COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Midazolam Accord 1 mg/ml solution for injection/infusion in prefilled syringe

(midazolam)

NL/H/4842/001/DC

Date: 2 September 2020

This module reflects the scientific discussion for the approval of Midazolam Accord 1 mg/ml solution for injection/infusion in prefilled syringe. The procedure was finalised at 8 July 2020. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

ASMF	Active Substance Master File
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EEA	European Economic Area
ERA	Environmental Risk Assessment
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
Ph.Eur.	European Pharmacopoeia
PL	Package Leaflet
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TSE	Transmissible Spongiform Encephalopathy

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Midazolam Accord 1 mg/ml solution for injection/infusion in prefilled syringe, from Accord Healthcare B.V.

Midazolam is a short-acting sleep-inducing drug 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

A comprehensive description of the indications and posology is given in the SmPC.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Hypnovel 1 mg/ml and 5 mg/ml solution for injection which have been centrally registered in the EEA by Roche Products Limited since 1992 and 1986 respectively (original product). In addition, reference is made to Hypnovel/Dormicum 5 mg/ml authorisations in the individual member states (reference product).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Ireland, Norway, Poland, Portugal, Romania, Spain and Sweden.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, a hybrid application as:
- The pharmaceutical form is different than the reference drug product. The reference product is available as solution for injection/infusion, while applicant's drug product is available as solution for injection/infusion in prefilled syringe.

- The strength is filed as a different strength as compared to the reference product, although the innovator product is also available in a 1 mg/ml presentation in some European markets.

Withdrawal of the 5 mg/ml strength
Initially the application included another strength: Midazolam Accord 5 mg/ml solution. A positive benefit/risk balance was not demonstrated and therefore this strength was not considered approvable. The company MAH withdrew Midazolam Accord 5 mg/ml solution from the application before finalisation of the procedure.

II. QUALITY ASPECTS

II.1 Introduction

Midazolam Accord is a clear, colourless to pale yellow solution free from foreign particles with a pH in the range of 2.9 - 3.7 and 270 mOsm/kg to 330 mOsm/kg osmolality.

Each ml of solution contains midazolam hydrochloride corresponding to 1 mg midazolam. Each 5 ml pre-filled syringe contains midazolam hydrochloride corresponding to 5 mg midazolam.

The solution for injection/infusion packed in 5 ml clear glass pre-filled syringe having graduation marking (graduation per 0.1 ml) with bromobutyl plunger stopper, styrene butadiene tip cap and polypropylene plunger rod.

The excipients are: sodium chloride, concentrated hydrochloric acid, (for solubilizer and pH adjustment), sodium hydroxide (for pH adjustment) and water for injections.

II.2 Drug Substance

The active substance is midazolam, an established active substance described in the European Pharmacopoeia (Ph.Eur.). Midazolam is a white or yellowish crystalline powder. It is practically insoluble in water, freely soluble in acetone and in ethanol (96%) and soluble in methanol. The polymorphic form and particle size of the active substance are not of relevance, as the product is a solution.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This

procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and CEP with additionally tests for the residual solvents, microbial purity and bacterial endotoxins. Batch analytical data demonstrating compliance with this specification have been provided for two batches.

Stability of drug substance
The active substance is stable for 60 months when stored under the stated conditions. Assessment thereof was part of granting the CEP and has been granted by the EDQM.

II.3 Medicinal Product

Pharmaceutical development
The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. Development studies included evaluation of drug substance properties, the choice of excipients, selection of packaging material (prefilled syringe, stopper material), filter, sterilisation method, storage conditions and stability of the product. The proposed product is a hybrid equivalent to the reference product Hypnovel, which is available in ampoules. The proposed product is a prefilled syringe. Both products are solutions for injection/infusion. The drug substance concentration and volume of proposed product and reference product are identical. As the hybrid product is a solution for injection/infusion containing the same active substance in the same concentration as the reference product, this product may be exempted from bioequivalence study with the reference product.

Manufacturing process
The manufacturing process consists of preparation of the bulk solution, prefiltration, filling, stoppering and terminal sterilisation. It is a standard process and has been validated according to relevant European guidelines. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients
The excipients comply with the Ph. Eur. requirements. The specifications are acceptable.

Quality control of drug product
The finished product specifications are adequate to control the relevant parameters for the dosage form. The specification includes tests for description, identification, pH, extractable volume, particulate contamination (sub-visible), bacterial endotoxins, sterility, colour of

solution, related substances, assay, dose accuracy, gliding force and break-loose force. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. Satisfactory validation data for the analytical methods have been provided. Batch analytical data three production scaled batches from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three exhibit batches stored at 25°C/60% RH (18 months data) and 40°C/75% RH (6 months data). On basis of the data submitted, a shelf life was granted 2 years. Photostability studies performed during development show that the drug product is sensitive to light. Therefore, the storage condition "Store in the original package in order to protect from light" is justified.
Chemical and physical in-use stability of the diluted product has been demonstrated for 24 hours at room temperature (15 – 25°C) or for 3 days at 2 to 8 °C. From the microbiological point of view, the diluted product 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 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

There are no substances of ruminant animal origin present in the product nor have any been used in the manufacturing of this product, so a theoretical risk of transmitting TSE can be excluded.

II.4 Discussion on chemical, pharmaceutical and biological aspects

Based on the submitted dossier, the member states consider that Midazolam Accord has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product. No post-approval commitments were made.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Midazolam Accord is intended for hybrid substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Hypnovel which is available on the European market. Reference is made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. Therefore, the member states agreed that no further non-clinical studies are required.

IV. CLINICAL ASPECTS

IV.1 Introduction

Midazolam is a well-known active substance with established efficacy and tolerability. A clinical overview has been provided, which is based on scientific literature. The overview justifies why there is no need to generate additional clinical data. Therefore, the member states agreed that no further clinical studies are required.

IV.2 Pharmacokinetics

Midazolam Accord 1 mg/ml solution for injection/infusion in prefilled syringe is a parenteral formulation and therefore fulfils the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition ofMidazolam Accord is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current product can be used instead of its reference product.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating toMidazolam Accord.

Table 1. Summary table of safety concerns as approved in RMP

Important identified risks	None
Important potential risks	None
Missing information	None

The member states agreed that routine pharmacovigilance activities and routine risk minimisation measures are sufficient for the risks and areas of missing information.

IV.4 Discussion on the clinical aspects

For this authorisation, reference is made to the clinical studies and experience with the innovator product Hypnovel. No new clinical studies were conducted. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product.

V. USER CONSULTATION

A user consultation with target patient groups on the package leaflet (PL) has been performed on the basis of a bridging report making reference to Midazolam Injection 1 mg/ml ampoule presentations, (NL/H/1077/001-002/DC). The bridging report submitted by the MAH has been found acceptable; bridging is justified for both content and layout of the leaflet.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Midazolam Accord 1 mg/ml solution for injection/infusion in prefilled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Hypnovel 1 mg/ml solution for injection. Hypnovel is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The Board followed the advice of the assessors.

There was no discussion in the CMD(h). Agreement between member states was reached during a written procedure. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Midazolam Accord with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 8 July 2020.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Procedure number*	Scope	Product Information affected	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse