The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

18 July 2012

Buccolam 2.5 mg, oromucosal solution
Prefilled syringe of 0.5 ml, B/4 (CIP code: 221 084-2)

Buccolam 5 mg, buccal solution
Prefilled syringe of 1 ml, B/4 (CIP code: 221 085-9)

Buccolam 7.5 mg, buccal solution
Prefilled syringe of 1.5 ml, B/4 (CIP code: 221 086-5)

Buccolam 10 mg, buccal solution
Prefilled syringe of 2 ml, B/4 (CIP code: 221 087-1)

Applicant: VIROPHARMA SAS

midazolam
ATC code: N05CD08 (benzodiazepine derivatives)

List I

Initial annual prescription restricted to specialists in neurology or paediatrics. Unrestricted renewal.
Medicinal product which may be administered by any doctor working in an emergency situation or as part of a mobile medical assistance or repatriation unit (article R.5121-96 of the French Public Health Code)
Prescribed by secure prescription, through the decree of 16 April 2012 (Official Gazette of 28 April 2012)

Date of Marketing Authorisation (centralised procedure): 5 September 2011 (specific MA for paediatric use)

Reason for request: Inclusion on the list of medicines refundable by National Health Insurance and approved for hospital use.

Medical, Economic and Public Health Assessment Division
1. CARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient

Midazolam

1.2. Indications

“Treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years).
BUCCOLAM must only be used by parents/carers where the patient has been diagnosed to have epilepsy.
For infants between 3-6 months of age treatment should be in a hospital setting where monitoring is possible and resuscitation equipment is available.”

1.3. Dosage

“Posology
Standard doses are indicated below:

<table>
<thead>
<tr>
<th>Age range</th>
<th>Dose</th>
<th>Label colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 to 6 months in a hospital setting</td>
<td>2.5 mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>&gt; 6 months to &lt; 1 year</td>
<td>2.5 mg</td>
<td>Yellow</td>
</tr>
<tr>
<td>1 year to &lt; 5 years</td>
<td>5 mg</td>
<td>Blue</td>
</tr>
<tr>
<td>5 years to &lt; 10 years</td>
<td>7.5 mg</td>
<td>Purple</td>
</tr>
<tr>
<td>10 years to &lt; 18 years</td>
<td>10 mg</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Carers should only administer a single dose of midazolam. If the seizure has not stopped within 10 minutes after administration of midazolam, emergency medical assistance must be sought and the empty syringe given to the healthcare professional to provide information on the dose received by the patient.
A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice.

Special populations

**Paediatric population**
The safety and efficacy of midazolam in children aged 0 to 3 months has not been established. No data are available.

**Renal impairment**
No dose adjustment is required, however, BUCCOLAM should be used with caution in patients with chronic renal failure as elimination of midazolam may be delayed and the effects prolonged.

**Hepatic impairment**
Hepatic impairment reduces the clearance of midazolam with a subsequent increase in terminal half-life. Therefore, the clinical effects may be stronger and prolonged, hence careful monitoring of the clinical effects and vital signs is recommended following administration of midazolam in patients with hepatic impairment.

BUCCOLAM is contraindicated in patients with severe hepatic impairment.
Method of administration
BUCCOLAM is administered orally. The full dose of the solution must be administered slowly into the space between gum and cheek. Avoid inserting the syringe into the larynx or trachea in order to prevent accidental aspiration of the solution. If necessary (for larger volumes and/or smaller patients), approximately half a dose should be administered slowly on one side of the mouth and then the other half on the other side of the mouth.
Precautions to be taken before handling or administering the medicinal product.
Do not attach a needle, intravenous catheter or any other device for parenteral administration to the syringe for oral administration.
BUCCOLAM must not be administered intravenously.
Before use, remove the stopper from the syringe for oral administration to avoid any risk of asphyxiation.”

### 2. SIMILAR MEDICINAL PRODUCTS

#### 2.1. ATC Classification (2012)

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Nervous system</td>
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<tr>
<td>N05</td>
<td>Psycholeptics</td>
</tr>
<tr>
<td>N05C</td>
<td>Hypnotics and sedatives</td>
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<tr>
<td>N05CD</td>
<td>Benzodiazepine derivatives</td>
</tr>
<tr>
<td>N05CD08</td>
<td>Midazolam</td>
</tr>
</tbody>
</table>

#### 2.2. Medicines in the same therapeutic category

BUCCOLAM is the only proprietary medicinal product with MA for oral use in convulsive seizures.

Injectable solutions:
- **Lorazepam** - ATIVAN (named TUA) – available in hospital
- **Clonazepam** - RIVOTRIL (hospital use) for IM or slow IV use

Emergency treatment *status epilepticus* in adults and children (> 12 months old)

- **Diazepam** - VALIUM (National Insurance and Hospital approved) for IM, IR or slow IV use
  - Neuropsychiatric emergencies:
    - Emergency treatment *status epilepticus* in adults and children (infants 0.5 mg/kg, children 0.2 to 0.3 mg/kg)
  - Paediatrics:
    - Emergency treatment of convulsive seizures in infants and children, for rectal use
      - Rectal injection for the treatment of convulsive seizures in infants and children:
        - The injectable solution is given at a dose of 0.5 mg/kg of body weight (i.e. 0.1 ml of solution/kg), not exceeding 10 mg. The desired amount is drawn up using a syringe and injected into the rectum using a cannula which can be attached to the syringe.

For information: **midazolam** (HYPNOVEL) for IV, IM or rectal use has MA from 6 months old in: conscious sedation, before and during diagnostic or therapeutic procedures - Anaesthesia – Intensive care unit sedation.
3. PAYMENT FOR THE MEDICINAL PRODUCT IN EUROPE

On the date of the opinion, BUCCOLAM is paid for in Great Britain and in Germany.

4. ANALYSIS OF AVAILABLE DATA

4.1. Efficacy

The file is literature-based and comprises five randomised controlled studies versus active treatment conducted in children and adolescents:
- four studies versus rectal diazepam\textsuperscript{1,2,3,4}
- one study versus intravenous diazepam.\textsuperscript{5}

These studies are summarised in the table below.

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<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methodology/Nb of patients (nb of convulsive seizures)</th>
<th>Endpoints:</th>
<th>Efficacy results (ITT)</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott 1999 (UK)</td>
<td>Specialist centre, Severe epilepsy, Convulsive seizure &gt;5 min (tonic-clonic, myoclonic, tonic, partial complex), Past history of emergency intra-rectal diazepam treatment</td>
<td>R, O, PG, superiority?** n= 28 (79) Generalised seizures: 24/40 (BM) and 22/39 (RD)</td>
<td>Disappearance of clinical signs and convulsive seizure within 10 minutes following the administration of the medicinal product</td>
<td>% cessation of convulsive seizures &lt;10 min: - BM: 30/40 (75%) - RD: 23/39 (59%) No difference (p = 0.16)</td>
<td>Incidence of AE not stated Minimum O2 saturation recorded: 93%</td>
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<tr>
<td></td>
<td>Age: 5 to 19 years old 5-9 years old (2.5%), 10-18 years old (97.5%)</td>
<td>Midazolam buccal: 14 (40) Single dose: 10mg</td>
<td>Time to response</td>
<td>Median time to cessation of the seizure: - BM: 6 min - RD: 8 min No difference (p = 0.31)</td>
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<tr>
<td></td>
<td></td>
<td>Rectal diazepam: 14 (39) Single dose: 10mg</td>
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<tr>
<td>Baysun 2005 (Turkey)</td>
<td>Emergency Department, Prolonged convulsive symptoms regardless of type and cause (tonic-clonic, tonic, partial simple)</td>
<td>Pseudo-R, PG, superiority?** n=43 (43) Commonest type of seizure: generalised tonic-clonic</td>
<td>Disappearance of the convulsive seizure within 10 min after administration of the medicinal product</td>
<td>% cessation of convulsive seizures &lt;10 min: - BM: 18/23 (78%) - RD: 17/20 (85%) No difference (p &gt;0.05)</td>
<td>Incidence of AE not stated</td>
</tr>
<tr>
<td></td>
<td>Age: 2 months to 12 years old (mean 3 to 4 years old), ≤ 6 months (6 children), &lt;12 months (30%), 1-4 years old (33%), 5-9 years old (35%), 10-18 years old (2%)</td>
<td>Midazolam, buccal: 23 (23) Single dose: 0.25 mg/kg</td>
<td>Percentage of patients who respond within a period of 3 min</td>
<td>Response time 3 min - BM: 12/23 (52%) - RD: 10/20 (50%)</td>
<td>- BM: 1 case of non-paroxysmal cough - RD: 1 case of bradypnoea and saturation of 84%</td>
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<tr>
<td></td>
<td></td>
<td>Diazepam, rectal: 20 (20) Single dose: 0.5 mg/kg</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td>(≤ 5 years old) / 0.3 mg/kg (≥ 6 years old)</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>
**Study** | **Patients** | **Methodology/Nb of patients (nb of convulsive seizures) / Treatments** | **Endpoints:** | **Efficacy results (ITT)** | **Safety results**
---|---|---|---|---|---
McIntyre 2005 (United Kingdom) | Emergency department | Acute convulsive seizure (no IV line inserted) - Emergency treatment, not excluding pre-hospital - partial or non-convulsive seizure excluded. Age: 7 months to 15 years old <12 months (6%), 1-4 years old (62%), 5-9 years old (23%), 10-18 years old (9%) Mean length of the seizure before starting treatment: BM 30 min, RD 41 min | Pseudo-R, O, PG, superiority n=177 (219), re-inclusions, pre-hospital treatment: lorazepam iv (30), rectal paraldehyde (7) anti-epileptic treatment (52%) Midazolam, buccal: 92 (109) Diazepam, rectal: 85 (110) Single doses: 2.5 mg (6 to 12 months), 5 mg (1 to 4 years old), 7.5 mg (5 to 9 years old), 10 mg (10 to 12 years old) | Disappearance of clinical signs of convulsive seizure within 10 min following administration of the medicinal product, without respiratory depression or recurrence within one hour Percentage of convulsive seizures resolving in less than 10 min Time to response | % of convulsive seizures which stopped in <10 min, without respiratory depression or recurrence within one hour: - BM: 61 (56%) - RD: 40 (27%) p <0.001 (logistic regression*) Median time for the seizure to stop: - BM: 8 min - RD: 15 min p = 0.01 | Incidence of AE not stated Respiratory depression: - BM: 5 (5%) - RD: 7 (6%) Intubation: BM (2 cases), RD (3 cases)
Mpimbaza 2008 (Uganda) | Emergency department | Patients presenting with a convulsive seizure on arrival at the emergency department or who had had a convulsive seizure lasting more than 5 min in the emergency department - no IV diazepam or phenobarbital treatment within the previous 24 hours - persistent convulsive seizure when treatment was started. Age: 3 months to 12 years old (median age 18 months), 3 months to 5 years old (95%) | R, SB, PG, superiority n=330 (330) 81.5% generalised seizures 92.5% tonic-clonic seizures Midazolam, buccal: 165 (165) Single doses: 2.5 mg (3 to 11 months, 5 mg (1 to 4 years old), 7.5 mg (5 to 9 years old), 10 mg (10 to 12 years old). Diazepam, rectal: 165 (165) Single doses: 2.5 mg (3 to 11 months), 5 mg (1 to 4 years old), 7.5 mg (5 to 9 years old), 10 mg (10 to 12 years old). | Disappearance of clinical signs of convulsive seizure within 10 min following administration of the medicinal product with no recurrence within one hour | Percentage of convulsive seizures resolving in less than 10 min Recurrence over 24 hours | % of convulsive seizures which stopped in <10 min, with no recurrence within one hour: - BM: 115/165 (70%) - RD: 94/165 (57%) p = 0.016 | Incidence of AE not stated BM: Respiratory depression 2 (status epilepticus 1, malaria 1), aphasia 1, intense pruritus, possibly related, 1 (concomitant oral phenobarbital) RD: Respiratory depression 2, (death from cerebral malaria 1, meningitis 1) Deaths: BM 8, RD 12 (attributed to underlying diseases – severe malaria 10, malnutrition 3, septicaemia 3, pneumonia 2, meningitis 2)
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Methodology/Nb of patients (seizures)/Treatments</th>
<th>End point:</th>
<th>Efficacy results (ITT)</th>
<th>Safety results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talukdar 2009 (India)</td>
<td>Emergency department</td>
<td>R, O, PG, superiority?**</td>
<td>Disappearance of clinical signs of convulsive seizure within 5 min following administration of the medicinal product</td>
<td>No difference (p = 0.142)</td>
<td>CNS depression, respiratory depression, apnoea, cardiac dysrhythmia: 0 cases</td>
</tr>
<tr>
<td></td>
<td>Prolonged convulsive seizures of various causes (tonic, clonic and tonic-clonic, partial or generalised)</td>
<td>n=120 (120)</td>
<td>Time to resolution of the seizures</td>
<td>Mean time to starting treatment (min):</td>
<td></td>
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<tr>
<td></td>
<td>Age: &lt;12 years old (mean age 3.2-3.5 years old), &lt;12 months (53%), 2-5 (20%), 6-12 (27%)</td>
<td>Percentage of generalised seizures and duration of seizure before treatment not stated</td>
<td></td>
<td>BM (1.0) versus ID (2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Midazolam, buccal: 60 (60)</td>
<td></td>
<td>Time between administration and seizures stopping:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Single dose: 0.2 mg/kg</td>
<td></td>
<td>BM (1.7) versus ID (1.1)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Diazepam iv: 60 (60)</td>
<td></td>
<td>Total time:</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Single dose: 0.3 mg/kg</td>
<td></td>
<td>BM (2.4) versus ID (3.0)</td>
<td></td>
</tr>
</tbody>
</table>

R: randomised, O: open, SB: single-blind (patient), DB: double-blind, PG: parallel groups, BM: buccal midazolam RD: rectal diazepam, ID: intravenous diazepam, Pseudo-R: Pseudo-randomised based on even/uneven days of the month (Baysun study) or on weeks of the month (MacIntyre study)

*adjusted by centre, age, diagnosis of epilepsy, presence of fever, use of anti-epileptics, previous treatment and duration of seizure before treatment

**the power calculations for these studies suggest that the objective was to test the superiority of efficacy of midazolam compared to diazepam.
Methodology

The five controlled clinical studies versus active treatments were exclusively performed in hospital or hospital centre emergency departments. They were all open except for the Mpimbaza study which was single-blind. Two of the four comparative studies against rectal diazepam (Baysun and McIntyre) were pseudo-randomised (cf. table).

The convulsive seizures included in these studies were of various types and durations. The majority, however, were generalised tonic-clonic. Only the McIntyre study excluded partial seizures. The duration of the seizure before treatment was not stated in most of the studies. The mean duration of the convulsive seizure before treatment was started in the McIntyre study was reported as being between 10 and 49 minutes in the midazolam group and between 10 and 61 minutes in the diazepam group.

In the Baysun and Talukdar studies, single doses of midazolam and diazepam were calculated per kg of child body weight and ranged from 0.20 to 0.25 mg/kg for buccal midazolam and 0.3 to 0.5 mg/kg for rectal diazepam. In two of the five studies (McIntyre and Mpimbaza), the doses of midazolam and diazepam administered were determined according to the age of the child: 2.5 mg (3-11 months), 5 mg (1-4 years old), 7.5 mg (5-9 years old) and 10 mg (>10 years old).

The primary efficacy endpoint was the percentage in whom visible activity of the convulsive seizure stopped within 10 minutes in the Scott and Baysun studies, with no relapse during the hour following administration in the Mpimbaza and McIntyre studies. The percentage of convulsive seizures which stopped within 5 minutes was the primary efficacy endpoint in the Talukdar study, which was conducted versus IV diazepam. Only the Mpimbaza study evaluated the risk of recurrence of the seizure over 24 hours.

Results (cf. table)

- Convulsive seizures stopping:
  The percentages of convulsive seizures which stopped within 10 minutes after administration of the medicinal product was similar for buccal midazolam and intra-rectal diazepam in three of the four studies which compared buccal midazolam to rectal diazepam (75 to 78% for buccal midazolam compared to 59 to 85% for rectal diazepam). In the McIntyre study, a larger percentage of convulsive seizures stopped within 10 minutes in the buccal midazolam group than in the rectal diazepam group (65% for buccal midazolam compared to 41% for rectal diazepam).

  The EMA has carried out a meta-analysis to evaluate the percentage of convulsive seizures which stopped within 10 minutes from the four studies. The meta-analysis results were in favour of buccal midazolam, with a relative risk of 1.24 (95% CI: 1.11 to 1.39).

  Two studies (Mpimbaza, McIntyre) evaluated the percentage of convulsive seizures which stopped within 10 minutes and had no recurrence within the next hour. Buccal midazolam was superior to rectal diazepam in these two studies.

  No conclusion can be drawn as to the superiority of buccal midazolam over rectal diazepam because of the methodology of these four studies (open or single-blind, pseudo-randomisation, dose of diazepam etc.).

  According to the EMA, buccal midazolam can be deemed to be non-inferior to rectal diazepam in the treatment of acute convulsive seizures in children.

  One study compared buccal midazolam to IV diazepam. The percentages of convulsive seizures which stopped within 5 minutes was similar for both treatments. In this study, the seizure was controlled more quickly after administration of IV diazepam than after buccal midazolam. However, the treatment was started earlier with buccal midazolam because of the ease of administration.
Recurrence of convulsive seizures within 24 hours: Recurrence of the convulsive seizures within 24 hours after initial control of the seizure was only measured in the Mpimbaza study. In this study, the percentage of recurrence rates were similar between the two treatments (39% of children treated with buccal midazolam and 46% of children treated with rectal diazepam).

4.2. Adverse effects

4.2.1. Clinical trial data

The safety reports for these studies were brief. The incidence of adverse events was not stated; and there is limited information about the adverse events which occurred during these studies.

Buccal midazolam was administered for prolonged convulsive seizures to 294 children in four comparative studies versus rectal diazepam. Seven of the 16 cases of respiratory depression reported in these studies occurred after administration of buccal midazolam. The McIntyre study reported 5 cases out of 109 convulsive seizures treated with the substance. Intense pruritus, possibly related to the treatment, was reported for buccal midazolam.

Three deaths attributed to complications of malaria and two cases of respiratory depression treated with flumazenil were reported in the children treated with buccal midazolam in the uncontrolled clinical study (n=142); three cases of respiratory depression and one case of severe bradycardia were deemed to be unrelated to the treatment.

4.2.2. Pharmacovigilance monitoring data on the proprietary medicinal products HYPNOVEL and VERSED

Midazolam has been used since December 1982 in Europe (HYPNOVEL) and December 1985 in the United States (VERSED). It can be administered IV, IM or rectally in adults and children, including IV in neonates of gestational age under 32 weeks. The orally administered medicinal product indicated for postoperative sedation in children, has been marketed in the United States since October 1998 (VERSED 2 mg/ml, syrup) and in Germany since January 2007 (Midazolam-Ratiopharm). The approved dosages vary according to the indications and age up to 0.12 mg/kg/h IV and 0.2 mg/kg IM in patients between 1 and 15 years old, 0.3 to 0.5 mg/kg rectally in patients over 6 months and 0.25 to 1 mg/kg orally (maximum 20 mg).

Exposure to midazolam has been estimated to be more than 32 million paediatric patients treated IV or IM between September 1982 and April 1997 and 874 million patients (children and adults) treated parenterally or orally between May 1998 and August 2008 (Hoffman-La Roche data).

The tolerance profile of midazolam is known. The main side-effects of the substance are a class effect of benzodiazepines and include drowsiness, hypotonia, hypotension, respiratory depression, anterograde amnesia and paradoxical reactions.

Six cases of respiratory depression or excessive sedation (<0.2%) were reported in the 69 published studies evaluating oral midazolam administration as premedication before anaesthesia in children (2400 patients). Five episodes of respiratory depression were reported in two studies conducted by Hoffmann-La Roche Ltd in 508 patients treated with oral midazolam (<1%). The most commonly reported adverse events were nausea (4%) and vomiting (7%).

For buccal midazolam, the CHMP highlights the fact that there are insufficient available data in children between 3 and 6 months old and a higher risk of respiratory depression and hypoventilation in these children compared to older children. In light of the pharmacokinetic data, a risk of under-dosage has been suggested in children over 12 years old (>40 kg) at the proposed doses. The CHMP also described a risk of misuse leading to unnecessary
sedation, such as the use of the substance to reduce a partial convulsive seizure without altered consciousness, which could possibly resolve rapidly and spontaneously.

The risk management plan stipulates pharmacovigilance monitoring for the following adverse effects: respiratory and cardiac impairment, anterograde amnesia, paradoxical reactions, nausea/vomiting, pruritus, asphyxia due to aspiration, buccal irritation, overdose and under-dose in adolescents. Use in children under 6 months old will be monitored particularly carefully.

In view of the pharmaceutical form, and the pharmacokinetic and pharmacodynamic properties of the substance, the potential risks of abuse, misappropriation, off-label use and overdose have been highlighted by the French National Narcotics and Psychotropics Committee. The Committee recommends that additional risk management and minimisation measures be put in place, such as the development of secure packaging and a formulation including a dye (despite the bitter taste of midazolam), registration of a single unit packaging, distribution of risk minimisation documents for the patient’s close contacts and setting up surveys about the use of the medicinal product in practice.

4.3. Conclusion

The efficacy of buccal midazolam has been evaluated in five published comparative studies.

- Buccal midazolam has been compared to rectal diazepam to treat prolonged convulsive seizures in four studies (294 children). Between 65 and 78% of convulsive seizures stopped within 10 minutes with buccal midazolam compared to between 41 and 85% with rectal midazolam. The incidence of convulsive seizure recurrence within 24 hours measured in one of these studies was the same for buccal midazolam and rectal diazepam. No conclusion can be drawn as to the superiority of the buccal midazolam over rectal diazepam because of the methodology of these four studies (open or single-blind, pseudo-randomisation, dose of midazolam etc). The EMA has deemed that buccal midazolam was not inferior to rectal diazepam for the treatment of acute convulsive seizures in children.

- Buccal midazolam was compared to IV diazepam in one study. The percentage of convulsive seizures which stopped within 5 minutes was similar for both treatments. Buccal diazepam was effective less quickly, although administered earlier (ease of administration), than IV diazepam.

It should be noted that none of these studies were carried out on an outpatient basis whereas the primary utility of buccal midazolam is its use in pre-hospital emergency medicine.

The tolerance profile of midazolam is known. The main adverse effects of the substance are those of benzodiazepines: drowsiness, hypotonia, hypotension, respiratory depression, anterograde amnesia and paradoxical reactions. Based on the information available from the studies, the tolerance of midazolam was similar to that of diazepam, particularly in terms of the incidence of respiratory depression.

Because of the inadequate data in children between 3 and 6 months old, who are particularly at risk of respiratory tract obstruction and hypoventilation, the use of the substance in this age band has been restricted to a hospital setting or where monitoring of respiratory function and respiratory assistance equipment are accessible.
5. TRANSPARENCY COMMITTEE CONCLUSIONS

5.1. Actual benefit

Epileptic seizures are symptoms of very heterogeneous disorders. Prolonged seizures can be life-threatening or cause complications. The main determinants of morbidity and neurological complications of a status epilepticus are the age of the child when the status epilepticus occurs, and its cause and duration.

These proprietary medicinal products are intended to stop the prolonged acute convulsive seizure activity.

The efficacy/adverse effects ratio of these proprietary products in the treatment of these prolonged convulsive seizures in epileptic children is high.

There are treatment alternatives to these proprietary medicinal products. BUCCOLAM is the only proprietary medicinal product administered oromucosally which has an MA in this indication.

Public health benefit:

Epilepsy is a common disease and repeated seizures in some patients are liable to markedly reduce their quality of life. Epilepsies in children are associated particularly with cognitive developmental disorders, learning difficulties and behavioural disorders with serious consequences on social and family life.\(^6\) Status epilepticus can also lead to motor and cognitive neurological complications and increased mortality, which is higher in children and rises increasingly as the seizures begin at a younger age. Overall, epilepsy in children is a moderate public health burden.

The prevention of the functional and cognitive limitations and their consequences in children to which BUCCOLAM could contribute, is a public health need contained in established priorities (objective 62 on the public health policy law of 9 August 2004). This need remains for children as there are few well-tolerated treatments appropriate for paediatric use.

The available data compared to rectal diazepam do not demonstrate an additional impact in terms of morbidity or mortality or on quality of life. In addition, it is not possible to guarantee that clinical study data can be extrapolated into practice as none of the studies presented were carried out in an outpatient situation. In actual practice, firstly because of greater ease of use compared to rectal diazepam enabling it to be used by non-medical personnel, and secondly an administration route which is more appropriate for older children and parents with a child seated in a chair mean that midazolam could contribute to faster management of acute convulsive seizures. Progression to status epilepticus could therefore be avoided. The impact of treatment on other factors such as the quality of life of children and adolescents or of their parents, cognitive development, educational progress and the child’s family life have not been documented.

In addition, its ease of use, particularly by parents, in stressful situations or by community staff (crèches, schools, leisure centres etc.) could have a positive impact on the organisation of care if treatment with BUCCOLAM reduced the need for emergency care. There are, however, no data at present to demonstrate this.

BUCCOLAM therefore should be able to provide a supplementary response to the identified public health need.

As a result, BUCCOLAM could be expected to have a low public health benefit in this indication.

As a result, the actual benefit of the proprietary medicinal products is substantial.

5.2. Improvement in actual benefit (IAB)

BUCCOLAM offers a level IV improvement in actual benefit in the management of prolonged acute convulsive seizures in children and adolescents suffering from epilepsy in view of its buccal administration and presentation in ready-to-use syringe form.

5.3. Therapeutic use

All generalised convulsive seizures lasting for more than five minutes require rapid treatment. Status epilepticus is generally defined by persistence of a seizure or repeated attacks of epileptic seizures close together, with a neurological deficit or altered consciousness in the intercritical period, over a period of 30 minutes. The management of a convulsive seizure lasting for more than 5 minutes, and particularly of status epilepticus, requires the intervention of an emergency medical team before hospital.

Investigations into aetiology are carried out in parallel with the treatment and are based on investigating causes (hyperpyrexia, blood glucose, meningitis etc.) with specific emergency treatment. Symptomatic treatment combines antiepileptic therapy and general measures (prevention of injury, keeping the respiratory tract open, oxygen therapy).

Because of their speed of action and efficacy, the benzodiazepines are considered to be the first-line antiepileptics.

Before hospital (at home, in institutions), in the absence of venous access, benzodiazepines need to be administered transmucosally: rectal diazepam or buccal midazolam. The carer should call an emergency medical unit rapidly, possibly before or immediately after administering the substance when it is first used if the convulsive seizure has not stopped within 5 minutes of administration, or if the child has breathing difficulties. The empty syringe must be given to the health professional in order to provide information about the dose received by the patient. A second or repeated dose following initial response must not be given without a prior medical opinion.

In a hospital setting or during medical transport, if venous access is rapidly accessible, slow intravenous administration of a benzodiazepine (clonazepam or diazepam), under cardiorespiratory monitoring, is recommended. A second injection may be required if the seizure persists. If benzodiazepines do not control the status epilepticus, a long-acting antiepileptic must be started. Phenytoin or its precursor, fosfenytoin (off-label in children

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under 5 years old) and IV phenobarbital are the recommended treatments. Cardiorespiratory monitoring is then essential.

*Status epilepticus* which has not responded to two different antiepileptic agents is deemed to be refractory. This requires transfer to the paediatric intensive care unit.

Therapeutic use of BUCCOLAM:

Buccal midazolam is an alternative to rectal diazepam in the treatment of acute prolonged convulsive seizure in children and adolescents. The buccal use is more appropriate for outpatient treatment than rectal diazepam, particularly in older children and adolescents. BUCCOLAM may be appropriate in a hospital setting or during medical transport if venous access is difficult and delays administration of the medicinal product, particularly in infants. The management of persisting seizures and particularly of *status epilepticus* requires intravenous administration of medicinal products, continuous monitoring of vital signs and detailed investigations into the cause of the seizures.

In terms of the management of children who have failed treatment or if the seizure recurs, the SPC of the product states that a second or repeated dose must not be given without prior medical advice if seizures recur after an initial response.

Because of inadequate data in children between 3 and 6 months old, who are particularly at risk of respiratory tract obstruction and hypoventilation, the substance is restricted to hospital use in this age band, where access to respiratory function monitoring and respiratory assistance equipment is available.

### 5.4. Target population

The wording of the indication for BUCCOLAM states that the proprietary medicinal product must only be used in infants, toddlers, children or adolescents when a diagnosis of epilepsy has been made. These children may then be treated with emergency IV, rectal or buccal benzodiazepine to avoid the complications of a prolonged acute convulsive seizure.

The prevalence of epilepsy reported in the paediatric population varies greatly, with an average reported prevalence of between 3.6 and 6.8 per 1000 children.\(^ {10}\)

A prevalence of 3.8 per 1000 in the 16-19-year-old age band was found in Picot’s epidemiological study, carried out in France in a population over 15 years old.\(^ {11}\)

If the prevalence of childhood epilepsy in France is estimated as being between 3.6 and 6.8 per 1000, the numbers of children between 3 months and 17 years old liable to be given BUCCOLAM would be between 52,000 and 98,000.\(^ {12}\)

### 5.5. Transparency Committee recommendations

The transparency Committee recommends inclusion of BUCCOLAM 2.5 mg, 5 mg, 7.5 mg and 10 mg buccal solution on the list of medicines refundable by National Health Insurance (in children over 6 months old) and on the list of medicines approved for use by hospitals and various public services (in children over 3 months old) for the treatment of prolonged acute convulsive seizures in infants, toddlers, children and adolescents (from 3 months to under 18 years old).

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\(^{11}\) Picot MC et al. The prevalence of epilepsy and pharmaco-resistant epilepsy in adults: A population-based study in a Western European country. Epilepsia 2008; 49 (7): 1230-38.

\(^{12}\) Population between 0 and 17 years old on 01/01/2012: 14,457,187 (source: www.insee.fr)
The opinion of the Committee for inclusion on the list of medicines refundable by National Health Insurance for infants between 3 and 6 months old does not apply as the treatment must be administered in a hospital setting in order to ensure monitoring and availability of resuscitation equipment.

5.5.1 Packaging

Secure packaging and a smaller number of syringes contained in the box can be recommended by the National Narcotics and Psychotropics Committee. Information for the patient and/or carer should accompany each of the syringes contained in the external packaging.

5.5.2 Reimbursement rate: 65%