LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Senozam
(midazolam)

SE/H/2203/01-02/DC

This module reflects the scientific discussion for the approval of Senozam. The procedure was finalised on 2022-12-07. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Senozam, 1 mg/ml, 5 mg/ml, Solution for infusion.

The active substance is midazolam. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Senozam, 1 mg/ml, 5 mg/ml, Solution for infusion, is an application submitted according to Article 10a of Directive 2001/83/EC. The applicant applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and DE, IS and NL as concerned member states (CMS).

Potential similarity with orphan medicinal products

According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

There were no new non-clinical data generated for the purpose of this application. This well-established use application was solely based on the published literature references for midazolam.

Pharmacology

Midazolam is a short-acting benzodiazepine with general properties similar to those of diazepam, except that it has a more potent amnestic action. The primary pharmacodynamic effects of midazolam

have been adequately presented based on the literature reviewed. The major metabolite of midazolam identified in man, 1'-hydroxymidazolam, is reported to be active but less potent than midazolam in rotarod, chimney and anticonvulsant tests in mice.

The secondary pharmacodynamic effects, and the effects of midazolam on the respiratory, cardiovascular, CNS and GI systems have been adequately presented based on the literature reviewed. The potential adverse impact of concomitant use of opioids is well known.

Pharmacokinetics

Senozam will be administered by intravenous and intramuscular of administration. There is limited information on the non-clinical pharmacokinetics of midazolam following these administration routes. This is considered acceptable given the long clinical experience with midazolam.

Toxicology

The toxicological information for midazolam submitted by the Applicant is sparse. However, midazolam has been in clinical use for many years and its clinical safety profile is well-known. In accordance with the Guideline on the non-clinical documentation for mixed marketing authorization applications (CPMP/SWP/799/95), focus can be put on genotoxicity, reproductive toxicity and carcinogenicity.

No studies on single dose toxicity have been submitted by the Applicant, but reference is made to LD_{50} and lowest published toxic dose (TD_{LO}) values in the literature. Single dose toxicity studies are no longer a regulatory requirement and the presented data are of limited relevance. It is acknowledged, however, that for old substances, such as midazolam, these types of toxicological data are often available in the literature. Intravenous LD_{50} values were 50 to 75 mg/kg in mice and rats, respectively. The main effects observed include CNS depressant effects and respiratory depression.

Repeat-dose toxicity oral studies of up to 13-weeks in rats and dogs are described in the literature.

In rats dose levels of up to 200 mg/kg were evaluated and in dogs, doses up to 45 mg/kg. These top doses in rats and dogs correspond to HEDs of 32 and 25 mg/kg, respectively, are considerably higher than the single dose levels used for anaesthesia and sedation in the clinic.

In rats, reductions in body weight gain, increased liver weight and microscopical hepatocyte alterations (higher content of fat and acid mucopolysaccharides) are reported. In dogs, muscle relaxation, ataxia and sedation were observed and a marked proteinuria and a dose-related increase in alkaline phosphatase.

Midazolam is reported to be negative in the Ames test, the fluctuation test, and in *in vitro* and *in vivo* cytogenicity tests. Although the published data on genotoxicity on midazolam is very limited, the available information indicates that there is no relevant signal for genotoxicity.

In 2-year carcinogenicity studies in rodents, an increased incidence of hepatic tumors was observed in female mice following dose levels of 1, 9, 80 mg/kg/day, and an increased incidence in benign thyroid follicular cell tumors was observed in male rats at 80 mg/kg/day. Given the short-term clinical use, the non-clinical carcinogenicity findings are of no concern to the therapeutic use of midazolam.

Regarding reproductive toxicity, the provided original references are scarce. However the pregnancy section in the SmPC is line with that of other midazolam products and therefore considered acceptable.

The literature references on the effects of midazolam on human and animal fertility are sparse. The SmPC section 4.6 has been updated with information that there are no or limited amount of data from the effect of midazolam on fertility and that animal studies are insufficient with respect to fertility. This is considered acceptable.

The absence of dedicated juvenile studies is considered acceptable.

It is well-known that long-term treatment with benzodiazepines can lead to tolerance and, as evidenced by withdrawal signs that emerge upon discontinuation of treatment, dependence.

Environmental Risk Assessment (ERA)

An ERA in accordance with relevant guidelines has not been submitted. On the other hand, a justification for not performing an ERA was provided. Senozam is intended as a substitution of other midazolam products already available on the market and the environmental exposure to the drug substance is not expected to increase significantly. The justification for absence of an environmental risk assessment is considered acceptable.

IV. CLINICAL ASPECTS

Pharmacokinetics

There were no new pharmacokinetic (PK) data generated for the purpose of this application. This well-established use application was solely based on the published literature references for midazolam as presented by the Applicant. No bioequivalence/relative bioavailability study was conducted with Senozam product, which appears acceptable when considering the characteristics of the active substance and the drug formulation (i.e., water solution with common inorganic excipients: sodium-chloride, hydrochloric acid, sodium hydroxide) as well as the intended parenteral route of administration (*I.V.* and *I.M.*).

Absorption

The absolute bioavailability after *I.M.* injection is reported to be over 90%. Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes.

Distribution

The volume of distribution at steady state is 0.7-1.2 L/kg. Midazolam is 96-98% bound to plasma proteins, primarily to albumin. There is a slow and insignificant passage of midazolam into the cerebrospinal fluid. In humans, midazolam has been shown to cross the placenta slowly and to enter foetal circulation. Small quantities of midazolam are found in human milk.

Biotransformation/Elimination

Midazolam is almost entirely eliminated by biotransformation. The fraction of the dose extracted by the liver has been estimated to be 30-60 %. Midazolam is hydroxylated by the CYP3A isozymes, and the major urinary and plasma metabolite is 1'-hydroxymidazolam. Plasma concentrations of 1'-hydroxymidazolam are 12% of those of the parent compound. 1'-hydroxymidazolam is pharmacologically active.

The elimination half-life of midazolam is between 1.5-2.5 hours. Plasma clearance is in the range of 300-500 mL/min. Midazolam metabolites are excreted mainly by renal route (60-80% of the injected dose) and recovered as glucuro-conjugated 1'-hydroxymidazolam. Less than 1% of the dose is recovered in urine as unchanged drug. Repeated administrations of midazolam do not induce drug metabolising enzymes involved in biotransformation.

Special populations

In adults over 60 years of age, the elimination half-life may be prolonged up to four times.

The elimination half-life after *I.V.* and rectal administration is shorter in children 3-10 years old (1-1.5 hours) as compared with that in adults. The difference is consistent with an increased metabolic clearance in children.

In premature and full-term neonates, the elimination half-life is on average 6-12 hours, probably due to liver immaturity and the reduced clearance.

The mean half-life is greater in obese than in non-obese patients (5.9 vs 2.3 hours). This is due to an increase of approximately 50% in the volume of distribution corrected for total body weight. The clearance is not significantly different in obese and non-obese patients.

The elimination half-life in cirrhotic patients may be longer and the clearance smaller as compared to those in healthy volunteers.

The pharmacokinetics of unbound midazolam are not altered in patients with severe renal impairment. The pharmacologically mildly active major midazolam metabolite, 1'-hydroxymidazolam glucuronide, which is excreted through the kidney, accumulates in patients with severe renal impairment. This accumulation produces a prolonged sedation.

Interactions

Midazolam is a sensitive substrate of CYP3A, and as such represents a potential "victim" drug of many drug-drug interactions (DDIs) when co-administered with substances that impact the CYP3A activity. These concomitant medications include inhibitors of CYP3A (e.g., azole antifungals such as ketoconazole, voriconazole, fluconazole; macrolide antibiotics such as erythromycin and clarithromycin; HIV protease inhibitors, etc) and inducers of CYP3A (e.g., rifampicin, St John's Wort, etc).

Discussion on pharmacokinetics

This is a well-established use application based on bibliographic data on midazolam. The Applicant has provided sufficient literature data in terms of pharmacokinetics to support the present application.

Pharmacodynamics

Midazolam, in common with other benzodiazepines, is an anxiolytic and sedative with about twice the sedative potency of diazepam. It also has anticonvulsant, sleep inducing, and muscle relaxant properties and powerful anterograde amnestic action similar to that of diazepam. Seven to 9 hours following midazolam, patients feel more awake and have better psychomotor performance than after an equivalent dose of diazepam. When used in higher dosage for induction of anaesthesia, there is considerable interindividual variation in response, especially in the young. Variations in binding to protein and to benzodiazepine receptor sites may be partially responsible for this.

Maturation processes of receptors may influence the functional activity of the GABA-receptor and thereby alter the pharmacodynamic response. Little is known about the developmental influences of receptor interaction or signal transduction processes leading to the clinical response. No data are available on developmental aspects in human neonates.

While there is extensive clinical experience of IV midazolam as a sedative, there is limited understanding of PK/PD relations, and current posology in premature infants has recently been questioned by new population PK data. It has been difficult to identify reliable PD markers for effects of midazolam. It is therefore essential to recognise that midazolam needs to be titrated to effect and not strictly be administered according to a fixed posology, to ensure sufficient effectiveness with minimised adverse effects.

Clinical efficacy

The efficacy studies reviewed have evaluated midazolam against placebo in some cases, but mostly against active comparators, which is appropriate for the applied indications. We therefore consider the characterisation of efficacy separately for each proposed indication:

In adults

• *Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia*

Midazolam has been compared to diazepam in several studies of various diagnostic or therapeutic procedures. Efficacy has been comparable or in some respect superior to diazepam, with shorter recovery and higher preference by patients and physicians, perhaps partly related to a more pronounced amnesia. The studies reviewed by the applicant provides sufficient support for efficacy in this indication in adults and children aged 2 years and older.

• *Anaesthesia*

- *Premedication before induction of anaesthesia*
Midazolam 0.04 mg/kg has been demonstrated to be an effective anxiolytic, reduce the frequency of postoperative nausea (25% vs. 50%; p = 0.03), and increase patient satisfaction compared to placebo in adults. Midazolam premedication has also been shown to reduce the dose of propofol and the incidence of apnoea during propofol anaesthesia.
Literature data to characterise efficacy in children and adolescents with the posology and administration route specified in the product information has not been provided and the indication has therefore been restricted to adults.

- *As a sedative component in combined anaesthesia.*
Sufficient literature data on efficacy as a sedative component in combined anaesthesia has been provided for adults.

• *Sedation in intensive care units*

Several randomized controlled trials where midazolam has served as the active comparator to propofol and dexmedetomidine. The studies provide sufficient support for efficacy of midazolam for sedation during intensive care.

In children

• *Conscious sedation before and during diagnostic or therapeutic procedures with or without local anaesthesia*

The indication is restricted to children aged 2 years and older.

• *Sedation in intensive care units*

Sufficient published study data covering children from 28 days to 16-year-olds supports an indication in this age range. The studies provide observations regarding development of tolerance and the need to titrate to effect. The studies also support the need to combine midazolam with morphine or fentanyl. The proposed modification of the wording of the indication is therefore in line with the data provided, and also in line with clinical experience.

Clinical safety

The provided literature overall provides a relevant characterisation of general safety concerns with midazolam. Its use requires careful titration to effect and preparedness to handle adverse respiratory impact. The potential adverse impact of concomitant use of opioids is well known. Circulatory effects are rare. The overall safety profile is considered well characterised.

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 Senozam.

Safety specification

Summary of safety concerns	
Important identified risks	-overdose -use in patients with renal impairment -use in patients with hepatic impairment -use in patients with respiratory depression -respiratory depression -apnoea -respiratory arrest -cardiac arrest -dependence -withdrawal -paradoxical reactions
Important potential risks	-use in patients less than 6 months (risk of airway obstruction and hypoventilation) -use in patients 6 months to 12 years (risk of hypoventilation) -tolerance -anterograde amnesia -interaction with alcohol -interaction with CNS depressants -interaction with opioids
Missing information	Not applicable.

Midazolam has been extensively used clinically for several decades. The safety profile is well characterized and well known to clinicians. Routine risk minimisation is suggested, and no additional risk minimisation activities are proposed by the applicant, which is endorsed. In line with the intentions of GVP module V (rev. 2) the RMS has proposed important identified risks, important potential risks, and missing information can be removed from the summary of safety concerns. This is in line with most midazolam IV products published on the CMDh website. The Applicant has despite this maintained the position to keep the above Summary of Safety Concerns. This issue is not further pursued by the RMS and the proposed Summary of Safety Concerns accepted.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

Routine risk minimisation is suggested and no additional risk minimisation activities are proposed by the applicant, which is endorsed.

Summary of the RMP

The submitted Risk Management Plan, version 0.2 signed 19 May 2022 is considered acceptable.

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the RMS;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

Periodic Safety Update Report (PSUR)

Active substance is currently listed in the published EURD list

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- In case the active substance will be removed in the future from the EURD list because the MAs have been withdrawn in all but one MS, the MAH shall contact that MS and propose DLP and frequency for further PSUR submissions together with a justification.

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 language used for the purpose of user testing the PL was English.

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.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The application for Senozam, 1 mg/ml, 5 mg/ml, Solution for infusion, was submitted according to Article 10a of Directive 2001/83/EC. The benzodiazepine midazolam has been on the market for more than 35 years and is the most common benzodiazepine used for procedural sedation.

The quality of the generic product, Senozam, is found adequate. There are no objections to approval of Senozam, 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.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Senozam, 1 mg/ml, 5 mg/ml, Solution for infusion was positively finalised on 2022-12-07.

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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)

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