Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe

(midazolam)

PL 00142/1263

Accord-UK Ltd

LAY SUMMARY

Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe (midazolam)

This is a summary of the Public Assessment Report (PAR) for Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Midazolam injection in this lay summary for ease of reading.

For practical information about using Midazolam injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Midazolam injection and what is it used for?

This application is for a hybrid medicine. This means that the medicine is similar to a reference medicine already authorised in the European Union (EU) called Hypnovel 10 mg/2 mL solution for injection albeit with certain differences. In this case, Midazolam injection is for a change in strength and pharmaceutical form.

Midazolam injection is used for:

- Conscious sedation (an awake but very relaxed state of calm or drowsiness during a medical test or procedure) in adults and children.
- Sedation of adults and children, in intensive care units.
- Anaesthesia in adults, used alone or with other medicines.
- Premedication (medicine used to cause relaxation, calm and drowsiness before an anaesthetic) in adults and children.

How does Midazolam injection work?

Midazolam injection contains the active substance midazolam, which belongs to a group of medicines known as benzodiazepines. It is a short-acting medicine that is used to induce sedation (a very relaxed state of calm, drowsiness or sleep) and relieves anxiety and muscle tension.

How is Midazolam injection used?

The pharmaceutical form of this medicine is a solution for injection/infusion in pre-filled syringe and the route of administration is by slow injection into a vein (intravenous injection), through a tube into one of the patient's veins (intravenous infusion) or by injection into a muscle (intramuscular injection).

Midazolam injection should be given only by experienced healthcare professionals (doctor or nurse). It should be given in a place (hospital, clinic or surgery) equipped to monitor and support the patient's breathing, heart and circulation (cardiovascular function) and recognise the signs of and manage the expected side effects of anaesthesia.

How much Midazolam injection is given

The patient's doctor will decide on a suitable dose for them. The dose the patient is given will depend on why they are being treated and the type of sedation needed. The patient's weight,

age, state of health, how they respond to Midazolam injection and whether other medicines are needed at the same time will also influence the dose that they are given.
If the patient needs strong painkillers, they will be given these first and then be given Midazolam injection.

The patient's doctor will decide on a suitable dose for them.

The patient should always be taken home by a responsible adult after their treatment.

Children and babies
In infants and babies under 6 months of age Midazolam injection is only recommended for sedation in intensive care units. The dose will be given gradually into a vein.

Children 12 years and under will usually be given Midazolam injection into a vein.

For further information on how Midazolam injection is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Midazolam injection have been shown in studies?
No additional studies were needed as Midazolam injection contains the same active substance as the reference medicine, and satisfactory data to justify the differences have been provided.

What are the possible side effects of Midazolam injection?
Because Midazolam injection is a hybrid medicine and is therapeutically equivalent to the reference medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of all side effects reported with this medicine, see Section 4 of the package leaflet or the Summary of Product Characteristics (SmPC) available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at www.mhra.gov.uk/yellowcard or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Midazolam injection approved?
It was concluded that, in accordance with EU requirements, Midazolam injection has been shown to be therapeutically equivalent to the reference medicine. Therefore, the MHRA decided that, as for the reference medicine, the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Midazolam injection?

A Risk Management Plan (RMP) has been developed to ensure that Midazolam injection is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the package leaflet, 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/healthcare professionals will be monitored and reviewed continuously.

Other information about Midazolam injection

A Marketing Authorisation for Midazolam injection was granted in the UK on 07 September 2020.

Following approval, the Marketing Authorisation underwent a change of ownership procedure from the company Lambda Therapeutic Limited (PL 29959/0021) to the company Accord-UK Ltd (PL 00142/1263) on 05 October 2020.

The full PAR for Midazolam injection follows this summary.

This summary was last updated in July 2021.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe (PL 29959/0021) could be approved.

Midazolam is a short acting sleep-inducing active substance that is indicated:

In adults

- conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Anaesthesia:
  - Premedication before induction of anaesthesia
  - Induction of anaesthesia
  - As a sedative component in combined anaesthesia
- Sedation in intensive care units

In children

- conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia
- Anaesthesia:
  - Premedication before induction of anaesthesia
- Sedation in intensive care units

Midazolam belongs to the pharmacotherapeutic group: Hypnotics and sedatives (benzodiazepine derivatives).

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

Chemically midazolam is a derivative of the imidazobenzodiazepine group, the basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of midazolam to form water-soluble salts with acids, producing a stable and well tolerated injection solution. At physiological pH the diazepine ring closes and the free base is formed resulting in a lipophilic substance with rapid onset of action. Rapid metabolic transformation and redistribution are key reasons for the short duration of effects.

This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended, claiming to be a hybrid medicinal product of a suitable originator product, Hypnovel 10 mg/2 mL solution for injection (PL 00031/0126) that has been licensed within the EU for a suitable time, in line with the legal requirements.

No new non-clinical studies were conducted, which is 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.

A biowaiver was submitted with this application which was accepted. No bioequivalence or therapeutic equivalence studies were required and none were provided with this application.

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

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the UK on 07 September 2020.

Following approval, the Marketing Authorisation underwent a change of ownership procedure from the marketing authorisation holder (MAH) Lambda Therapeutic Limited (PL 29959/0021) to the MAH Accord-UK Ltd (PL 00142/1263) on 05 October 2020.

II QUALITY ASPECTS

II.1 Introduction

Each 5 ml pre-filled syringe contains 5 mg of midazolam (as midazolam hydrochloride).

In addition to midazolam, this product also contain the excipients sodium chloride, concentrated hydrochloric acid (for pH-adjustment), sodium hydroxide (for pH-adjustment) and water for injections.

The finished product is packaged in 1 x 5 ml clear glass pre-filled syringe with plunger stopper and plunger rod. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current European regulations concerning materials in contact with food.

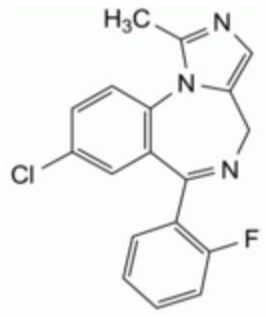
II.2 ACTIVE SUBSTANCE

rINN: Midazolam

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

Molecular Formula: $C_{18}H_{13}ClFN_3$

Chemical Structure:



Molecular Weight: 325.8

Appearance: White or yellowish, crystalline powder.

Solubility: Practically insoluble in water, freely soluble in acetone and in ethanol (96 per cent), soluble in methanol.

Midazolam is the subject of a European Pharmacopoeia monograph.

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines and Healthcare (EDQM) Certificate of Suitability.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

Comparative *in vitro* impurity profiles have been provided for the proposed and reference products.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

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

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification
The finished product specification is satisfactory. The test methods have been described and adequately validated. Batch data have been provided that 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 guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 2 years for the unopened syringe, with the storage conditions 'Store in the original package in order to protect from light', is acceptable.

Shelf life after dilution
Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature (15°C -25°C) or for 3 days at +2°C to +8 °C.

From the microbiological point of view, the dilutions should be used immediately. If not used immediately, in-use storage times and conditions prior to use are at the responsibility of the user and would normally not be longer than 24 hours at +2°C to +8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well-known, no new non-clinical studies are required, and none have been provided. An overview based on the literature review is, thus, appropriate.

III.2 Pharmacology
No new pharmacology data were provided and none were required for this application.

III.3 Pharmacokinetics
No new pharmacokinetic data were provided and none were required for this application.

III.4 Toxicology
No new toxicology data were provided and none were required for this application.

III.5 Ecotoxicity/Environmental Risk Assessment
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As this is a hybrid application of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects
The grant of a marketing authorisation is recommended.

IV CLINICAL ASPECTS
IV.1 Introduction
In accordance with the regulatory requirements, the applicant has provided a suitable biowaiver. No bioequivalence or therapeutic equivalence studies have been submitted with this application.

IV. 2 Pharmacokinetics
No new pharmacokinetic data have been submitted for this application and none were required.

IV.3 Pharmacodynamics
No new pharmacodynamic data have been submitted for this application and none were required.

IV.4 Clinical efficacy
No new efficacy data have been submitted for this application and none were required.

IV.5 Clinical safety
No new safety data were submitted with this application and none were required. The safety profile for this product is considered to be the same as Hypnovel 10mg/2ml solution for injection.

IV.6 Risk Management Plan (RMP)
The applicant has submitted an RMP, in accordance with the requirements of Directive 2001/83/EC, as amended. The applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation is recommended for this application.

V USER CONSULTATION
A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to Midazolam Injection, 1 mg/mL and 5 mg/mL, solution for injection or infusion (NL/H/1077/001-002/DC; Accord Healthcare Ltd) The bridging report submitted by the applicant is acceptable.

VI OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Extensive clinical experience with midazolam is considered to have demonstrated the therapeutic value of the product.

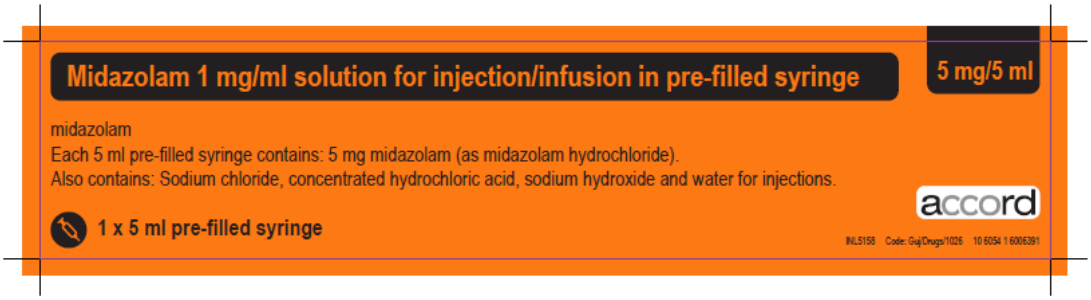
The benefit/risk is, therefore, considered to be positive.

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

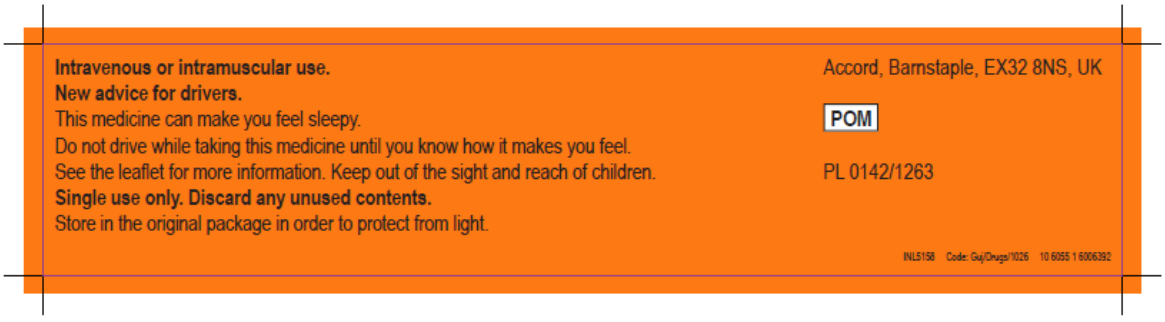
In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

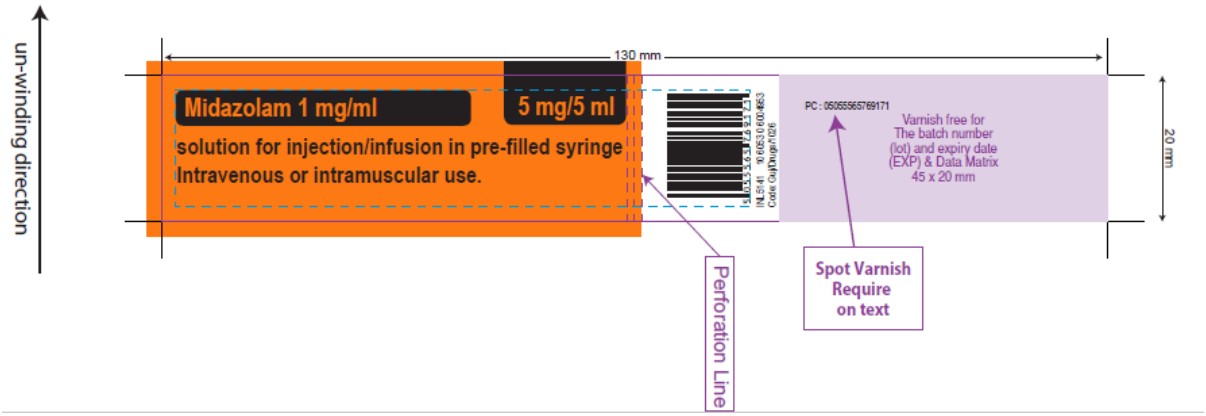
Representative copies of the current approved labels are provided below.

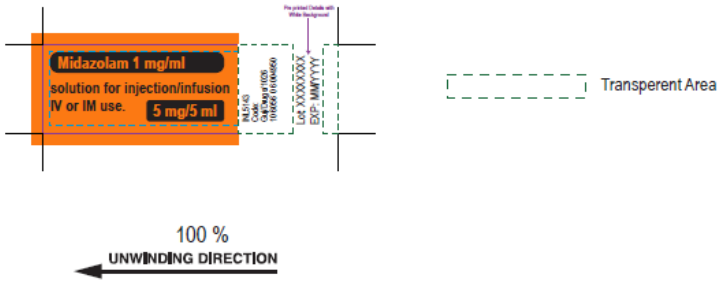
Twist Box Label Front Panel



Twist Box Label Back Panel




un-winding direction
130 mm
Midazolam 1 mg/ml
5 mg/5 ml
solution for injection/infusion in pre-filled syringe
Intravenous or intramuscular use.
PC : 05055565769171
Varnish free for
The batch number
(lot) and expiry date
(EXP) & Data Matrix
45 x 20 mm
20 mm
Perforation Line
Spot Varnish
Require
on text


Midazolam 1 mg/ml
solution for injection/infusion
IV or IM use.
5 mg/5 ml
Lot: XXXXXXXX
EXP: MM/YYYY
Transperent Area
100 %
UNWINDING DIRECTION

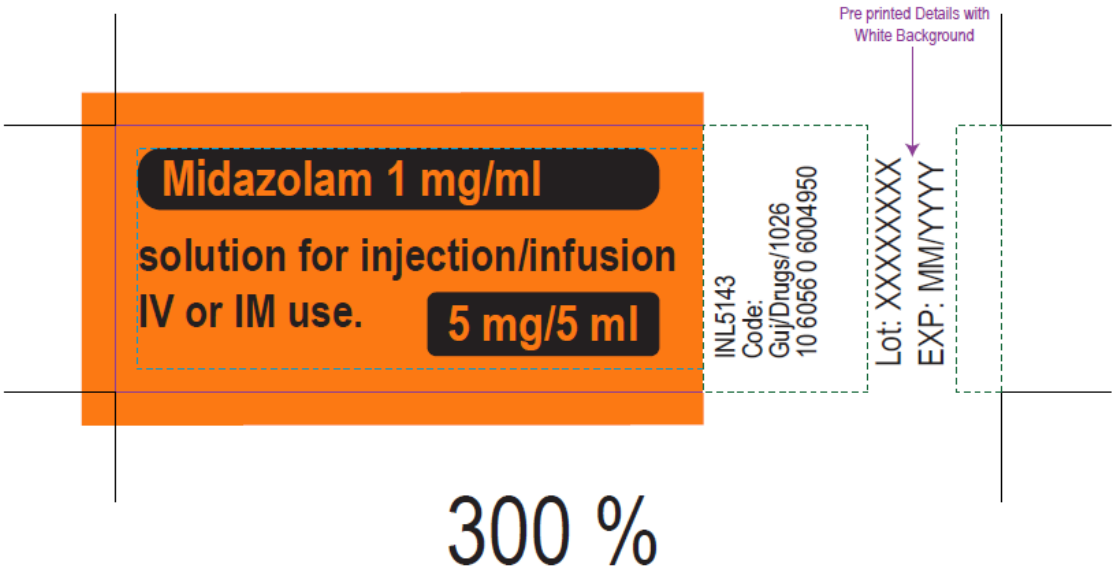

Pre printed Details with
White Background
Midazolam 1 mg/ml
solution for injection/infusion
IV or IM use.
5 mg/5 ml
INL5143
Code:
Guj/Drugs/1026
10 6056 0 6004950
Lot: XXXXXXXX
EXP: MM/YYYY
300 %

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	Scope	Product information affected	Date of grant	Outcome	Assessment report attached Y/N
Type IB	To update section 5.2 of the SmPC in line with the reference product Hypnovel 10mg/2ml solution for injection (PL 45043/0037). Consequentially, the PIL has been updated	SmPC and PIL	24 June 2021	Approved	Y

Annex I

Reference: **PL 00142/1263-0004**

Product: Midazolam 1 mg/ml solution for injection/infusion in pre-filled syringe

Type of Procedure: National

Submission category: Type IB Variation

Reason
To update section 5.2 of the SmPC in line with the reference product Hypnovel 10mg/2ml solution for injection (PL 45043/0037). Consequentially, the PIL has been updated.

Supporting evidence
The Company has submitted an updated SmPC.

Evaluation
The updated document is satisfactory.

Conclusion
The proposed changes are acceptable.

In accordance with legal requirements, the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

Decision: Grant

Date: 24 June 2021.