



## Question: What is the difference between buccal midazolam preparations Epistatus® and Buccolam®?

February 2017

### Summary:

- Epistatus® and Buccolam® contain different salts of midazolam.
- Epistatus® 10mg/ml buccal liquid contains **midazolam maleate** and is an unlicensed product in Ireland. It is not currently available on the medical card (GMS) or Drug Payment Schemes (DPS). Epistatus is supplied as 5mls of liquid solution in a 30ml bottle.
- Buccolam® oromucosal solution contains **midazolam hydrochloride**.  
Buccolam® is presented in four, colour-coded, pre-filled oral syringes, specially prepared for oromucosal (buccal) administration;  
*2.5mg/0.5mls (yellow), 5mg/1ml (blue), 7.5mg/1.5mls (purple) and 10mg/2mls (orange)*  
It is licensed in Ireland for the treatment of seizures in paediatric patients aged from 3months to <18 years, who have been diagnosed with epilepsy. The four preparations outlined above are currently available on the GMS and DPS schemes.
- There are no known published head-to-head studies comparing the safety and efficacy of midazolam hydrochloride with midazolam maleate administered via the oromucosal (buccal) route.
- The products should not be considered bioequivalent but it is unlikely that the choice of product should impact on the dose of midazolam prescribed.

### Introduction

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The information outlined above is intended for healthcare professionals only. The information outlined above is believed to accurately reflect the medical literature at the time of writing. Healthcare professionals must use their own judgment to determine the accuracy and relevance of the information. See [www.olh.ie](http://www.olh.ie) for full terms and conditions.

Epistatus® 10mg/ml buccal liquid contains midazolam maleate.<sup>1</sup> Buccolam® oromucosal solution contains midazolam hydrochloride.<sup>2</sup> Epistatus is an unlicensed preparation in Ireland. Buccolam® presented in four age-specific, colour-coded, pre-filled oral syringes, specially prepared for oromucosal (buccal) administration; 2.5mg/0.5mls (yellow), 5mg/1ml (blue), 7.5mg/1.5mls (purple) and 10mg/2mls (orange)<sup>2</sup>. Buccolam® is licensed in Ireland for the treatment of prolonged, acute, convulsive seizures in infants, toddlers, children and adolescents (from 3 months to < 18 years) who have been diagnosed with epilepsy.<sup>3</sup> Buccolam® is currently available on the medical card (GMS) and Drug Payment Schemes (DPS) through community pharmacies.<sup>4</sup>

### **Midazolam Hydrochloride and Midazolam Maleate**

It is debatable whether the pharmacokinetic variations between the two salts (hydrochloride or maleate) are clinically significant. There are no known published head-to-head studies comparing the safety and efficacy of midazolam hydrochloride with midazolam maleate administered via the oromucosal (buccal) route. Therefore, the products should not be considered bioequivalent but it is unlikely that the choice of product should impact on the dose of midazolam prescribed. For patients with palliative care needs receiving a dose of midazolam on a regular basis, it may be prudent to avoid switching between products.

### Dose Equivalents

Midazolam hydrochloride 8.3 mg and midazolam maleate 10.2 mg are both equivalent to about 7.5 mg of midazolam base.<sup>5</sup> However, both products express the dose of midazolam in terms of the base.<sup>1,2,3</sup> Therefore, 1ml of Epistatus® (10mg/ml) contains midazolam (base) 10mg as 13.6mg of midazolam maleate.<sup>1</sup> Buccolam® 10mg/2ml prefilled oral syringe contains midazolam (base) 10mg as 11mg of midazolam hydrochloride.<sup>5</sup> Therefore, the product should not affect the dose of midazolam that is prescribed.

### pH

Buccolam® (midazolam hydrochloride) is formulated to have a pH of 3.3.<sup>2</sup> Midazolam maleate has a pH of  $\pm 3.5$ .<sup>2</sup> After administration to the buccal mucosa, midazolam is rapidly buffered to the physiological pH of 7.4 and becomes lipid soluble.<sup>2</sup> This

lipophilicity of midazolam allows for a significant increase in transmucosal permeation, maintaining the drug's efficacy and enabling it to rapidly cross the blood-brain barrier.<sup>2</sup>

#### Absorption from the buccal cavity

There is some suggestion that the maleate salt may be better absorbed in the buccal cavity.<sup>6</sup> The reported bioavailability of midazolam hydrochloride ranges from 74% in young healthy adults to 87% in children with severe malaria and convulsions.<sup>2</sup> The Data Sheet for Epistatus<sup>®</sup> reports that the mean bioavailability of midazolam is 74%.<sup>1</sup> It is unclear if this is based on the bioavailability of buccal midazolam hydrochloride. Epistatus<sup>®</sup> contains ethanol as an excipient.<sup>1</sup> It has been suggested that the addition of ethanol may enhance the buccal absorption of midazolam from the maleate (Epistatus<sup>®</sup>) product.<sup>7</sup>

#### **Comparison of Midazolam hydrochloride and Midazolam Maleate administered via the oromucosal route**

There are no known published head-to-head studies comparing the safety and efficacy of midazolam hydrochloride with midazolam maleate administered via the oromucosal (buccal) route.<sup>2</sup>

#### **Comparison of midazolam hydrochloride with midazolam maleate administered via intravenous route for the induction of anaesthesia**

Blackmon et al assessed whether the same intravenous doses (mg/kg) of midazolam hydrochloride and midazolam maleate are required for the induction of anaesthesia.<sup>8</sup> The study compared intravenous midazolam hydrochloride and intravenous midazolam maleate in a prospective double-blind fashion, in which both cardiopulmonary and sedative effects were measured in 12 patients who required repeated anaesthesia for serial gynaecologic radium insertions.<sup>8</sup> The results showed no significant differences in clinical activity between midazolam maleate and midazolam hydrochloride.<sup>8</sup> Time of onset, recovery time, lack of venous irritation, and stability of cardiopulmonary variables when using the hydrochloride, were essentially the same with the maleate.<sup>8</sup>

#### **Drug Safety Issues associated with Buccal Midazolam**

- Buccolam<sup>®</sup> pre-filled oral syringes are available in four different strengths;
  - 2.5mg/0.5ml

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- 5mg/ml
- 7.5mg/1.5mls
- 10mg/2mls

It is important to ensure that the correct preparation is prescribed.

- Administration errors have occurred when 2.5mls (25mg) of a buccal midazolam preparation was administered instead of 2.5mg (0.5ml). The dose should always be prescribed in **mg and mL**.<sup>9</sup>
- There is a potential for an administration error if buccal midazolam is administered through an IV administration device with a 'luer' connector.<sup>9</sup>
- The most common adverse reactions in clinical trials of buccal midazolam were sedation, somnolence, depressed levels of consciousness, respiratory depression, and nausea and vomiting.<sup>6</sup>
- Once a Buccolam<sup>®</sup> oromucosal syringe has been opened it should be discarded immediately after use, as directed.<sup>3</sup> Any remaining solution should not be stored for use at a later stage.<sup>3</sup>

## References

- 1) Data Sheet Epistatus. Version 11. Available from Special Products Ltd. Accessed on the 25/01/2017.
- 2) Direct Communication from Shire Medicines Information Department. Buccolam<sup>®</sup>: Formulation and Pharmacokinetics. Reference:GB-GGM-Feb17-8164E-Letter. February 2017.
- 3) Summary of Product Characteristics Buccolam 2.5mg, 5mg, 7.5mg and 10mg oromucosal solution. Available from [www.medicines.ie](http://www.medicines.ie). Accessed on the 13/01/2017.
- 4) Primary Care Reimbursement Services Reimbursable Items. Available from <http://www.hse.ie/eng/staff/PCRS/items/>. Accessed on the 06/02/2017.
- 5) Monograph Midazolam. Martindale, the complete drug reference. Available from [www.medicinescomplete.com](http://www.medicinescomplete.com). Accessed on the 23/01/2017.
- 6) The Medicines and Healthcare products Regulatory Agency (MHRA). Drug Safety Update. Volume (5) Issue (3). October 2011. Available from <http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131931>. Accessed on the 31/01/2017.

- 7) Tomlin S. Medicines tailored for children – the introduction of buccal midazolam. The Pharmaceutical Journal. 2011; 287:161. Available from [www.pjonline.com](http://www.pjonline.com).
- 8) Blackmon BB, Mahaffey JE and Baker JD 3rd. Clinical comparison of midazolam hydrochloride and midazolam maleate for anesthesia induction. Anesthesia and Analgesia 1984 Dec; 63(12):1116-20.
- 9) Prevention of Harm with Buccal Midazolam, National Patient Safety Association Signal. Available from <http://www.nrls.npsa.nhs.uk>. Accessed on the 30/01/2017.