

Shared Care Guidelines: Use of Oromucosal Midazolam as an intervention for prolonged seizures and prevention of Status Epilepticus in children under 10 years of age (TLS amber) (Epistatus®)

PLEASE NOTE: Epistatus is the brand of choice in NHS BaNES/NHS Swindon/NHS Wiltshire. Prescribe by BRAND NAME. Community nurses can only provide training on the use of this brand in carer & school settings. ALL patients should now be prescribed pre-filled syringes and should NOT receive the multi-dose bottle.

For children 10 years and above, please refer to the separate shared care agreement for that age group on the formulary websites.

AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines ways in which the responsibilities for managing the prescribing of midazolam for paediatric patients under 10 years of age prone to prolonged generalised seizures (lasting longer than 5 minutes), clusters of seizures or status epilepticus can be shared between the specialist and the general practitioner (GP). GPs are invited to participate but if the GP is not confident to undertake these roles, they are under no obligation to do so. In such an event, the clinical responsibility for the patient in respect of this diagnosed condition remains with the specialist. **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.**

Sharing of care assumes communication between the specialist, GP, patient and their carers. The intention to share care should be explained to the patient and their carers by the specialist initiating treatment.

It is important that it is explained that the use of Epistatus for the treatment of prolonged epileptic seizures in this age group is **unlicensed** and that both patients and/or carers are consulted and in agreement with this treatment. It should be noted that Epistatus® is licensed for the treatment of prolonged, acute, convulsive seizures in children and adolescents aged 10 to less than 18 years. The manufacturers are currently pursuing a license for this age group as well as in adults, which is expected within the next 12 months.

The doctor or nurse who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

PLACE IN TREATMENT

Rectal Diazepam is another licensed product available to children for the treatment of status epilepticus, clusters of seizures and prolonged seizures but using this route can be practically difficult and socially unacceptable. Midazolam is as effective as rectal diazepam, is absorbed rapidly through the buccal cavity and has practical advantages of ease and social acceptability in administration. Midazolam oromucosal solution is available as:

Epistatus® - containing **midazolam maleate 10mg in 1mL**.

Prefilled Oral Syringes :

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| <p>2.5mg / 0.25ml 5mg / 0.5ml 7.5mg / 0.75ml</p> | } | UNLICENSED. For use in children under 10 years of age. Individually wrapped pre-filled oral syringes (pack of 4) |
| 10mg / 1ml | | LICENSED product for children aged 10 to less than 18 years of age. Available as a single pre-filled syringe. |

Bottle: UNLICENSED. 5-ml multi dose bottle with four oral syringes in the packaging. Any patients already using this should be moved from this format to the licensed pre-filled 10mg in 1ml syringe.

▼ **Buccolam®** - a licensed preparation for children containing **midazolam hydrochloride 5mg in 1mL (note the different strength)** in pre-filled oral syringes of 2.5mg, 5mg, 7.5mg and 10mg. ▼ **Buccolam® is NOT currently included in local formularies and so should not be prescribed.**

The consensus view of local specialists is to continue to use the Epistatus® as the product of choice at the current time. (July 2017)

KEY MESSAGES

- **Epistatus®** (unlicensed brand currently recommended) is **TWICE** the strength of ▼ **Buccolam®**
- Midazolam oromucosal solution should be **prescribed by brand name**; if this is not prescribed by brand name, pharmacists should check the intended product with prescribers.
- Care is required to ensure that patients and carers receive the product they are expecting and are familiar with.

RESPONSIBILITIES and ROLES

| Specialist responsibilities | |
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| 1 | Initiate treatment and provide at least 2 doses of the correct dose of pre-filled syringes. All children under 2 years of age who require oromucosal midazolam will ONLY be initiated on the advice of a Consultant Paediatric Epilepsy specialist. |
| 2 | Discuss the benefits and side effects of treatment with the patient and/or carers and consider the use of unlicensed medicines and only use when the benefits outweigh the risks. The prescriber must make every effort to obtain consent to treatment and inform the patient and carer of the Medicine's license status and that the effects of an unlicensed product will be less well understood than those of a licensed product. |
| 3 | Ensure that the patient/carer understands when and how to give the medication (An identified member of the specialist team such as epilepsy specialist nurse and Public Health School Nurse (PHSN), will work with the parents / carer to develop an Emergency Treatment Plan for child/young person with epilepsy for administration, train in use, ensure appropriate storage and provide written/verbal advice in a way that the individuals can understand (as per Joint Epilepsy |
| 4 | Ask the GP whether they are willing to participate in shared care. The GP must be informed of the medicine's license status when asking them to use unlicensed medicines. |
| 5 | Supply the GP with background information about diagnosis, the reasons for selecting midazolam and details of how to prescribe it, including details of how often doses can be repeated, maximum dose in 24 hours and details of any combination therapy. This summary should be received within 14 days of a hospital outpatient review, in-patient stay or Community review. |
| 6 | Inform the appropriate community service that Buccal Midazolam has been prescribed. A Health Care Plan/Flow Chart should be put into place by the appropriate community service to support use. |
| 7 | Review the patient's condition and monitor response to treatment regularly (at least 6 monthly). |
| 8 | Advise GP on when to stop, alter or change treatment. |
| 9 | Report adverse events to the MHRA: https://yellowcard.mhra.gov.uk/ |
| 10 | Ensure clear arrangements for GP and carer back-up, advice and support |

| General Practitioner responsibilities | |
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| 1 | Reply to the request for shared care as soon as practicable. |
| 2 | Prescribe midazolam after communication with specialist about need for treatment and the formulation to be used and the dose recommended. See BCAP aid to prescribing on GP prescribing systems (appendix) |
| 3 | Midazolam is a schedule 3 controlled drug and therefore subject to the requirement for the quantity to be supplied to be written in words and figures. |
| 4 | Refer promptly to specialist if frequency of use increases, lack of clinical efficacy is suspected or any concerns arise. |
| 5 | Report to and seek advice from specialist on any aspect of patient care that is of concern to the GP and may affect treatment. |
| 6 | Stop treatment on the advice of the specialist. |
| 7 | Report adverse events to the specialist and MHRA: https://yellowcard.mhra.gov.uk/ |

| Community Pharmacist's role | |
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| 1 | If the prescription is written generically confirm with the patient &/or GP as to which brand the patient uses (should be Epistatus). Endeavour to get the GP practice to change the patient's records to the correct brand. |
| 2 | Epistatus is not licensed for use in children under the age of 10. However, it is the product of local choice and the manufacturers are pursuing a license for this age group. Meanwhile, it is important that parents/carers understand the licensing position. |
| 3 | Ensure that each Epistatus 10mg in 1ml pre-filled syringe (PFS) is labelled on the outside of the box it comes in. Usually, 1 or 2 PFS will be supplied for each patient at a time. |
| 3 | Check that the patient/carer collecting the prescription understands how to use it. |

| Patient's/carers role | |
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| 1 | Report to the specialist or GP if he or she does not have a clear understanding of the treatment. |
| 2 | Share any concerns in relation to treatment with medicine. |
| 3 | Report any adverse effects to the specialist or GP whilst taking the medicine. |

Epilepsies: diagnosis and management NICE CG137 (Updated February 2016): <https://www.nice.org.uk/Guidance/cg137>

- Only prescribe buccal midazolam for use in the community for children, young people and adults who have had a previous episode of prolonged or serial convulsive seizures
- Over- and potentially inappropriate prescription of emergency benzodiazepines should not be used as a means to alleviate individual, parental or carer's anxiety.

Review and discontinuation of treatment

- An ongoing review of the continued need for emergency rescue treatment with buccal midazolam should be carried out

by a **specialist** at least every 6 months to ensure the seizure management plan is still appropriate and to prevent unnecessary long term prescribing.

- Midazolam may be withdrawn if the patient has been fit free over a 2 year period.

SAFETY: MHRA Guidance

The MHRA issued a warning (Drug Safety Update in October 2011) that care was needed if transferring between **Epistatus**[®] and **Buccolam**[®] due to the differences in strengths between the products.

<http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON131931>

There have also been other errors reported to the National and Reporting Learning System (NRLS) involving confusion between the mg and mL e.g. 2.5mL (25mg) was prescribed when 0.25mL (2.5mg) was intended.

<http://www.nrls.npsa.nhs.uk/resources/type/signals/?entryid45=132975>

MEDICATION DETAILS

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| Indication | Status epilepticus and prolonged seizures. Midazolam is a short acting benzodiazepine that offers an alternative to rectal diazepam. |
| Products available | Midazolam oromucosal solution is available from Special products Ltd. It should be prescribed by the BRAND NAME Epistatus [®] . This product is not licensed for use in this age group. |
| Form | Midazolam 10mg in 1ml maleate is available as prefilled syringes (PFS) for use in children under the age of 10: 7.5mg in 0.75ml, 5mg in 0.5ml, 2.5mg in 0.25ml The 10mg in 1m PFS is now licensed to be used in children from the age of 10 to under 18. |
| Administration | Using the prefilled syringe: half the contents should be squirted into each buccal cavity. |
| Dose and frequency | The amount of midazolam buccal liquid used depends on weight and age. The usual doses are: <ul style="list-style-type: none"> • Children under 3 months- to 1 year: Hospital only • Children 1 to 5 years -5mg (0.5ml) • Children 5 to 10 years- 7.5mg (0.75ml) • Children over 10 years and adults- 10mg (1ml) (LICENSED age 10 to under 18) <p>If a response is not seen 5 minutes after the first dose then call 999 for an ambulance.</p> <p>If the seizure is still continuing 10 minutes after the first dose then a second dose can be given. This is generally only advisable if the child is in hospital or the ambulance crew are present, due to the risk of respiratory depression.</p> <p>What to do if a seizure starts again:</p> <p>Only 2 doses of buccal midazolam to be given in 24 hours. Follow Advanced Paediatric Life Support (APLS) status epilepticus algorithm if seizures continuing: https://www.apls.org.au/sites/default/files/uploadedfiles/Algorithms%20-%20Status%20Epilepticus.pdf</p> |
| Contra-indications | Hypersensitivity to the active substance (midazolam), benzodiazepines or to any of the excipients Myasthenia gravis. Severe respiratory insufficiency. Sleep apnoea syndrome. Severe hepatic impairment. |
| Cautions | Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration. Midazolam should be used with caution in patients with chronic renal failure, impaired hepatic or cardiac function. Midazolam may accumulate in patients with chronic renal failure or impaired hepatic function whilst in patients with impaired cardiac function it may cause decreased clearance of midazolam. Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines and, therefore, lower doses may be required. Midazolam may cause anterograde amnesia. |
| Side effects | The most common side effects with Epistatus (seen in 1/100 to 1/10) are sedation, somnolence, depressed levels of consciousness, respiratory depression and nausea and vomiting. All patients receiving midazolam are likely to be drowsy for several hours after administration Rare: agitation, restlessness and disorientation have been reported. |
| Monitoring | No specific monitoring is necessary. |
| Drug interactions | Calcium channel blockers, erythromycin, other macrolides and cimetidine reduce the clearance of midazolam. This may result in prolonged duration of sedative effect. |
| Storage | Do not store above 25 ^o C. Do not store in a fridge as crystallisation may occur. |

| BACK-UP ADVICE AND SUPPORT | | | | |
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| Carol Jackson Paediatric Pharmacist Pharmacy Royal United Hospital Bath BA1 3NG | 01225 428331 | 7194 | | caroljackson@nhs.net |
| <u>RUH Hospital Pharmacy Dept:</u> Pharmacy dispensary (for prescription queries) Pharmacy out-patients | 01225 824640 01225 825869 | | | |
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| <u>GWH paediatric epilepsy specialist nurse:</u> Susan Mulhall <u>GWH paediatric specialist pharmacist:</u> Cathy Dewdney | 01793 604969 (24 hour voicemail) 01793 605193 | - 1327 | | susan.mulhall@nhs.net Cathy.Dewdney@gwh.nhs.uk |

References

- Drug Tariff http://www.ppa.org.uk/ppa/edt_intro.htm
- Epilepsy Action <https://www.epilepsy.org.uk/>
- Epilepsy Society <http://www.epilepsysociety.org.uk/>
- Joint Epilepsy Council <http://www.jointepilepsycouncil.org.uk/>
- NICE Guidance, The Epilepsies <http://www.nice.org.uk/Guidance/cg137>
- Special Products <http://www.specialproducts.biz/>
- Young Epilepsy <http://www.youngepilepsy.org.uk/about-us/>