence). IV formulations (e.g. lorazepam or midazolam) are not considered in the economic analysis, although they may be used in emergency settings where IV access is possible or required.
Population	The modelled population includes children and adolescents up to 18 years of age who have a diagnosis of epilepsy and suffer from prolonged, acute, convulsive seizures. The model considers seizure episodes that occur in the community setting.	The economic model presented by the company considers children and adolescents with epilepsy only, which represents a subset of the licensed population. No data are provided regarding the cost-effectiveness of BUCCOLAM®▼ for the treatment of non-epileptic seizures (e.g. febrile seizures) and, as the model considers seizures that occur in the community, no consideration is given to infants aged 3–6 months who may only be treated with oromucosal midazolam in the hospital setting[1].
Analysis type	The submission includes a CUA of midazolam oromucosal solution (BUCCOLAM®▼) compared to "current care", which is considered to be a mix of treatment with unlicensed oromucosal midazolam and rectal diazepam. A Markov model has been developed which consists of two health states: "child with epilepsy not suffering a prolonged, acute, convulsive seizure" and "child with epilepsy suffering a prolonged, acute, convulsive seizure". A one-month model cycle is used. Once an epileptic seizure is experienced, a decision-tree represents the possible management pathways for that seizure episode. It is assumed that patients experience their epileptic seizure outside of the hospital setting. The seizure may resolve after one treatment dose, require a further treatment dose and then resolve, or require ambulance to hospital for further treatment and assessment. Once at hospital, patients may be admitted, admitted to ICU/HDU, or may return home. No deaths are assumed to occur.	CUA is the preferred type of analysis. The modelled pathway seems reasonable for children and adolescents with epilepsy who experience a seizure episode outside of the hospital setting. The modelled pathway assumes that 30% of patients may receive a second dose of treatment before calling for ambulance, based on company-sought expert opinion. It should be noted that the SPC for BUCCOLAM®▼ states that carers should only administer a single dose and must seek emergency medical assistance if the seizure has not stopped within ten minutes of first administration[1]. However, the model estimates BUCCOLAM®▼ to be dominant irrespective of the proportion receiving a second dose prior to calling an ambulance. It is assumed that all treatment received in A&E is administered by oromucosal or rectal routes, and not the IV route.
Perspective	NHS Wales.	The analysis considers direct medical costs from the perspective of NHS Wales. It does not consider any potential personal social service costs.

Table 1. Continued.

	Base case model	Appropriate?
Time horizon	The model assumes a six-year time horizon of analysis, with an assumed mean seizure frequency of 1.2 per month, based on a survey of 19 Welsh epilepsy patient carers. The company explains that the six-year time horizon has been chosen as this is the first time period over which the expiry dates of the unopened oromucosal midazolam preparations coincides and permits comparison of their wastage.	Epilepsy is a chronic condition which may be life-long. The assumption of a time horizon of six years is a pragmatic approach under an assumption that no deaths occur, and under the company's assumptions regarding product wastage.
Discount rate	A 3.5% p.a. discount rate is applied to both costs and outcomes.	Yes.
Efficacy	BUCCOLAM®▼ was licensed on the basis of efficacy data from trials relating to the unlicensed use of IV midazolam delivered oromucosally. These data are assumed to demonstrate equivalence in efficacy between the licensed and unlicensed midazolam preparations. Duration of seizures and seizure recurrence in the model are derived from one clinical trial comparing the unlicensed IV midazolam solution delivered oromucosally versus rectal diazepam[7]. Probabilities of other events (e.g. carer cannot administer treatment; second dose being given; ambulance call-out; administering a second dose; admittance as an inpatient; admittance to ICU following admission as inpatient) are based on a survey of Welsh epilepsy patient carers and/or expert opinion.	Collectively, there is considerable uncertainty associated with the efficacy assumptions used in the model. The trial used by the company to model treatment response and seizure recurrence was selected on the basis of it being the largest comparative trial relevant to the UK. However, as this trial was conducted in the hospital setting, the possibility of selection bias cannot be ruled out as patients who received successful emergency treatment in the community setting are excluded from the trial. The trial also included patients with seizure types other than epilepsy, and the possibility of observer bias exists due to a need for unblinded treatment. CHMP noted that all available trial data have methodological flaws, due in part to the emergency situation in which they are conducted, and a claim of superiority (based on all trials, including seizure types other than epilepsy) may not be justified, but a claim of non-inferiority would be plausible[3]. The company has not explored the possibility of no difference in efficacy between BUCCOLAM®▼ and rectal diazepam. Data on the success of re-treatment with the same emergency medication are lacking, and re-treatment success appears to be assumed to be the same as for initial treatment. The patient carer survey, providing probabilities of seizure frequency, location and availability of emergency medication, probability of administering emergency medicine, was small (n = 19) and its results are therefore subject to uncertainty. In the absence of trial or observational data, probabilities of admittance to hospital and ICU/HDU are based on expert opinion and are assumed to be the same irrespective of treatment received. Probabilities of difficulties administering BUCCOLAM®▼ and each of the comparators is also based on expert opinion, and the range of probabilities appear to overlap, although the company assumes lower rates for BUCCOLAM®▼.

Table 1. Continued.

	Base case model	Appropriate?
Adverse effects	Adverse events were not considered in the model.	Adverse events are not included in the model on the basis that adverse events appear to be similar for midazolam and diazepam. Rates of respiratory depression were reported to be similar in the trial by McIntyre et al. (2005)[7]. The SPC precludes the use of BUCCOLAM®▼ in the community setting in children aged less than six months due to the possibility of respiratory depression[1]. The model therefore reflects use of BUCCOLAM®▼ in patients with epilepsy aged over six months.
Utility values	Due to reported lack of utility data for children with prolonged, acute, convulsive seizures, utility values were derived from Scottish clinicians' assessments using EQ-5D-5L. Welsh clinician estimates were used to determine time to recovery from seizures in order to determine duration of health decrements.	The company suggests that the estimation of utility values represents an exploratory analysis, as the main driver of the model outputs is the cost of treatment. It is assumed that between seizures, patients have a steady baseline utility, and decrements are made for the duration of the seizure and the recovery phase as estimated by Welsh clinicians. It is assumed that the utility decrements are the same for the licensed and unlicensed midazolam preparations, but marginally greater decrements are assumed for diazepam. There is uncertainty in the proxy utility values, and no sensitivity analyses have been conducted to explore the specific impact of the assumed values.
Resource use and costs	Costs considered in the economic model include the cost of drugs delivered in community, hospital and ambulance settings, as well as costs associated with ambulance attendance, A&E, inpatient admission and ICU/HDU admission. A simulation model has been developed to estimate seizure frequency and midazolam wastage using data from the patient carer survey. No rectal diazepam wastage is assumed to occur as it is provided as a single-dose pack.	A number of assumptions have been made about resource use and wastage, derived from a small number of patient carer responses to a survey regarding the storage location of treatment, etc. Expert opinion is used to determine the number of bottles of unlicensed IV midazolam that would be ordered per prescription in both the community and the hospital setting, which is assumed to be two 5 ml bottles in both cases. It is possible this may inflate the assumed cost per dose of the unlicensed product when administered in the A&E or ward setting. It is assumed that each bottle provides only four doses, on the assumption that the four syringes provided with the bottle are not re-used; however, four (25%) of carers who completed the survey report that they do re-use syringes. Scenario analysis indicated that BUCCOLAM®▼ was still dominant when up to six doses of unlicensed midazolam was permitted per bottle. The modelled costs of the use of unlicensed midazolam in the community may also be inflated. The company has appropriately used the current NHS drug tariff price of specials-manufactured oromucosal midazolam for costing this comparator and

Table 1. Continued.

	Base case model	Appropriate?
		assumes in the base case model that each bottle will be reimbursed at the full price of a 5 ml bottle, as listed in the tariff. Scenario analysis explores the impact of assuming that only the first 5 ml bottle is charged at the full bottle price, with subsequent bottles charged at the drug tariff listed incremental price per ml of solution. Under the remaining assumptions of the base case model, BUCCOLAM®▼ is still estimated to be less costly than the comparator. Exploration of the possibility that each bottle provided up to six doses results in acquisition costs for BUCCOLAM®▼ exceeding the acquisition costs for the unlicensed product, but total costs remain lower for BUCCOLAM®▼.
Uncertainty and scenario analyses	A range of univariate and probabilistic sensitivity analyses have been conducted. Ten specific scenario analyses have also been conducted: 1. Unlicensed oromucosal midazolam disposed of after three months if opened in all locations; shelf life of 24 months for BUCCOLAM®▼. 2. ± 50% change in standard deviations surrounding seizure frequency. 3. All patients in the "current care" arm receive unlicensed oromucosal midazolam. 4. All patients in the "current care" arm receive rectal diazepam. 5. Where patients currently receive oromucosal midazolam, no treatment is given. 6. Length of inpatient and ICU/HDU stay increased by one day. 7. Threshold analysis on price of BUCCOLAM®▼. 8. Threshold analysis on price of unlicensed oromucosal midazolam. 9. Assumption of re-use of syringes allowing more doses per bottle of unlicensed oromucosal midazolam. 10. Assumption that any additional bottles ordered in the same prescription cost £4.35 rather than £97.51.	The only univariate sensitivity analysis which resulted in BUCCOLAM®▼ no longer being the least costly treatment option was where the probability of response to BUCCOLAM®▼ was reduced compared with unlicensed oromucosal midazolam. The company notes that this is an unlikely assumption given the similarity of the products. In all other sensitivity and scenario analyses, BUCCOLAM®▼ is estimated to be cost-saving and more effective. It should be noted that scenario 1 appears biased in favour of BUCCOLAM®▼, since it assumes a reduced shelf-life for the unlicensed oromucosal midazolam, but an extended shelf-life of 24 months for BUCCOLAM®▼, which is longer than the 18 months noted in the SPC[1]. No sensitivity or scenario analyses have been conducted to specifically address the uncertainty around the proxy-derived utility values used in the model. The company has provided supplementary analyses to explore the possibility of no difference in effectiveness in outcomes between midazolam preparations and rectal diazepam, in which BUCCOLAM®▼ remains the least costly. If there was no assumed difference in effectiveness and outcomes, the cost savings reported with BUCCOLAM®▼ would be influenced by the assumed acquisition costs of the unlicensed midazolam product and the proportion of use of unlicensed midazolam to rectal diazepam in the "current care" arm.
Model provided?	Yes.	Yes.

CUA = cost-utility analysis; CHMP = Committee for Medicinal Products for Human Use; EQ-5D-5L = EuroQoL 5-dimension 5-level questionnaire; HDU = high dependency unit; ICU = intensive care unit; SPC = Summary of Product Characteristics