

EPISTATUS® 2.5 mg, 5 mg, 7.5 mg, 10 mg oromucosal midazolam maleate solution Prescribing Information. Please consult Summary of Product Characteristics (SmPC) before prescribing.

Presentation & composition: Oromucosal solution. Each pre-filled, oral syringe (0.25ml, 0.5ml, 0.75ml and 1ml) contains midazolam maleate corresponding to 2.5 mg/ 5 mg/ 7.5 mg/ 10 mg midazolam respectively. Excipients with known effect: ethanol 49/ 99/ 148/ 197 mg per dose, liquid maltitol 169/ 338/ 506/ 675 mg per dose.

Indication: 2.5 mg, 5 mg, 7.5 mg, 10 mg: Treatment of prolonged, acute, convulsive seizures in adults, adolescents, children and infants aged 3 months and above. Epistatus must only be used by parents/caregivers 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.

Dosage:

Age range	Dose	Labelled packaging colour
3 to 6 months, hospital setting	2.5 mg (0.25 ml)	Yellow
> 6 months to < 1 year	2.5 mg (0.25 ml)	Yellow
1 year to < 5 years	5 mg (0.5 ml)	Blue
5 years to <10 years	7.5 mg (0.75 ml)	Purple
10 years and above	10 mg (1 ml)	Orange

Carers should only administer a single dose. If the seizure does not stop shortly after administration, emergency medical assistance must be sought, considering prior instructions from the prescribing physician, or local guidelines. The empty syringe must be given to the healthcare professional. Patients should be kept under supervision by a carer who remains with the patient. A second or repeat dose when seizures re-occur after an initial response should not be given without prior medical advice.

Administration: For oromucosal use only – in the mouth. Using the prefilled oral syringe provided, administer, over a period of 2-3 seconds, approximately half of the prescribed dose to each buccal cavity. Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If difficult to get the syringe into the buccal cavity, administer the whole dose, over a period of 4-5 seconds, to one buccal cavity. For detailed instructions please refer to the SmPC.

Contraindications: Hypersensitivity to midazolam, benzodiazepines or to any of the excipients; myasthenia gravis; severe respiratory insufficiency; sleep apnoea syndrome; severe hepatic impairment.

Warnings & Precautions: For oromucosal use only. Take care to avoid the risk of choking. **Paediatric patients aged 3 to 6 months:** Given the higher metabolite to parent drug ratio in younger children, a delayed respiratory depression as a result of high active metabolite concentrations in the 3-6 months age group cannot be excluded. Therefore, the use of Epistatus in the 3-6 month age group should be limited for use only under the supervision of a health care professional where resuscitation equipment is available and where respiratory function can be monitored and equipment for respiratory assistance, if needed, is available. **Respiratory insufficiency:** Caution in patients with chronic respiratory insufficiency (may further depress respiration). **Renal Impairment:** No efficacy studies in patients with chronic renal failure have been reported. Epistatus should be used with caution in patients with chronic renal failure as multiple doses of midazolam in patients with chronic renal failure may result in delayed elimination of midazolam and prolongation of effects. **Hepatic Impairment:** No efficacy studies in patients with chronic hepatic impairment have been reported. Hepatic impairment reduces midazolam clearance. Careful monitoring of clinical effects and vital signs is recommended following administration. Epistatus is contraindicated in patients with severe hepatic impairment. **Elderly:** Use with caution in elderly patients as elimination of midazolam may be delayed and the clinical effects of midazolam prolonged. **Obesity, critically ill and cardiac insufficiency:** No efficacy studies of

midazolam in obese, critically ill, cardiac insufficiency patients have been reported. Please see SmPC for full information on special populations. Midazolam should be used with caution in patients with impaired cardiac function (may decrease clearance). Debilitated patients are more prone to the central nervous system (CNS) effects of benzodiazepines. The concomitant use of Epistatus and opioids increases the risk of sedation, respiratory depression, coma, and death. Epistatus with opioids should be reserved for patients for whom alternative treatment options are not possible. The lowest dosage and shortest duration of concomitant opioid use should be used. Inform patients and caregivers of the need to monitor closely for respiratory depression and sedation. Midazolam should be avoided in patients with a medical history of alcohol or drug abuse. May cause anterograde amnesia. Contains maltitol (Patients with rare hereditary problems of fructose intolerance should not take this medicine) and ethanol, and less than 1mmol sodium (23mg) per dose.

Interactions: Please consult the SmPC for full details. Midazolam is metabolized by cytochrome P450 3A4 isozyme (CYP3A4). Inhibitors and inducers of CYP3A4 may increase and decrease the plasma concentration respectively and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. In the presence of CYP3A4 inhibition the duration of effect of a single dose of oromucosal midazolam may be prolonged; careful clinical monitoring is recommended. Midazolam may interact with other hepatically metabolized medicinal products. Co-administration with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression. Alcohol intake should be strongly avoided. The dosage and duration of concomitant opioid use should be limited.

Fertility, Pregnancy, and lactation: There are no or limited amount of data from the use of midazolam in pregnant women. The administration of high doses of midazolam in the last trimester of pregnancy, during labour has been reported to produce maternal or foetal adverse effects. Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be considered in the event of administration in the third trimester. Midazolam passes in low quantities into breast milk (0.6%); it may not be necessary to stop breast-feeding following a single dose. Animal studies did not show an impairment of fertility.

Driving and machines: Midazolam has a major influence on the ability to drive or use machines. The patient should be warned not to drive or use machines until fully recovered.

Undesirable effects: Respiratory depression occurs at a rate of up to 5%, although this is a known complication of convulsive seizures as well as being related to benzodiazepine use. Common: sedation, somnolence, depressed level of consciousness, respiratory depression, ataxia*, dizziness*, headache*, nausea, vomiting & fatigue*. Uncommon: hallucination*, agitation*, anterograde amnesia*, pruritus, rash, urticaria. Very rare: aggression*, movement disorders*, physical assault*, seizure, paradoxical reactions*, bradycardia*, cardiac arrest*, hypotension*, apnoea*, dyspnoea*. Unknown frequency: Angioedema, thrombosis, respiratory arrest* and anaphylactic reaction*. **Description of selected adverse reactions:** Increased risk of falls and fractures in the elderly and in those taking concomitant sedatives (including alcohol). Life-threatening incidents are more likely to occur in those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when a high dose is administered. Consult the SmPC for the full list of adverse drug reactions and before prescribing.

* These adverse reactions have been reported to occur when midazolam is injected in children and/or adults, which may be of relevance to oromucosal administration.

Overdose: Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. Following overdose with oral midazolam, vomiting should be induced (within one hour) if the patient is conscious or gastric lavage undertaken with the airway protected if the patient is unconscious. If there is no advantage in emptying the stomach,

activated charcoal should be given to reduce absorption. Special attention should be paid to respiratory and cardiovascular functions in intensive care. Flumazenil may be useful as an antidote.

Excipients: Ethanol, Saccharin Sodium, Glycerol, Purified Water, Sodium Hydroxide, Maltitol (Liquid)

Shelf life and Storage: 18 months. Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light.

Legal classification: POM

NHS Price: 2.5 mg in 0.25 mL, 5 mg in 0.5 mL and 7.5 mg in 0.75 mL - £43.75, 10 mg in 1 mL prefilled syringe - £45.76

United Kingdom (Great Britain) Marketing Authorisation numbers: 2.5 mg PLGB 43956/0010, 5 mg PLGB 43956/0011, 7.5 mg PLGB 43956/0012, 10 mg PLGB 43956/0009.

Marketing Authorisation holder: SERB S.A., Avenue Louise 480, 1050 Brussels, Belgium.

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Adverse events should be reported. Reporting forms and information can be found at <https://yellowcard.mhra.gov.uk/> or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Serb SA via email at safety@serb.com