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Public Assessment Report

Scientific discussion

Midazolam Eignapharma 5 mg/ml, solution for injection or infusion (midazolam)

ES/H/0938/01/DC

Date: 14/04/2025

This module reflects the scientific discussion for the approval of Midazolam Eignapharma 5 mg/ml solution for injection or infusion. The procedure was finalised at 24 February 2025. For information on changes after this date please refer to the module ôUpdateô.

I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, the Member States have granted a marketing authorisation for Midazolam Eignapharma 5 mg/mL, solution for injection or infusion from Eignapharma S.L.

The product 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 the 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 the intensive care units

II. QUALITY ASPECTS

II.1 Introduction

The finished product is presented as solution for injection or infusion containing 5 mg/mL of Midazolam as active substance. The maximum daily dose is 306 mg.

The product is available in colourless glass ampoule with brown one point cut, type I glass primary packaging as described in section 6.5 of the SmPC.

II.2 2.2Drug Substance

CEP procedure is used to support the quality of the drug substance, Midazolam.

General Information

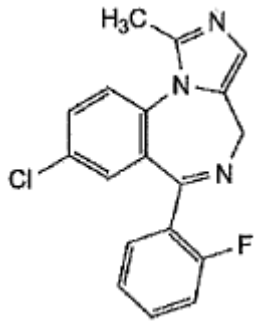
Nomenclature:

INN: Midazolam

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

CAS-No: [59467-70-8]

Structure:



Molecular mass 325.8

Molecular formula $C_{18}H_{13}ClFN_3$

General Properties:

Midazolam is a white or yellowish crystalline powder, practically insoluble in water, freely soluble in acetone and in ethanol 96 %, soluble in methanol.

Manufacture, process controls and characterisation

As CEP procedure is used, information on manufacture, process controls and characterisation of the active substance has been assessed by EDQM.

Specification, analytical procedures, batch analysis

Active substance specifications are in accordance with Ph. Eur. monograph and additional relevant tests are included.

Container closure system

As CEP procedure is used, information on packaging material of active substance has been assessed by EDQM.

Stability

Stability studies have been performed in accordance with current guidelines. Protocol, controlled parameters and test methods are considered adequate. The packaging material is similar to that proposed for storage. Proposed re-test period and storage conditions are justified.

II.3 Medicinal Product

Description of the product

The product is a clear, colourless to light yellow colour solution that contains 5 mg/mL of Midazolam and can be filled. Other ingredients are sodium chloride, hydrochloric acid, sodium hydroxide and water for injections.

Pharmaceutical Development

The development of the product has been described, the choice of excipients is justified and their functions explained.
The physicochemical characteristics of the active substance that may affect the pharmaceutical form are identified and their control strategy is justified.
The proposed method of sterilization has been appropriately justified.

Manufacture of the product

The manufacturing process is fully described and in-process controls are appropriate considering the nature of the product and the manufacturing process. The industrial batch size is well-defined.

The process validation scheme is provided.

Excipients

Excipients used are well known and of appropriate quality.

None of the excipients is of animal origin.

Product specification, analytical procedures, batch analysis

The finished product specifications are adequate to control the finished product. Provided description and validation data for the analytical methods are adequate. Batch analysis data have been submitted and the results show that the finished product meets the proposed release specification.

Container closure system

The finished product is packaged in 3 mL flint ampoules with brown one point cut or filled in 10 mL flint ampoules with brown one point cut. The choice of the container closure system is justified considering the nature of the finished product. Compliance with the relevant requirements and/or regulations is confirmed.

Stability

Stability studies have been performed in accordance with current guidelines. The proposed protocol is considered adequate. The packaging material is the same as that intended for marketing. Proposed shelf-life and storage conditions are properly established.

Shelf-life: 36 months.

Storage conditions: This medicinal product does not require any special temperature storage conditions.

Keep the container in the outer carton in order to protect from light.

After first opening/dilution:

Midazolam 5 mg/ml Solution for Injection or Infusion was found to be physically compatible and chemically stable for 24 hours at room temperature at 25°C, or 3 days at 5°C with the following diluents (dilution range 0.015 mg/mL to 0.15 mg/mL) when stored in glass bottle and PVC bottle.Diluents:

1. Sodium chloride intravenous infusion 0.9% w/v

2. Dextrose intravenous infusion 5% w/v

3. Compound Sodium Lactate injection/ Ringer-Lactate Solution for Injection

4. Dextrose intravenous infusion 10% w/v

5. Ringer solution for injection

From a microbiological point of view, the product 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 5ºC.

III. NON-CLINICAL ASPECTS

III.1 Critical evaluation of the Non-Clinical Overview

Pharmacodynamic, pharmacokinetic and toxicological properties of midazolam are well known. As midazolam is a widely used, well-known active substance, the applicant has not provided additional studies, and further studies are not required. Overview based on literature review is, thus, appropriate.

III.2 Ecotoxicity/environmental risk assessment (ERA)

Since Midazolam Eignapharma 5 mg/ml solution for injection/infusion is a generic product, it will not lead to an increased exposure to the environment. Therefore, additional ERA studies are not deemed necessary.

IV. CLINICAL ASPECTS

IV.1 Introduction

Midazolam is a well-known active substance with established efficacy and safety. A clinical overview has been provided, which is based on scientific literature. The clinical overview justifies that there no need to generate additional clinical data.

For this generic application of an immediate release formulation, the MAH has not submitted any bioequivalence studies according to the *Guideline on the investigation of bioequivalence* since the test product is an aqueous intravenous solution at time of administration and contains an active substance (midazolam) in the same concentration as an approved intravenous solution.

The PI documents has been amended according to the RMS and CMSs comments, and it is fully aligned with the reference product and the guidelines of application.

IV.2 Pharmacokinetics

Biowaiver

The current application consists in a medicinal product in the same pharmaceutical form (solution for injection or infusion) as the reference medicinal product. The applied product also contains qualitatively the same excipients in similar amounts as the reference product and the quantitative differences are not expected to affect the bioavailability.

The bioequivalence between the test and the reference product can be assumed.

IV.3 Risk Management Plan

The MAH has submitted a risk management plan (version 0.1, 18 January 2024), 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 Eignapharma 5 mg/ml solution for injection/infusion

There are neither proposed additional pharmacovigilance activities nor proposed additional risk minimisation measures planned for Midazolam Eignapharma 5 mg/ml solution for injection/infusion (midazolam).

IV.4 Discussion on the clinical aspects

For generic applications please refer to section IV.2.

V. USER CONSULTATION

The package leaflet 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 results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

The test consisted of 3 rounds; a pilot test with 2 participants, followed by 2 rounds with 10 participants each. The data processing is satisfactory as it is clear, well processed and complies with the protocol.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product Midazolam Eignapharma 5 mg/mL, solution for injection or infusion is found adequate. There are no objections to the approval of Midazolam Eignapharma 5 mg/mL, solution for injection or infusion from a non-clinical and clinical point of view. The product information is acceptable. The benefit/risk is considered positive, and the application is therefore recommended for approval.