

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Epistatus 10 mg Oromucosal Solution.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains 10 mg of midazolam (as maleate).

Excipients with a known effect:

Ethanol 197 mg/mL.

Liquid maltitol qs to 1 mL (675 mg).

Includes less than 1 mmol sodium (saccharin sodium and sodium hydroxide) per dose.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Oromucosal solution.

Clear colourless to pale yellow solution.

pH 4.6 - 5.6

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Epistatus is indicated for the treatment of prolonged, acute, convulsive seizures in children and adolescents aged 10 to less than 18 years.

Epistatus must only be used by parents / caregivers where the patient has been diagnosed to have epilepsy.

4.2 Posology and method of administration

Posology

For children and adolescents aged 10 to less than 18 years of age the standard dose is 10 mg (1.0 mL).

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 and product received by the patient.

After receiving midazolam, 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 (see section 5.2).

Obesity

No efficacy studies of midazolam in obese children have been reported. Therefore, no data is available.

Renal Impairment

No efficacy studies of midazolam in children with chronic renal failure have been reported. Multiple doses of midazolam in patients with chronic renal failure may result in delayed elimination of midazolam and prolongation of effects. However, in the setting of treatment of an acute epileptic seizure with a single or 2 doses of midazolam, accumulation of parent drug or metabolite is unlikely to occur causing prolongation of clinically significant pharmacological effects.

Hepatic Impairment

No efficacy studies of midazolam in children with chronic hepatic impairment have been reported.

Critically Ill Patients

No efficacy studies of midazolam in critically ill children have been reported.

Cardiac Insufficiency

No efficacy studies of midazolam in children with cardiac insufficiency have been reported.

Method of Administration

Epistatus is for oromucosal use. It is only to be used in the mouth.

The amber sheath cap should be removed before use.

Using the pre-filled oral syringe provided, administer, over a period of 2-3 seconds, approximately half of the prescribed dose to each buccal cavity (space between the gum and the cheek). Laryngo-tracheal insertion should be avoided to prevent accidental aspiration of the solution. If it is particularly difficult to get the syringe into the buccal cavity, then administer the whole dose, over a period of 4-5 seconds, to one buccal cavity.

For detailed instructions on how to administer the medicinal product see Section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance (midazolam), benzodiazepines or to any of the excipients listed in section 6.1.

Myasthenia gravis.

Severe respiratory insufficiency.

Sleep apnoea syndrome.

Severe hepatic impairment.

4.4 Special warnings and precautions for use

Midazolam should be used with caution in patients with chronic respiratory insufficiency because midazolam may further depress respiration.

No needle, intravenous tubing or any other device for parenteral administration should be attached to the oral syringe. Epistatus is for oromucosal use only.

Care must be taken when administering the product to avoid the risk of the patient choking.

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 should be avoided in patients with a medical history of alcohol or drug abuse.

Midazolam may cause anterograde amnesia.

MALTITOL

This product contains maltitol. Patients with rare hereditary problems of fructose intolerance should not be given this medicine unless the benefits are considered to outweigh the risks.

ETHANOL

This medicinal product contains 25 vol % ethanol (alcohol), i.e. 197 mg per dose, equivalent to 5 mL of beer, 2 mL wine per dose.

Harmful for those suffering from alcoholism.

To be taken into account in pregnant or breast-feeding women, children and high-risk groups such as patients with liver disease.

4.5 Interaction with other medicinal products and other forms of interaction

Midazolam is metabolized by cytochrome P450 3A4 isozyme (CYP3A4). Inhibitors and inducers of CYP3A4 have the potential to respectively increase and decrease the plasma concentrations and, subsequently, the effects of midazolam thus requiring dose adjustments accordingly. Pharmacokinetic interactions with CYP3A4 inhibitors or inducers are more pronounced for oral as compared to oromucosal or parenteral midazolam as CYP3A4 enzymes are also present in the upper gastro-intestinal tract. After oromucosal administration, only systemic clearance will be affected. After a single dose of oromucosal midazolam, the consequence on the maximal clinical effect due to CYP3A4 inhibition will be minor while the duration of effect may be prolonged. Hence, careful monitoring of the clinical effects and vital signs is recommended during the use of midazolam with a CYP3A4 inhibitor even after a single dose.

Anaesthetics and narcotic analgesics: Fentanyl may reduce midazolam clearance.

Antiepileptics: Co-administration with midazolam may cause enhanced sedation or respiratory or cardiovascular depression. Midazolam may interact with other hepatically metabolised medicinal products, e.g. phenytoin, causing potentiation.

Calcium-channel blockers: Diltiazem and verapamil have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Dopaminergic agents: Midazolam may cause inhibition of levodopa.

Muscle relaxants: e.g. baclofen. Midazolam may cause potentiation of muscle relaxants, with increased CNS depressant effects.

Nabilone: Co-administration with midazolam may cause enhanced sedation or respiratory and cardiovascular depression.

Ulcer-healing medicinal products: Cimetidine, ranitidine and omeprazole have been shown to reduce the clearance of midazolam and other benzodiazepines and may potentiate their actions.

Xanthines: Metabolism of midazolam and other benzodiazepines is accelerated by xanthines.

Medicinal products that inhibit CYP3A4

Medicinal product interactions following oromucosal administration of midazolam are likely to be similar to those observed after intravenous midazolam rather than oral administration.

Food:

Grapefruit juice: reduces the clearance of midazolam and potentiates its action.

Azole antifungals:

- Ketoconazole increased the plasma concentrations of intravenous midazolam by 5-fold while the terminal half-life increased by about 3-fold.
- Voriconazole increased the exposure of intravenous midazolam by 3-fold whereas its elimination half-life increased by about 3-fold.
- Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 to 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole.
- Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide antibiotics:

- Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 to 2-fold associated with an increase of the terminal half-life of midazolam by 1.5 to 1.8-fold.
- Clarithromycin increased the plasma concentrations of intravenous midazolam by up to 2.5-fold associated with an increase in terminal half-life by 1.5 to 2-fold.

HIV Protease inhibitors Saquinavir and other HIV protease inhibitors:

Co-administration with protease inhibitors may cause a large increase in the concentration of midazolam. Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life.

Calcium-channel blockers:

Diltiazem: A single dose of diltiazem increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by 43%.

Various medicinal products:

Atorvastatin showed a 1.4-fold increase in plasma concentrations of intravenous midazolam compared to control group.

Medicinal products that induce CYP3A4

Rifampicin (7 days of 600 mg once daily) decreased the plasma concentrations of intravenous midazolam by about 60%. The terminal half-life decreased by about 50-60%.

Herb:

St John's Wort decreased plasma concentrations of midazolam by about 20-40% associated with a decrease in terminal half life of about 15-17%. Depending on the specific St John's Wort extract, the CYP3A4-inducing effect may vary.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative/hypnotic agents and CNS depressants, including alcohol, is likely to result in enhanced sedation and respiratory depression.

Examples include opiate derivatives (used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate sedative antidepressants, non-recent H1-antihistamines and centrally acting antihypertensive medicinal products.

Alcohol (including alcohol-containing medicinal products) may markedly enhance the sedative effect of midazolam. Additional alcohol intake should be strongly avoided in case of midazolam administration (see section 4.4).

Disulfiram: Epistatus contains a small amount of alcohol and therefore should not be co-administered with disulfiram.

Midazolam decreases the minimum alveolar concentration (MAC) of inhalation anaesthetics.

The effect of CYP3A4 inhibitors may be larger in infants since part of the oromucosal dose is probably swallowed and absorbed in the gastro-intestinal tract.

4.6 Fertility, pregnancy and lactation

Pregnancy

Insufficient data are available on midazolam to assess its safety during pregnancy. Animal studies do not indicate a teratogenic effect, but foetotoxicity was observed as with other benzodiazepines. No data on exposed pregnancies are available for the first two trimesters of pregnancy.

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 (risk of aspiration of fluids and stomach contents during labour in the mother, irregularities in the foetal heart rate, hypotonia, poor suckling, hypothermia and respiratory depression in the new-born infant).

Midazolam may be used during pregnancy if clearly necessary. The risk for new-born infants should be taken into account in the event of administration of midazolam in the third trimester of pregnancy.

Breastfeeding

Midazolam passes in low quantities (0.6%) into breast milk. As a result it may not be necessary to stop breast feeding following a single dose of midazolam.

Fertility

Animal studies did not show an impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Midazolam has a major influence on the ability to drive and use machines.

Sedation, amnesia, impaired attention and impaired muscular function may adversely affect the ability to drive, ride a bicycle or use machines. After receiving midazolam,

the patient should be warned not to drive a vehicle or operate a machine until completely recovered.

4.8 Undesirable effects

Published clinical studies show that oromucosal midazolam was administered to approximately 446 children with seizures. Most studies did not indicate numbers of adverse reactions but stated that no severe events had been reported or there was no difference from the active comparator, rectal or intravenous diazepam. 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. One episode of pruritus was possibly attributed to the use of buccal midazolam.

The table below lists the adverse reactions reported to occur when oromucosal midazolam was administered to children in clinical studies.

The frequency of adverse reactions is classified as follows:

Common: $\geq 1/100$ to $< 1/10$

Uncommon: $\geq 1/1,000$ to $< 1/100$

Very rare: $\leq 1/10,000$

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness;

System Organ Class	Frequency: Adverse Drug Reaction
Nervous system disorders	Common: Sedation, somnolence, depressed levels of consciousness and respiratory depression
Gastrointestinal disorders	Common: Nausea and vomiting
Skin and subcutaneous tissue disorders	Uncommon: Pruritus, rash and urticaria

The following adverse reactions have been reported to occur (very rarely) when midazolam is injected in children and or adults, which may be of relevance to oromucosal administration:

System Organ Class	Frequency: Adverse Drug Reaction – All occur very rarely
Psychiatric disorders	Aggression, agitation, anger, confusional state, euphoric mood, hallucination, hostility, movement disorder, physical assault
Nervous system disorders	Anterograde amnesia, ataxia, dizziness, headache, seizure, paradoxical reactions
Cardiac disorders	Bradycardia, cardiac arrest, hypotension, vasodilatation
Respiratory, thoracic and mediastinal disorders	Apnoea, dyspnoea, laryngospasm, respiratory arrest

Gastrointestinal disorders	Constipation, dry mouth
General disorders and administration site conditions	Fatigue, hiccups

Description of selected adverse reactions

An increased risk of falls and fractures has been recorded in elderly midazolam users.

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 (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard.

4.9 Overdose

Midazolam overdose should not present a threat to life unless the patient has pre-existing respiratory or cardiac insufficiency, or when combined with other CNS depressants (including additional alcohol).

In the management of overdose with any medicinal product, it should be borne in mind that multiple agents may have been taken.

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.

Overdose of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. In mild cases, symptoms include drowsiness, mental confusion and lethargy, in more serious cases, symptoms may include ataxia, hypotonia, hypotension, respiratory depression, rarely coma and very rarely death.

Flumazenil may be useful as an antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hypnotics and sedatives (benzodiazepine derivatives), ATC code: N05CD08.

Midazolam is a derivative of the imidazobenzodiazepine group. The free base is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables midazolam to form salts with acids. These produce a stable solution suitable for oromucosal administration.

The pharmacological action of midazolam is characterized by short duration because of rapid metabolic transformation. Midazolam has an anticonvulsant effect. It also

exerts a sedative and sleep-inducing effect of pronounced intensity, and an anxiolytic and a muscle-relaxant effect.

In 5 rectal diazepam controlled studies and 2 studies versus intravenous diazepam in children involving a total of 478 children who received oromucosal midazolam, cessation of visible signs of seizures within 10 minutes was observed in 65% to 78% of patients receiving oromucosal midazolam. Additionally, in 3 of the studies, cessation of visible signs of seizures within 10 minutes without recurrence within 1 or 2 hours after administration was observed in 56% to 70% of patients. The frequency and severity of adverse drug reactions reported for oromucosal midazolam during published clinical trials were similar to the adverse drug reactions reported in the comparative group using rectal diazepam.

5.2 Pharmacokinetic properties

Simulated pharmacokinetic parameters for children 6 months to 18 years of age (including the recommended posology for children 10-18 years) are provided in tabulated format below:

Dose (mg)	Age (years)	Parameter	Mean	SD
2.5	0.5 – 1	AUC _{0-∞} (ng·h/mL)	351	147
		C _{max} (ng/mL)	125	40
5	1 - 4	AUC _{0-∞} (ng·h/mL)	362	120
		C _{max} (ng/mL)	140	45
7.5	5 – 9	AUC _{0-∞} (ng·h/mL)	317	96
		C _{max} (ng/mL)	103	36
10	10 – 18	AUC _{0-∞} (ng·h/mL)	233	79
		C _{max} (ng/mL)	63	25

AUC: area under the curve 0-infinity; C_{max}: maximum concentration; SD: standard deviation.

Absorption after oromucosal administration

Absorption of midazolam from the buccal mucosa is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. The absolute bioavailability is estimated to be about 74% in healthy adults. The bioavailability of oromucosal midazolam has been estimated at 87% in children with severe malaria and convulsions.

Distribution

Midazolam is highly lipophilic and distributes extensively. The steady state volume of distribution following oromucosal administration is estimated to be 5.3 L/kg.

Approximately 96 to 98% of midazolam is bound to plasma proteins. The major fraction of plasma protein binding is due to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

Metabolism

Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30 - 60%. Midazolam is hydroxylated by the CYP3A4 isozyme and is metabolized into an active metabolite, 1-hydroxymidazolam, and 2 minor metabolites: 4-hydroxy metabolite and

1,4-hydroxymetabolite. Based on a paediatric simulated population mean AUC ratio of the 1-hydroxymidazolam metabolite to midazolam, 40% of midazolam is converted into 1-hydroxymidazolam. In a bioavailability study of Epistatus, the conversion ratio in healthy adults was 22% with an estimated half-life of 2.7 hours. In published literature reports, 50-70% of midazolam is converted into the primary metabolite with an estimated half-life of 1-3 hours. These disparate values may be explained by the high inherent pharmacokinetic variability of midazolam.

Elimination

In children over 12 months, the half-life of parenteral midazolam was reported to be 0.8 to 1.8 hours, which was similar to or less than that in adults (range 1.7 to 2.6 hours). Plasma clearance in children over 12 months was 4.7 to 19.7 mL/min/kg which was similar to or higher than that in adults (range 6.4 to 11.0 mL/min/kg). The difference is consistent with an increased metabolic clearance in children. Midazolam is excreted mainly by the renal route (60 - 80% of the injected dose) and recovered as glucuroconjugated 1-hydroxymidazolam.

Less than 1% of the dose is recovered in urine as unchanged drug. The mean elimination half-life of 1-hydroxymidazolam was 5.6 hours in healthy adults.

Pharmacokinetics in special populations

Obese

The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

Patients with hepatic impairment

The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers (see section 4.4).

Patients with renal impairment

The elimination half-life in patients with chronic renal failure is similar to that in healthy volunteers.

Critically ill patients

The elimination half-life of midazolam is prolonged up to six times in the critically ill.

Patients with cardiac insufficiency

The elimination half-life is longer in patients with congestive heart failure compared with that in healthy subjects (see section 4.4).

Accumulation of midazolam after repeated doses

Repeated intravenous doses of midazolam for 4 to 6 days in mechanically ventilated patients in intensive care resulted in marked accumulation and prolonged sedation and respiratory depression (requiring prolonged ventilation). Midazolam terminal half-lives ranged from 8.9 to 19.4 hours (see section 4.2).

5.3 Preclinical safety data

In a rat fertility study, animals dosed up to ten times the clinical dose, no adverse effects on fertility were observed.

There are no other preclinical data of relevance to the prescriber which are additional to that already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol

Saccharin sodium

Glycerol

Purified water

Sodium hydroxide (for pH adjustment)

Liquid maltitol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

14 months.

6.4 Special precautions for storage

Do not store above 25°C.

Do not refrigerate or freeze.

Store in the original package to protect from light.

6.5 Nature and contents of container

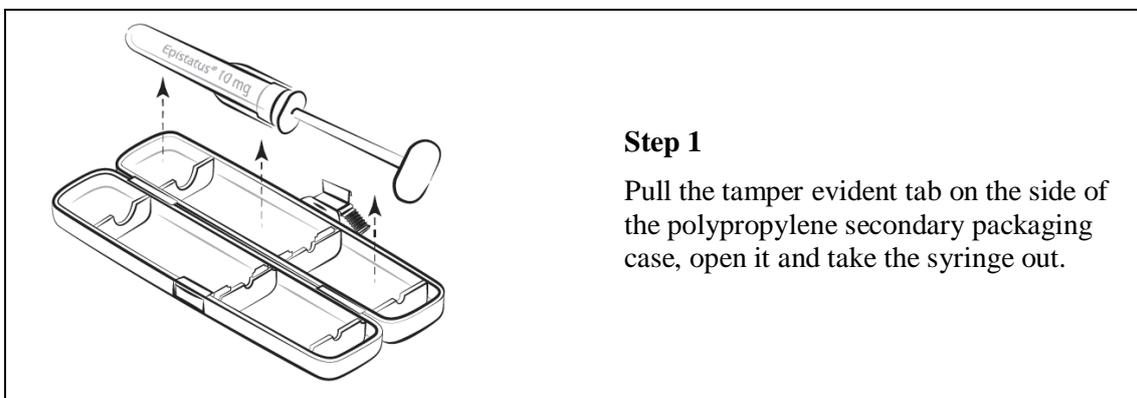
Epistatus is presented in a 1 mL oral syringe with a Cyclic Olefin Polymer (COP) siliconised barrel and COP amber sheath cap. The product is supplied as a single dose pack, in a polypropylene container, each containing one syringe with 1 mL of product.

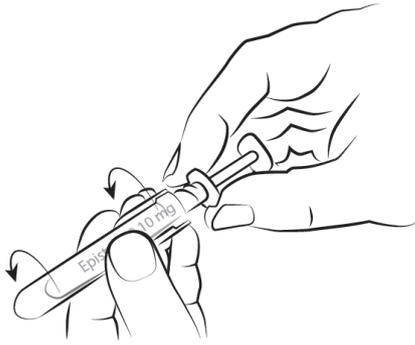
6.6 Special precautions for disposal

Do not use if the solution is not clear (e.g. cloudy or white particles are present).

Administration of Epistatus.

Epistatus is for oromucosal use. It is only to be used in the mouth.





Step 2

Holding the clear finger grips, unscrew the amber sheath cap in an anti-clockwise direction and remove the amber sheath cap.



Step 3

Dispose of the amber sheath cap safely.



Step 4

Using your finger and thumb, gently pinch and pull back the patient's cheek. Place the tip of the syringe into the back of the space between the inside cheek and the lower gum (buccal cavity).



Step 5

Slowly administer approximately half of the solution to the buccal cavity on one side of the mouth, and then administer the remainder slowly to the other side, by pressing the syringe plunger until it stops. If it is particularly difficult to get the syringe into one buccal cavity, then administer the whole dose over a duration of 4 – 5 seconds into the other buccal cavity.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 16786/0003

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

Date of first authorisation: 07 April 2017

10 DATE OF REVISION OF THE TEXT

11 September 2017