LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Epistatus
midazolam maleate

SE/H/1958/01/E/01

This module reflects the scientific discussion for the approval of Epistatus. The Public Assessment Report was written in June 2017 by the previous RMS UK after the initial procedure UK/H/6937/01/MR and is attached at the end of this document. RMS transfer from UK to SE was completed 2019-02-12. For information on changes after this date please refer to the module 'Update'.

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

Application/Legal Basis	Article 10(3) of Directive 2001/83/EC
Active substance	midazolam maleate
Pharmaceutical form	Oromucosal solution
Strength	10 mg
Applicant	Veriton Pharma Limited
EU-Procedure number (original)	UK/H/6937/01/MR

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Epistatus, 10 mg, oromucosal solution, could be approved.

LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

Postadress/Postal address: P.O. Box 26, SE-751 03 Uppsala, SWEDEN
Besöksadress/Visiting address: Dag Hammarskjölds väg 42, Uppsala
Telefon/Phone: +46 (0)18 17 46 00 Fax: +46 (0)18 54 85 66
Internet: www.lakemedelsverket.se E-mail: registrator@lakemedelsverket.se

Medicines & Healthcare products Regulatory Agency

MHRA
Regulating Medicines and Medical Devices

Public Assessment Report

Epistatus 10mg Oromucosal Solution (Midazolam (as maleate))

UK Licence No: PL 16786/0003

Special Products Limited

LAY SUMMARY

Epistatus 10mg Oromucosal Solution (Midazolam (as maleate))

This is a summary of the Public Assessment Report (PAR) for Epistatus 10mg Oromucosal Solution. It explains how the marketing authorisation application for Epistatus 10mg Oromucosal Solution was assessed and the authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Epistatus 10mg Oromucosal Solution.

This medicinal product will be referred to as Epistatus Oromucosal Solution in the remainder of the lay summary for ease of reading.

For practical information about using Epistatus Oromucosal Solution, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Epistatus Oromucosal Solution and what is it for?

Epistatus Oromucosal Solution is a 'Prescription Only Medicine' (legal status 'POM') containing the active ingredient midazolam (as maleate) in pre-filled syringes.

Epistatus Oromucosal Solution is used to stop a prolonged, acute (sudden) convulsive seizure ('fit') in children and adolescents aged 10 to less than 18 years.

This medicine must only be given by parents/caregivers where the patient has been diagnosed with epilepsy.

How does Epistatus Oromucosal Solution work?

Epistatus Oromucosal Solution contains the active ingredient midazolam (as maleate), a benzodiazepine, which acts as an anticonvulsant medicine.

How is Epistatus Oromucosal Solution used?

Epistatus Oromucosal Solution is for oromucosal use only. It is only to be used in the mouth. The solution is given in the side of the mouth, into the space between the gum and the cheek.

Always give this medicine exactly as a doctor has told you. Check with a doctor or pharmacist if you are not sure.

Please read Section 3 of the PIL for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How has Epistatus Oromucosal Solution been studied?

Special Products Limited has provided data from clinical studies to show that Epistatus Oromucosal Solution is bioequivalent to the reference medicine, Hypnovel 10 mg/2 mL solution for injection (PL 00031/0126), when administered by the oromucosal route. Two medicines are bioequivalent when they produce the same levels of the active substance in the body.

What are the benefits and risks of Epistatus Oromucosal Solution?

Reports from the published literature confirmed that oromucosal use of midazolam is effective in stopping seizures in children and adolescents. Epistatus Oromucosal Solution has been shown to be bioequivalent to the reference product which has been used in the studies underlying the published literature. The safety profile of the active substance is also well-known. The benefits are, therefore, considered to outweigh the risks.

Why is Epistatus Oromucosal Solution approved?

Based on the bibliographical information on the well-established use of midazolam solutions administered via buccal mucosa for stopping seizures and safety and efficacy information provided by Special Products Limited, it was considered that the benefit/risk balance for Epistatus Oromucosal Solution is positive and the grant of Marketing Authorisation was recommended.

What measures are being taken to ensure the safe and effective use of Epistatus Oromucosal Solution?

A Risk Management Plan (RMP) has been developed to ensure Epistatus Oromucosal Solution is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics (SmPC) and the PIL for Epistatus Oromucosal Solution, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side-effects are continuously monitored. Furthermore, new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously, as well.

Other information about Epistatus Oromucosal Solution.

A Marketing Authorisation was granted in the UK on 07 April 2017 to Special Products Limited (PL 16786/0003).

The full PAR for Epistatus Oromucosal Solution follows this summary.

For more information about treatment with Epistatus Oromucosal Solution, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in June 2017.

TABLE OF CONTENTS

I INTRODUCTION

The MHRA granted Special Products Limited a Marketing Authorisation (licence) for the medicinal product Epistatus 10mg Oromucosal Solution (PL 16786/0003) on 07 April 2017.

Epistatus Oromucosal Solution is a 'Prescription Only Medicine' (legal status 'POM'), 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.

The application was submitted as hybrid application under Article 10(3) of Directive 2001/83/EC, as amended, with proposed changes to the therapeutic indications, pharmaceutical form, strength and route of administration compared to the reference product. The reference product for this application was Hypnovel 10 mg/2 mL solution for injection (PL 00031/0126), first licensed to Roche Products Limited on 08 December 1982.

Midazolam is a short-acting drug in the benzodiazepine class that is used for treatment of acute seizures, moderate to severe insomnia, and for inducing sedation and amnesia before medical procedures.

The non-clinical data submitted are adequate for this hybrid application.

In support of the application, two bioequivalence studies and one *in silico* simulation study have been conducted. Assurance has been provided that the bioequivalence studies have been conducted according to the principles of Good Clinical Practice (GCP).

An Environmental Risk Assessment (ERA) has been performed to evaluate the potential environmental risk in the UK for Epistatus 10mg Oromucosal Solution and it was concluded that Epistatus Oromucosal Solution does not pose a risk to the environment.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture and assembly of this product.

During the initial assessment of the application, one major and 29 additional points for consideration concerning quality, non-clinical and clinical aspects were raised. The application was referred to the Commission on Human Medicines (CHM) who met on 10 November 2016 to consider the application. In response to the CHM consultation, the applicant provided adequate data to resolve all outstanding issues.

II QUALITY ASPECTS

II.1 Introduction

The product "Epistatus 10 mg Oromucosal Solution" is presented for oromucosal use as a 10 mg/mL solution of midazolam (13.60 mg/mL midazolam maleate) in a pre-filled 1 mL oral syringe.

The other pharmaceutical excipients present are ethanol, saccharin sodium, glycerol, purified water, sodium hydroxide (for pH adjustment), and liquid maltitol.

All excipients used comply with their respective European Pharmacopoeia monograph. Satisfactory Certificates of Analysis have been provided for all excipients. The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in, or used in the manufacturing process for the proposed product. Furthermore, no genetically modified organisms are used in the manufacture of the finished product.

Epistatus 10mg Oromucosal Solution is licensed for marketing in a pre-filled 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.

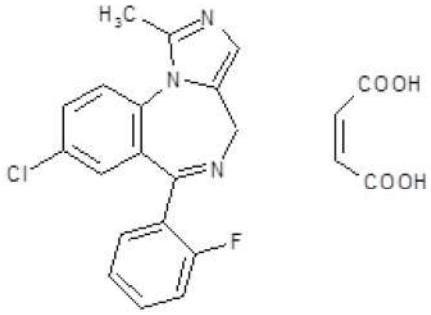
Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory.

II.2 Drug Substance

INN: Midazolam maleate

Chemical name: 8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine maleate

Structure:



Molecular formula: $C_{18}H_{13}ClFN_3 \cdot C_4H_4O_4$

Molecular weight: 441.8

Appearance: Midazolam maleate is a white or yellowish crystalline powder

Solubility: Freely soluble in Methanol and in 0.1M HCl

Midazolam maleate is the subject of an Active Substance Master File (ASMF).

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active pharmaceutical ingredient. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3 Medicinal Product

Pharmaceutical Development

The aim of the pharmaceutical development programme was to produce a convenient, easy to administer, buccal treatment that could be used instead of the reference product Hypnovel 10 mg/2 mL solution for injection (PL 00031/0126), for the control of prolonged seizures.

A satisfactory account of the pharmaceutical development has been provided.

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

The manufacturing process has been validated using production-scale batches and has shown satisfactory results.

Finished Product Specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification.

Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current ICH guidelines. Based on the results, a shelf-life of 12 months with the storage conditions "Do not store above 25°C. Do not refrigerate or freeze. Store in the original package to protect from light." has been accepted.

Quality Overall Summary (Expert report)

The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to approval of Epistatus 10mg Oromucosal Solution, from a pharmaceutical point of view.

III NON-CLINICAL ASPECTS

III.1 Introduction

The application for Epistatus 10mg Oromucosal Solution, containing the known active substance midazolam (as maleate), was made under Article 10(3) of Directive 2001/83/EC, as amended.

The reference product is marketed in the UK as Hypnovel 10 mg/2mL solution for injection, and was first licensed on the 8 December 1982 to Roche Products Ltd (PL 00031/0126).

Midazolam is a short-acting benzodiazepine sedative-hypnotic licensed for parenteral administration in adult and paediatric patients for conscious sedation before and during diagnostic or therapeutic procedures and for other sedative/anaesthetic indications. Products containing midazolam have been on the EU market for at least 25 years for the indications stated above. Additionally, midazolam had a well-known "off-label" use for the emergency treatment of prolonged seizures (status epilepticus) via buccal cavity administration. Such off-licence use has become well-established in real-life clinical settings and literature before the regulatory approval of any oromucosal solution for this indication

The pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well-known and the non-clinical data provided are acceptable.

III.2 Pharmacology
Not applicable for this product type. Refer to section 'Introduction' detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section 'Introduction' detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section 'Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
An environmental risk assessment has been performed to evaluate the potential environmental risk in the UK for Epistatus 10mg Oromucosal Solution, based on the testing performed it was concluded that this product does not pose a risk to the environment.

III.6 Discussion on the non-clinical aspects
The non-clinical data are considered acceptable given that the application is based on being a hybrid medicinal product of a reference product that has been licensed for over 10 years.

The non-clinical overview was written by a suitably qualified person and is satisfactory.

The SmPC is acceptable.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of midazolam after IV, IM, PO and after intranasal and buccal administration of the intravenous solution is well-known. With the exception of data from two clinical studies and an *in silico* study detailed below, no new pharmacodynamic or pharmacokinetic data are provided, or are required for this application.

The applicant has conducted two clinical studies and one simulation of dosing regimens in order to support this application:

• A pharmacokinetic study (SPL-001) to assess the bioavailability of Epistatus 10mg Oromucosal Solution compared to Hypnovel 10 mg/2 mL solution for injection, administered by the oromucosal route, in healthy adults.
• A pharmacokinetic study (SPL-002) to assess the bioequivalence of Epistatus 10mg Oromucosal Solution and Hypnovel 10 mg/2 mL solution for injection administered by the oromucosal route in healthy adults.
• An *in silico* study to simulate the pharmacokinetics of Epistatus 10mg Oromucosal Solution administered by the oromucosal route in children.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of midazolam in the proposed indication.

Based on the data provided, Epistatus 10mg Oromucosal Solution can be considered bioequivalent to the reference medicine Hypnovel 10 mg/2 mL solution for injection (Roche Products Ltd).

IV.2 Pharmacokinetics

In support of the application two bioequivalence studies (SPL-001 and SPL-002) and one *in silico* simulation were submitted.

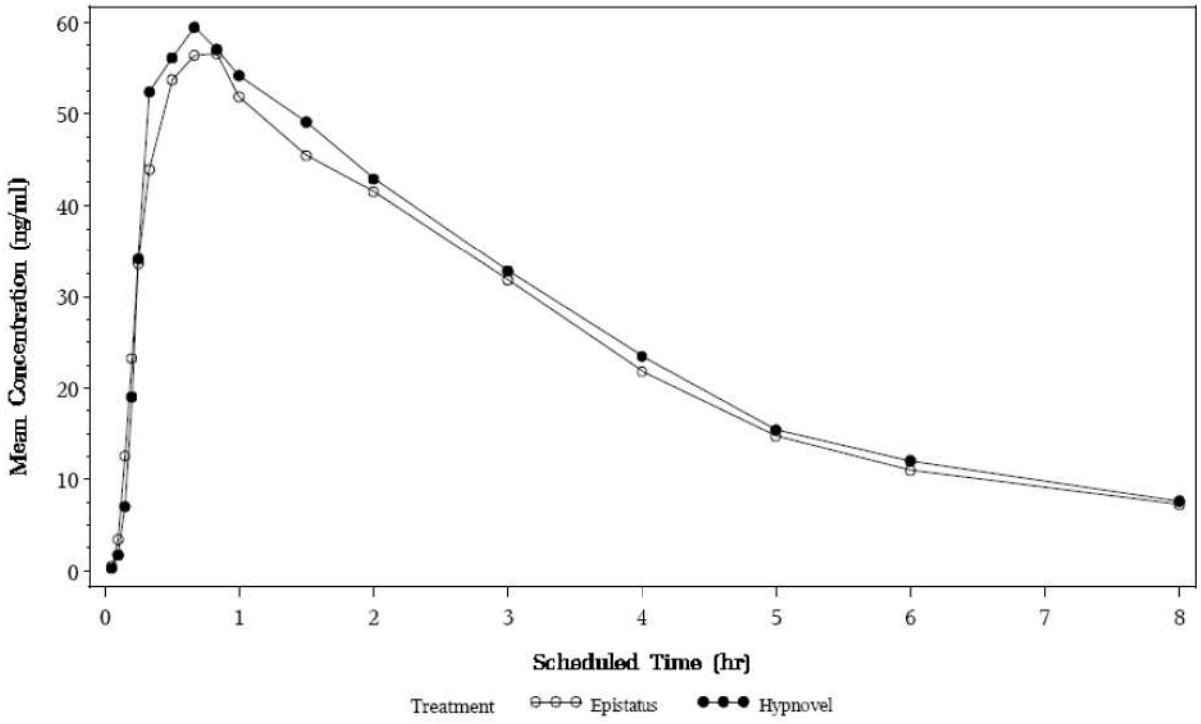
SPL-001: A pharmacokinetic study to assess the bioavailability of Epistatus 10mg Oromucosal Solution compared to Hypnovel 10 mg/2 mL solution for injection in healthy adults.

This was a Phase I, single-dose, randomised, open-label, two-period, two-treatment, healthy volunteer, crossover study comparing the pharmacokinetic (PK) profiles of midazolam and its primary metabolite after administration of either Epistatus 10mg Oromucosal Solution or Hypnovel 10 mg/2 mL solution for injection as a single oral dose administered by the oromucosal route, in healthy adults.

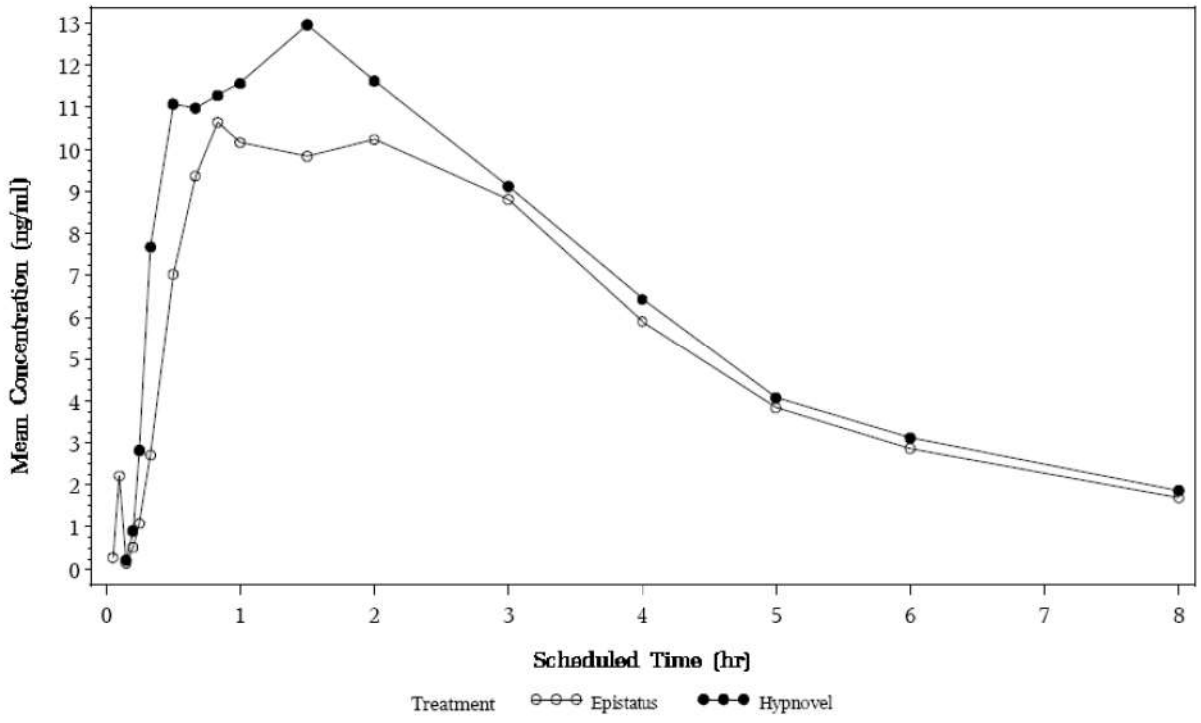
Single doses of Epistatus and Hypnovel were safe and well tolerated by all subjects in this study. There were no differences in the safety or tolerability of the two formulations.

The PK profiles for midazolam and 1-hydroxymidazolam for the two formulations were very similar (see the figures and summary tables below).

Mean Pharmacokinetic Plasma Concentration vs. Time of Midazolam from Epistatus® and Hypnovel®



Mean Pharmacokinetic Plasma Concentration vs. Time of 1-hydroxymidazolam from Epistatus® and Hypnovel®



Summary of Pharmacokinetic Parameters for midazolam

PK PARAMETER	Epistatus® (Mean±SD)	Hypnovel® (Mean±SD)
C_{max} (ng/mL)	63.9 ± 19.0	73.3 ± 27.5
AUC_{0-t} (ng·hr/mL)	201.1 ± 52.8	211.4 ± 57.5
$AUC_{0-\infty}$ (ng·hr/mL)	233.2 ± 64.8	242.2 ± 69.7
t_{max} (hr)	0.8 ± 0.4	0.9 ± 0.6
$t_{½}$ (hr)	2.7 ± 0.7	2.6 ± 0.8
Relative Bioavailability (F) Epistatus: Hypnovel (%)	96.7	

Summary of Pharmacokinetic Parameters for 1-hydroxymidazolam

PK PARAMETER	Epistatus® (Mean±SD)	Hypnovel® (Mean±SD)
C_{max} (ng/mL)	14.4 ± 5.4	19.2 ± 10.9
AUC_{0-t} (ng·hr/mL)	45.6 ± 12.8	52.0 ± 18.4
$AUC_{0-\infty}$ (ng·hr/mL)	51.4 ± 13.6	59.0 ± 20.2
tmax (hr)	1.6 ± 0.8	1.3 ± 0.9
$t_{½}$ (hr)	2.5 ± 0.8	2.7 ± 1.2
Relative Bioavailability (F) Epistatus: Hypnovel (%)	90.6	

The t_{max} of midazolam was approximately 40 minutes for both drugs. The distribution and elimination phases were also very similar. The midazolam mean $t_{½}$ values were 2.72 hours and 2.61 hours for Epistatus and Hypnovel, respectively. The PK analysis showed that midazolam C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ values were modestly higher with Hypnovel in comparison to Epistatus (mean relative bioavailability Epistatus: Hypnovel was 96.67%). For 1-hydroxymidazolam, C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were also modestly higher with Hypnovel in comparison to Epistatus (mean relative bioavailability Epistatus: Hypnovel was 90.60%). The median t_{max} was shorter for Hypnovel (1.3 hours as opposed to 1.6 hours for Epistatus). The $t_{½}$ values of 1-hydroxymidazolam were similar for the two drug products.

Bioequivalence analysis results are shown in the tables below.

Bioequivalence Results for C_{max} and AUC_{0-t} of midazolam

Parameter	Comparison	Ratio	90% confidence interval		Conclusion
			Lower	Upper	
C_{max}	A:B	0.89	0.75	1.04	**
AUC_{0-t}	A:B	0.95	0.83	1.09	*

A= Epistatus (midazolam) oromucosal solution, B= Hypnovel (midazolam) solution for injection
*Relative bioavailability confidence interval within CI equivalence limits
**Relative bioavailability confidence interval not within CI equivalence limits

Bioequivalence Results for C_{max} and AUC_{0-t} of 1-hydroxymidazolam

Parameter	Comparison	Ratio	90% confidence interval		Conclusion
			Lower	Upper	
C_{max}	A:B	0.81	0.64	1.03	**
AUC_{0-t}	A:B	0.89	0.77	1.04	**

A= Epistatus (midazolam) oromucosal solution, B= Hypnovel (midazolam) solution for injection
*Relative bioavailability confidence interval within CI equivalence limits
**Relative bioavailability confidence interval not within CI equivalence limits

The 90% confidence interval (CI) of the geometric mean ratio (Epistatus vs. Hypnovel) for the midazolam C_{max} was outside the bioequivalence range of 0.80-1.25. The 90% CI of the geometric mean ratio for the midazolam AUC0-t was within the bioequivalence range of 0.80-1.25. For 1-hydroxymidazolam, the 90% CIs for both the C_{max} and AUC_{0-t} ratios were outside the bioequivalence range of 0.80-1.25. In general, the 90% CIs were wide and in some cases crossed unity, making it impossible to determine if the two formulations were bioequivalent or not. This was likely a result of the inherent high variability of midazolam.

Overall, the mean midazolam and 1-hydroxymidazolam values for C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ were modestly higher for Hypnovel compared to Epistatus. The PK profiles for Epistatus and Hypnovel were quite similar and the observed differences were not deemed to be of clinical significance in terms of safety or efficacy. In the bioequivalence analysis, the results did not satisfy the conventionally accepted criteria for bioequivalence. However, the wide 90% CIs indicated that the study was not of sufficient power or appropriate design to assess bioequivalence with this highly variable drug.

SPL-002: A pharmacokinetic study to assess the bioequivalence of Epistatus 10mg Oromucosal Solution and Hypnovel 10 mg/2 mL solution for injection administered by the oromucosal route in healthy adults.

This was a single-dose, randomised, open-label, four-period, replicate, two-sequence crossover study to compare the pharmacokinetic profiles and assess bioequivalence of Epistatus (midazolam oromucosal solution 10 mg/mL) and Hypnovel (midazolam parenteral solution 5 mg/mL) administered via the oromucosal route in healthy adult subjects.

Fifty four (54) healthy subjects (45 male and 9 female) entered the study and were analysed for safety with 51 (42 male and 9 female) completing the study. Eligible subjects were randomised equally to one of two dosing (sequence) groups, designated as Group A and Group B, and were admitted to the unit for dosing in four identical study periods as follows:

Period 1: Group A (27) subjects received Epistatus and Group B (27) subjects received Hypnovel.

Period 2: Group A (27) subjects received Hypnovel and Group B (27) subjects received Epistatus.

Period 3: Group A (27) subjects received Epistatus and Group B (27) subjects received Hypnovel.

Period 4: Group A (27) subjects received Hypnovel and Group B (27) subjects received Epistatus.

In each of the four study periods, subjects received a single 10 mg dose of one of the two investigational medicinal products (IMPs) via the oromucosal route as follows:
• IMP1 was 1 mL (10 mg) of Epistatus (midazolam) oromucosal solution, 10 mg/mL (Dales (Dechra) Pharmaceuticals).
• IMP2 was 2 mL (10 mg) of Hypnovel (midazolam) solution for injection, 10 mg/2 mL (Roche Products Ltd.).

Single doses of Epistatus and Hypnovel were safe and well tolerated by all subjects in this study. There were no differences in the safety or tolerability of the two formulations.

The results of the PK analysis for midazolam indicated that the PK parameters were very similar between the Epistatus and Hypnovel formulations. Inter-subject variability was 26.8% for Epistatus and 25.5% for Hypnovel. There were secondary peaks for many subjects following either treatment, likely a result of midazolam that was swallowed and absorbed further down in the gastrointestinal tract.

Midazolam non-compartmental PK parameter estimates for the individual subjects who received Epistatus and/or Hypnovel are summarised in the table below.

Mean (% cumulative variance) Plasma Non-compartmental Midazolam Pharmacokinetic Parameters by Formulation

Formulation	Occasion	Cmax (ng/mL)	Tmax[a] (h)	AUClast (h•ng/mL)	Half-Life (h)	AUCinf (h•ng/mL)
Epistatus®	1	58.1 (30.2)	0.67 (0.33 – 4.00)	226.7 (25.1)	5.65 (30.8)	234.6 (26.4)
	2	62.5 (36.0)	0.67 (0.25 – 4.00)	246.2 (27.9)	5.60 (31.3)	255.2 (29.2)
	Overall	60.2 (33.4)	0.67 (0.25 – 4.00)	236.2 (26.8)	5.62 (30.9)	244.6 (28.1)
Hypnovel®	1	65.8 (30.8)	0.67 (0.25 – 4.00)	248.8 (24.2)	5.75 (37.7)	258.1 (25.9)
	2	63.6 (30.3)	0.67 (0.25 – 4.00)	244.0 (27.0)	5.42 (25.2)	252.2 (28.6)
	Overall	64.7 (30.5)	0.67 (0.25 – 4.00)	246.4 (25.5)	5.59 (32.5)	255.2 (27.1)

Source: Table 4-1 in Special Products Ltd SPL-002 Bioequivalence Study PK Report Final 11Aug2013.

[a] Median and Range.

The median T_{max} of midazolam was approximately 40 minutes for both Epistatus and Hypnovel and the ranges were nearly identical, suggesting the rate of absorption was similar for both formulations. However, midazolam from Hypnovel reached a higher mean C_{max} (64.7 ng/mL) in comparison to Epistatus (60.2 ng/mL). The distribution and elimination phases were also very similar. The midazolam mean $t_{½}$ values were 5.62 hours and 5.59 hours for Epistatus and Hypnovel, respectively. The PK analysis showed that midazolam C_{max}, AUC_{last} and AUC_{inf} values were modestly higher with Hypnovel in comparison to Epistatus.

For most subjects there was a 10 to 15 minute lag time in the appearance of 1-hydroxymidazolam in the plasma. The 1-hydroxymidazolam non-compartmental PK parameter estimates for the individual subjects who received Epistatus and/or Hypnovel are summarised in the table below.

Mean (% cumulative variance) Plasma Non-compartmental 1-hydroxymidazolam Pharmacokinetic Parameters by Formulation

Formulation	Occasion	Cmax (ng/mL)	Tmax[a] (h)	Half-Life (h)	AUCinf (h•ng/mL)
Epistatus®	1	13.8 (55.3)	2.00 (0.33 – 4.00)	5.71 (34.6)	53.3 (33.0)
	2	13.6 (52.1)	2.00 (0.50 – 4.00)	5.57 (31.5)	55.0 (31.1)
	Overall	13.7 (53.5)	2.00 (0.33 – 4.00)	5.64 (33.0)	54.1 (32.6)
Hypnovel®	1	15.1 (50.5)	1.50 (0.50 – 4.00)	5.60 (26.5)	56.8 (33.1)
	2	13.6 (49.7)	1.00 (0.25 – 4.00)	5.36 (27.3)	53.7 (33.4)
	Overall	14.4 (50.2)	1.50 (0.25 – 4.00)	5.48 (26.8)	55.2 (33.2)

Source: Table 4-2 in Special Products Ltd SPL-002 Bioequivalence Study PK Report Final 11Aug2013.

a Median and Range.

For 1-hydroxymidazolam, C_{max}, AUC_{last} and AUC_{inf} were also modestly higher with Hypnovel in comparison to Epistatus. The $t_{½}$ values of 1-hydroxymidazolam were similar for the two formulations. The metabolites to parent ratios were nearly identical averaging 0.22 for Epistatus and 0.21 for Hypnovel.

Results of the bioequivalence assessment for Epistatus and Hypnovel are shown in the table below.

Two One-sided Test Results for Bioequivalence Assessments

PK Parameter	Standard BE Test[1]							HVD BE Test[2]		
	Geometric Least Squares Means					90% Confidence Limits of Ratio		Within-subject Variability of Reference (Swr)	Geometric Mean Ratio % (A:B)	95% Upper Confidence Limit of the Adjusted Estimate
	Epistatus®		Hypnovel®		Ratio % (A:B)	Lower	Upper			
	A1	A2	B1	B2						
AUCinf (hr*ng/mL)	226.51	245.01	250.33	243.16	95.1	92.2	98.1	0.14	95.1	-0.008
AUClast (hr*ng/mL)	219.55	237.12	242.04	235.95	95.1	92.2	98.1	0.14	95.1	-0.007
Cmax (ng/mL)	55.67	59.03	62.85	60.82	92.2	87.6	97.2	0.23	91.7	-0.018
Tmax[3] (h)	0.67	0.67	0.67	0.67	0	-0.083	0.083	NA	NA	NA

Source: Table 6-7 in Special Products Ltd SPL-002 Bioequivalence Study PK Report Final 11Aug2013.

1. Standard BE Test required 90% confidence limits of the ratios to be between 80% - 125%. This test was applicable if Swr <0.294.

2. Highly variable drugs (HVD) BE Test was only applicable if Swr ≥ 0.294. The Test product (A) was determined to be bioequivalent to B if BOTH conditions were met: Geometric Mean Ratio (A:B) was between 80% - 125%; 95% Upper Confidence limit of the adjusted estimate was <=0.

3. Tmax was analyzed as differences in treatment medians, as opposed to the ratio. Hauschke's method was used to calculate the 90% confidence limits of the difference. HVD test were not applicable (NA) to Tmax

These results showed that the relative bioavailability of Epistatus to Hypnovel was high at 95.1% for midazolam AUC_{inf} and 92.2% for C_{max}. The bioequivalence assessment indicated that the Epistatus formulation was bioequivalent to Hypnovel with respect to C_{max}, AUC_{last} and AUC_{inf}. The standard bioequivalence test was applicable since the within subject variability for the reference formulation was less than 0.294 for each parameter. The results indicated that Epistatus was bioequivalent to Hypnovel for C_{max} with a geometric least squares mean (GLSM) ratio of 92.2% and a 90% confidence interval of 87.6 to 97.2%, which was well within the required 0.80 to 1.25 interval limit. The results also indicated that Epistatus was bioequivalent to Hypnovel for AUC_{last} and AUC_{inf} with identical GLSM ratios of 95.1% and identical 90% CIs of 92.2 to 98.1%.

T_{max} was analysed using a non-parametric approach by calculating the differences in treatment medians and by constructing a 90% confidence interval for the difference. The treatment medians for T_{max} for all occasions were 0.67 hours and thus the difference in the medians was 0.0 and the 90% confidence interval for the difference included zero, ranging from -0.083 to 0.083. Therefore, the results indicate there was no difference in the T_{max} values for the two formulations.

The results of the pharmacokinetic analysis for midazolam indicated that the pharmacokinetic parameters were very similar between the Epistatus and Hypnovel formulations. Similarly, pharmacokinetic parameters for 1-hydroxymidazolam were consistent between the two formulations.

The results of the bioequivalence assessment indicated that the Epistatus formulation was bioequivalent to Hypnovel with respect to C_{max}, AUC_{last} and AUC_{inf}, as the GLSM ratio 90% confidence intervals were well within the required 0.80 to 1.25 limit for all three parameters.

T_{max} results indicated there was no difference in the T_{max} values for the two formulations.

Exposure predictions for oromucosal administration of midazolam to paediatric populations

The goal of this *in silico* study was to evaluate midazolam and 1-hydroxymidazolam (primary metabolite) exposures after buccal administration of midazolam (Epistatus) in children. This was accomplished by developing a physiologically-based pharmacokinetic (PBPK) model for midazolam and 1-hydroxymidazolam in adults and children after buccal administration. The paediatric PBPK model was used to simulate midazolam and 1-hydroxymidazolam exposures in children receiving fixed and weight normalised buccal midazolam dosing.

Midazolam PBPK model simulations in children after buccal administration:
Virtual children (N=2500 per age group) were generated using demographic distributions (e.g., weight, age, height) in publicly available databases. Using PBPK model parameters, midazolam and 1-hydroxymidazolam plasma concentration vs. time profiles were generated for each individual and exposures of parent and metabolite were calculated.

The present *in silico* study shows that consistent midazolam and 1-hydroxymidazolam exposures across age groups are achieved using fixed doses of Epistatus in children. Simulated drug exposures are comparable to midazolam exposures achieved in adults after

intramuscular administration with doses proved efficacious against status epilepticus in clinical trials.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted. The information on the pharmacodynamics of the product is derived from the published sources.

IV.4 Clinical efficacy

No new efficacy data were submitted and data supporting the efficacy of Epistatus 10mg Oromucosal Solution is derived solely from bibliographic sources of midazolam.

IV.5 Clinical safety

The bibliographical safety data submitted confirms that the safety profile of midazolam is well-known and supports the conclusion that buccal midazolam is systemically and locally well-tolerated and safe in children and adolescents 10 to <18 years using the proposed 10 mg single-use pre-filled oral syringe.

IV.6 Risk Management Plan (RMP) and Pharmacovigilance system

The Pharmacovigilance System, as described by the applicant, is sufficient to identify and characterise the risks of the product. Routine pharmacovigilance remains sufficient to monitor the effectiveness of the risk minimisation measures.

A Risk Management Plan has been developed to ensure that Epistatus 10mg Oromucosal Solution is used as safely as possible when used for the proposed indication.

A summary of the risk minimisation activities is presented below:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Respiratory depression	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.3 Contraindications SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	None
CNS depression	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable effects	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	
Interactions with other CNS drugs	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.5 Interaction with other medicinal products and other forms of interaction PIL 2. What you need to know before you use Epistatus	None
Apnoea	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable effects PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	None
Respiratory or cardiac arrest	Ensure awareness. Appropriate statements and warnings are included in the product information.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC 4.8 Undesirable effects PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	
Anterograde amnesia	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	None
Paradoxical reactions	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable effects PIL 4. Possible side effects	None
Nausea/vomiting	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	effects PIL 4. Possible side effects	
Pruritis	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable effects PIL 4. Possible side effects	None
Important potential risks		
Physical dependence	Ensure awareness through identification of "at risk" patients. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus	None
Off label use	Provide clear prescribing information. Appropriate statements and warnings are included in the product information. SmPC 4.1 Therapeutic indications PIL 1. What Epistatus is and	Educational material will include a statement that it is not for use in children less than 10 years of age or in adults.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	what it is used for PIL 3. How to give Epistatus	
Buccal irritation	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.8 Undesirable effects PIL 4. Possible side effects	None
Asphyxiation/aspiration	Provide clear information on method of administration. Appropriate statements and warnings are included in the product information. SmPC 4.2 Posology and method of administration PIL 3. How to give Epistatus	None
Oral/facial trauma	Provide clear information on method of administration including illustrations in the PIL. Appropriate statements and warnings are included in the product information. SmPC 4.2 Posology and method of administration PIL 3. How to give Epistatus	Educational material This provides instructions on how to administer Epistatus.

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Abuse potential/diversion	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and precautions for use SmPC 4.2 Posology and method of administration PIL 2. What you need to know before you use Epistatus PIL 3. How to give Epistatus	None
Drug-facilitated sexual abuse	Ensure awareness Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus PIL 4. Possible side effects	None
Important missing information		
Patients with impaired renal function	Ensure awareness. Appropriate statements and warnings are included in the product information.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus	
Patients with impaired liver function	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.4 Special warnings and precautions for use PIL 2. What you need to know before you use Epistatus	None
Pregnant or lactating women	Ensure awareness. Appropriate statements and warnings are included in the product information. SmPC 4.6 Fertility, pregnancy and lactation PIL 2. What you need to know before you use Epistatus	None

IV.7 Discussion on the clinical aspects

A clinical expert report has been written by a suitably qualified person and is satisfactory.

There are no objections to approval of Epistatus 10mg Oromucosal Solution from a clinical point of view.

V USER CONSULTATION

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ('user testing'), in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The important quality characteristics of Epistatus 10mg Oromucosal Solution are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit-risk balance.

NON-CLINICAL

No non-clinical concerns have been raised in respect to excipients. There were no non-clinical concerns relating to the drug substance or drug product impurity profile, including the residual solvents and degradation products.

CLINICAL

Clinical pharmacology, safety and efficacy of the product are well-described and supported by the quoted references.

The applicant has conducted two bioequivalence studies to compare the pharmacokinetics of their product against the reference product Hypnovel. In one of the studies the confidence intervals for the C_{max} and AUC_{0-t} ratios of the two products were wide and the lower ends fell outside the acceptable 80% limits. The argument that the number of patients was insufficient to conclusively establish bioequivalence was accepted. In the repeated study, a larger number of subjects were included. In this study, the confidence intervals of C_{max} and AUC ratios were safely within the standard bioequivalence acceptance criteria, based on which the claim of bioequivalence with the reference product has been accepted.

The applicant also conducted additional *in silico* simulations to extrapolate the results from adults to the younger population.

Overall, a sound scientific link has been established between the proposed product and the recognised literary references quoted in the clinical parts of the dossier, and the claims of clinical safety and efficacy can be accepted.

SAFETY

Refer to section 'Clinical 'detailed above.

The SmPC, PIL and labelling are satisfactory, and contain suitable reference to the treatment of prolonged, acute, convulsive seizures in children and adolescents aged 10 to less than 18 years.

BENEFIT-RISK ASSESSMENT

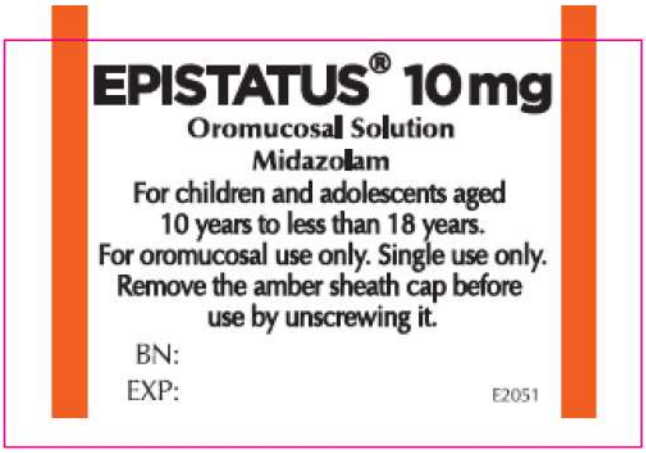
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. The clinical data provided show comparable efficacy with the reference product. Extensive clinical experience with midazolam is considered to have demonstrated the therapeutic value of the active substance. The benefit/risk ratio is considered to be positive.

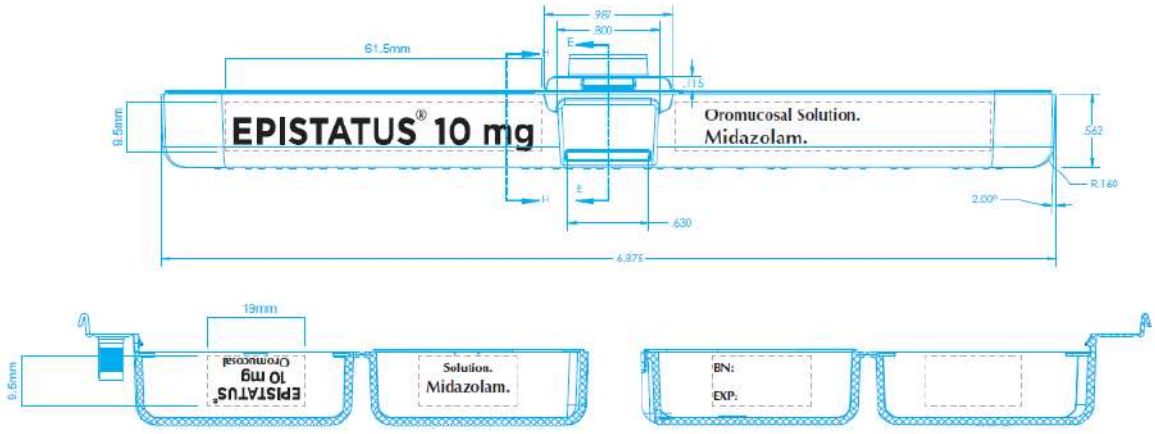
The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, in-line with current guidelines and consistent with the reference products.

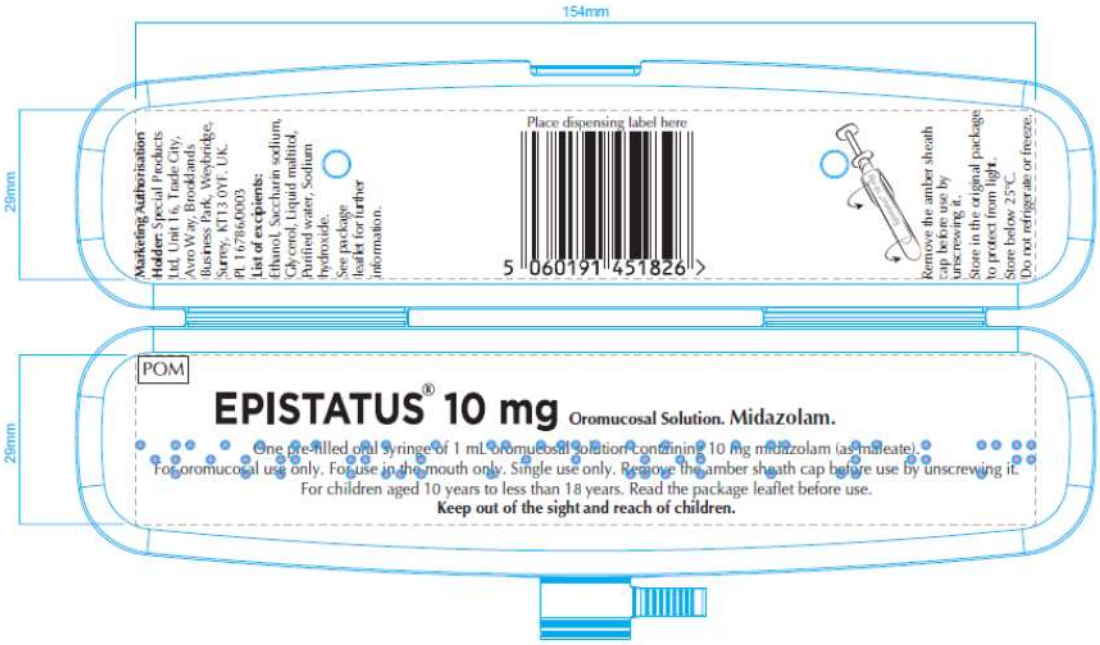
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

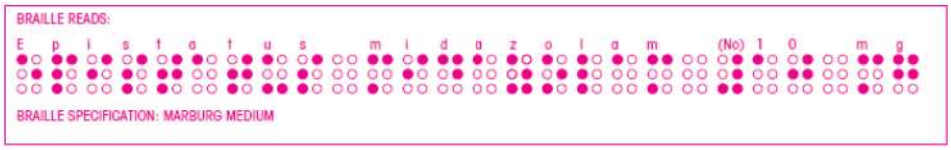
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

The approved labelling for Epistatus 10mg Oromucosal Solution is presented below:






154mm
29mm
29mm
Marketing Authorisation Holder: Special Products Ltd, Unit 16, Trade City, Avro Way, Brooklands Business Park, Weybridge, Surrey, KT13 0YF, UK.
PL 16786/0003
List of excipients: Ethanol, Saccharin sodium, Glycerol, Liquid maltitol, Purified water, Sodium hydroxide.
See package leaflet for further information.
Place dispensing label here
5 060191 451826
Remove the amber sheath cap before use by unscrewing it.
Store in the original package to protect from light.
Store below 25°C.
Do not refrigerate or freeze.
POM
EPISTATUS® 10 mg Oromucosal Solution. Midazolam.
One pre-filled oral syringe of 1 mL oromucosal solution containing 10 mg midazolam (as maleate).
For oromucosal use only. For use in the mouth only. Single use only. Remove the amber sheath cap before use by unscrewing it.
For children aged 10 years to less than 18 years. Read the package leaflet before use.
Keep out of the sight and reach of children.


BRAILLE READS:
E p i s t a t u s m i d a z o l a m (No) 1 0 m g
BRAILLE SPECIFICATION: MARBURG MEDIUM

Epistatus 10mg Oromucosal Solution
(Midazolam (as maleate))
PL 16786/0003

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome