COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Midazolam Baxter 1 mg/ml and 5 mg/ml solution for injection

(midazolam hydrochloride)

NL/H/4275/001-002/DC

Date: 14 November 2019

This module reflects the scientific discussion for the approval of Midazolam Baxter 1 mg/ml and 5 mg/ml solution for injection. The procedure was finalised at 26 March 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

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 Baxter 1 mg/ml and 5 mg/ml solution for injection from Baxter Deutschland GmbH.

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 generic application claiming essential similarity with the innovator product Hypnovel 1 mg/ml and 5 mg/ml solution for injection which has 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 Czech Republic, Estonia, France, Hungary, Ireland, Lithuania, Latvia, Poland, Portugal, Romania, Slovakia, and the United Kingdom.

The marketing authorisation has been granted pursuant to Article 10(1) of Directive 2001/83/EC.

II. QUALITY ASPECTS

II.1 Introduction

Midazolam Baxter is a clear, colourless to pale yellow solution practically free from any visible particles for injection/infusion.

- Midazolam Baxter 1 mg/ml contains as active substance 1 mg/ml of midazolam as midazolam hydrochloride. The pH of the 1 mg/ml solution is between 2.90 and 3.70 and osmolality should be 270 mOsmol/kg to 320 mOsmol/kg.
- Midazolam Baxter 5 mg/ml contains as active substance 5 mg/ml of midazolam as midazolam hydrochloride. The pH of the 5 mg/ml solution is between 2.90 and 3.70 and osmolality should be 180 mOsmol/kg to 220 mOsmol/kg.

The solution is packed in 1 ml, 3 ml, 5 ml, and 10 ml clear glass (type I) ampoules with marking of coloured dot. The two strengths of the drug product, 1 mg/ml and 5 mg/ml, are filled out in one (5 ml) and three (1 ml, 3 ml and 10 ml) volumes respectively. For the 5 mg/ml strength, the composition is identical for the different fill volumes.

The excipients are sodium chloride, sodium hydroxide (for pH adjustment) (E524), hydrochloric acid (for pH adjustment) (E507) and water for injections.

II.2 Drug Substance

The active substance is midazolam hydrochloride, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The drug substance is a crystalline powder and practically insoluble in water, freely soluble in acetone and in ethanol (96%), and soluble in methanol. Polymorphism is not relevant for the product at issue, since it concerns 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. It contains additional requirement for

bacterial endotoxins and microbial counts. Batch analytical data demonstrating compliance with this specification have been provided for six commercial scale batches.

Stability of drug substance
The active substance is stable for two years 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. The choice of excipients is justified and their functions explained. Essential similarity studies, container extractable-leachable studies and diluent compatibility studies were performed to demonstrate respectively that the test product and reference product are interchangeable, the container closure system is safe and which diluents are suitable. Pharmaceutical development has been adequately performed.

Manufacturing process
The product is manufactured using conventional manufacturing techniques. The solutions are manufactured by the following steps: mixing, filtrating, filling, and terminal sterilisation. The manufacturing process has been adequately validated according to relevant European guidelines. Process validation data on the product has been presented for at least three exhibit batches. Process validation for full scaled batches will be performed post authorisation.

Control of excipients
The excipients comply with Ph.Eur. requirements. These 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 characteristics, identification, extractable volume, acidity, particulate matter, assay, total chlorides, related substances, osmolality, bacterial endotoxins and sterility. 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 from at least six exhibit-scale batches of each strength from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability data on the product has been provided on at least six exhibit-scale batches of each strength stored at 25°C/60% RH (24 months), 30°C/65% RH (24 months) and 40°C/75% RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. All batches remained within the specification in all conditions. On basis of the data

submitted, a shelf life was granted of three years. The stability studies of larger batches are still pending. The batches were stored in the proposed packaging. Results of photostability studies have been provided and based on these results the ampoules should be stored in the outer packaging to protect from light.

Chemical and physical in-use stability of the dilutions has been demonstrated for 24 hours at room temperature and for three days at 5°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 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 (for dilution, see also SmPC section 6.6).

Microbial attributes
The product is terminally sterilised, no microbial preservatives are used and tests for bacterial endotoxins and sterility are part of the test specifications. In addition, endotoxin and microbial tests are controlled with the specifications of the drug substance and excipients, where relevant. This is in accordance with draft guideline EMA/CHMP/CVMP/QWP/BWP/850374/2015.

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 Baxter 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 Baxter is intended for generic 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 generic 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 hydrochloride 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 Baxter 1 mg/ml and 5 mg/ml solution for injection 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 of Midazolam Baxter 1 mg/ml and 5 mg/ml solution for injection 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 to Midazolam Baxter.

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

Important identified risks	--
Important potential risks	--

Missing information	--

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. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet (PL) has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The test consisted of: a pilot test, followed by two rounds with ten participants each. The questions covered the following areas sufficiently: traceability, comprehensibility and applicability. The results show that the PL meets the criteria for readability as set out in the Guideline on the readability of the label and PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Midazolam Baxter 1 mg/ml and 5 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Hypnovel 1 mg/ml and 5 mg/ml solution for injection. Hypnovel is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. 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 Baxter with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 26 March 2019.

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