DATA SHEET

EPISTATUS™

Midazolam 10mg in 1ml Oromucosal Solution

Product Codes
M11, M11-SCA, M11-AUS and M11-ROW

Active Ingredient
Midazolam maleate

Description of Product
Clear, sweetened (sugar-free) viscous solution containing 10mg of Midazolam base (as the maleate) in 1ml.

The carbohydrate content (for patients on a ketogenic diet) of Epistatus is 250mg of carbohydrate in 1ml. This is equivalent to 1kcal/ml.

Presentation
Epistatus is supplied as 5ml of solution in a 30ml bottle. The bottle is over-sized to enable the carer to grip it securely whilst removing the child-resistant closure. A 1ml overage is supplied to ensure that 4 x 1ml doses can be removed quickly and completely. Each 1ml of Midazolam Oromucosal Solution contains 10mg of midazolam.

The pack contains:
- A carton with instructions for use on side panel.
- An information leaflet.
- An amber glass bottle, containing Epistatus, with a tamper-evident, child-resistant closure.
- 4 x 1.0ml pale lilac oral dosing applicators calibrated with 0.1ml markings.

Storage
Store below 25°C. The cap must be replaced immediately to prevent evaporation. If the solution is allowed to evaporate some of the midazolam will precipitate. This will be exhibited as a cloudiness or as white particles in the solution. The pack must be discarded if the solution is not clear.

Shelf Life
2 years

Active Excipient
Ethanol

Potential Allergenic Excipients
Sugar-free, Aspartame-free, gluten-free, colourant-free.

Therapeutic Indications
Emergency treatment of status epilepticus by buccal administration; as an alternative to rectal administration of diazepam.
Dosage\textsuperscript{1,6.}

<table>
<thead>
<tr>
<th>Age of Patient</th>
<th>Dose of Midazolam Oromucosal Solution</th>
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</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>300 micrograms/kg as a single dose</td>
</tr>
<tr>
<td>1-6 months</td>
<td>300 micrograms/kg (max 2.5mg) repeated if necessary</td>
</tr>
<tr>
<td>6-12 months</td>
<td>2.5mg (0.25ml) repeated if necessary</td>
</tr>
<tr>
<td>1-5 years</td>
<td>5mg (0.5ml) repeated if necessary</td>
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<tr>
<td>5-10 years</td>
<td>7.5mg (0.75ml) repeated if necessary</td>
</tr>
<tr>
<td>10-18 years</td>
<td>10mg (1.0ml) repeated if necessary</td>
</tr>
<tr>
<td>Adult</td>
<td>12.5mg (1.25ml) \textbf{no repeat dosage}</td>
</tr>
<tr>
<td></td>
<td>15mg (1.5ml) \textbf{no repeat dosage}</td>
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</tbody>
</table>

Patients treated frequently with rectal diazepam, who have developed a tolerance to benzodiazepines, will require a higher dose of Midazolam Oromucosal Solution than that in the above recommendations.

Experience has shown that the dose of rectal diazepam can be replaced by same dose of buccal midazolam.

Advice on Repeated Doses

Neonates
If no effect is apparent 10 minutes after giving a dose, then call an ambulance. Do not administer a second dose\textsuperscript{1.}

Administration of second dose in older patients
1 month – 18 years
If no effect is apparent after 10 minutes, check that the patient is breathing normally and administer another dose. If the patient’s breathing becomes shallow, call an ambulance and do not administer a second dose. If no effect is apparent 5 minutes after the second dose, call an ambulance.

What to do if a seizure starts again
A second course of treatment must not be administered sooner than:
- 6 hours (children under 10 years old).
- 12 hours (10-18 years).

Optimised Dose:
Patients requiring recovery treatment on a frequent basis should have their dosage optimized by titrating the dose up to the required amount that stops seizures reliably, without a second dose being required. This should be recorded in their individual Patient Management Plan, also known as a “care plan.” The dose will depend on their weight and susceptibility to respiratory depression.

Suggestions for adults are shown below:

<table>
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<tr>
<th>Age of Patient</th>
<th>Optimized Single Dose of Midazolam Oromucosal Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult male and female</td>
<td>Titrate the dose upwards from 10mg – 20mg until the seizure stops reliably after one dose, without causing respiratory depression. The optimized dose must not be repeated if it is more than 10mg</td>
</tr>
<tr>
<td></td>
<td>Nakken and Lossius\textsuperscript{5} found that the mean dose to treat adult males and females with prolonged seizures was 15.5mg</td>
</tr>
</tbody>
</table>

Patients treated frequently with rectal diazepam, who have developed a tolerance to benzodiazepines, will require a higher dose of Midazolam Oromucosal Solution than that in the above recommendations.

Administration
Using the oral syringe provided, administer, over a period of 2-3 seconds, about half of the prescribed dose to each buccal cavity (cavity between the gums of the lower jaw and the cheek). If the patient is very difficult to control, then administer the whole dose, over a period of 4-5 seconds, to one buccal cavity.
As a last resort, Epistatus can be administered intra-nasally if the patient foams at the mouth.

**Contraindications and Precautions**
Marked neuromuscular respiratory weakness including unstable myasthenia gravis: severe respiratory depression: acute pulmonary insufficiency.

**Side-effects and Adverse Reactions**
Respiratory depression occurs in about 5% of patients. That incidence is equivalent to that exhibited by rectal diazepam.
Drowsiness for several hours after administration.
Refer to the current edition of the British National Formulary for Children (BNFC) for a comprehensive list.

Overdoses can be treated with Flumazenil, which is a short-acting benzodiazepine antagonist.
See current British National Formulary (BNF) for further guidance.

**Mode of Action**
Epistatus has the same mode of action as other benzodiazepines.

**Pharmacokinetics**
A reduction in brain activity can be detected by EEG 5-10 minutes after the buccal administration of midazolam. 
$T_{\text{MAX}}$ is 30 minutes. The median time to stop a seizure is 8 minutes (IQR 5-20).
Mean midazolam bioavailability is 74%. The mean terminal half life in adults is 143 minutes.

**Interactions with other Medications**
Please refer to the current edition of the BNF and BNFC.

**Pregnancy and Breastfeeding**
High doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia, and respiratory depression.
Please also refer to the latest edition of the BNF.

**Legal Category**
Midazolam Oramucosal Solution is an ‘Unlicensed Medicine’ within the meaning of the current legislation, governed by the UK Medicines Act 1968.

This publication is solely for the technical guidance of prescribers and dispensers of Midazolam Oramucosal Solution and must not be considered as a recommendation or endorsement for the clinical use of the product. The information provided in this publication may not be comprehensive.

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**Transmissible Spongiform Encephalopathies**
Midazolam Oramucosal Solution complies with the Unlicensed Medicinal Products for Human Use (Transmissible Spongiform Encephalopathies) (Safety) Regulations 2003 [S.I. 2003/1680].

Approved by: G. A. March PhD, MRPharmS
Date: 29/08/2012

**References:**
2. British National Formulary for Children 2012-2013, p641-642; BMJ Group, RPS Publishing
5. Schwagmeier R et al.; Midazolam pharmacokinetics following intravenous and buccal administration; Br J Clin Pharmacol; 1998;46; 203-206.