COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sugammadex Sandoz 100 mg/ml solution for injection
(sugammadex sodium)

NL/H/5118/001/DC

Date: 19 August 2021

This module reflects the scientific discussion for the approval of Sugammadex Sandoz 100 mg/ml solution for injection. The procedure was finalised at 25 February 2021. 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 Sugammadex Sandoz 100 mg/ml solution for injection, from Sandoz B.V.

The product is indicated for reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: sugammadex is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged 2 to 17 years.
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 Bridion 100 mg/ml solution for injection which has been registered in the EEA by Merck Sharp & Dohme B.V. since 25 July 2008 by a centralised procedure (EU/1/08/466).

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Croatia, Czech Republic, Finland, Germany, Greece, Ireland, Italy, Poland, Portugal, Romania, Slovenia, Spain 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

Sugammadex Sandoz is a clear and colourless to slightly yellow-brown solution for injection, practically free from visible particles. The pH is between 7.0 and 8.0 and osmolality is between 300 and 500 mOsmol/kg. 1 ml contains sugammadex sodium equivalent to 100 mg sugammadex.

The solution for injection is packed in clear tubing glass vials made of type I hydrolytic resistance with a grey bromobutyl rubber stopper with fluoropolymer coating. The rubber stopper is sealed with a silver aluminum cap with a salmon flip-off plastic component.

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

II.2 Drug Substance

The active substance is sugammadex sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.) or the United States Pharmacopeia. Sugammadex sodium is a white to off white powder. It is practically insoluble in acetonitrile, dimethyl sulfoxide (DMSO), methanol, ethanol, N,N-dimethylformamide and very soluble in water and aqueous solutions at different pH. The substance shows polymorphism (including amorphism) but this is considered to be of no significance for this product due to its high solubility in water and the fact that drug product is in the form of aqueous solution.

The Active Substance Master File (ASMF) procedure is used for the active substance. The main objective of the ASMF procedure, commonly known as the European Drug Master File (EDMF) procedure, is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the applicant or marketing authorisation holder (MAH) to take full responsibility for the medicinal product, the quality and quality control of the active substance. Competent Authorities/EMA thus have access to the complete information that is necessary to evaluate the suitability of the use of the active substance in the medicinal product.

Manufacturing process

The manufacturing process consists of five stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised.

Quality control of drug substance

The active substance specification is considered adequate to control the quality and meets the requirements of the ICH guidelines. The specification of the active substance is acceptable. The limits for specified, unspecified and total impurities have been set and are acceptable. The drug product manufacturer has controlled active substance batch data and is provided. The level of impurities, content of sodium and assay is within specification's limits. No decrease of assay or significant increase of impurities have been observed.

Stability of drug substance

The active substance is fully tested to ensure compliance with its specification immediately prior to its use in manufacture of the product. Sugammadex sodium is generally very stable at accelerated and long-term conditions and no specific degradational trends are being observed. Stability studies according to ICH are performed by active substance manufacturer. The re-test period of 24 months could be granted based on data provided. According to results of photostability studies the active substance is photostable.

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. Quality by design principles

are applied in the development of the product formulation and the manufacturing process, i.e. Quality Target Product Profile was established and critical material attributes, which can have potential impact on critical quality attributes of the drug product, were investigated throughout development process. Risk ranking is not presented and no design space is claimed. The development of the product has been presented in detail. General properties of the drug substance have been described satisfactorily. Excipients have been chosen to resemble those of the originator product. The developed product is qualitatively and quantitatively identical to the reference product Bridion. Essential similarity with the originator product Bridion is based on comparison of physico-chemical characteristics.

Manufacturing process

The manufacturing process has been validated according to relevant European/ICH guidelines. Factorisation is proposed to ensure claimed assay content. Calculation formula is provided. A flow chart of manufacturing process is presented indicating manufacturing steps, used materials and performed controls. Each step of manufacturing process is described, ranges of process parameters are indicated. The process consists of a simple preparation of a bulk solution, followed by filtration, filling and subsequent terminal sterilisation; it is considered a standard process. Proposed holding times were confirmed during manufacturing process validation and in-use photostability studies. Process validation data on the product have been presented for six batches in accordance with the relevant European guidelines.

Control of excipients

Water for injection is used as solvent and sodium hydroxide and/or hydrochloric acid may be added to adjust pH. All excipients are of pharmacopoeial quality. 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 appearance, identification, color and clarity of solution, osmolality, extractable volume, pH of solution, assay degradation products, uniformity of dosage units, particulate matter, foreign visible particles, sterility and bacterial endotoxins. 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 three batches for each presentation from the proposed production site have been provided, demonstrating compliance with the specification. The MAH has provided comprehensive risk assessment on potential presence of nitrosamine impurities. All potential sources listed in the EMA document (now EMA/409815/2020, formerly EMA/CHMP/428592/2019 Rev.3) have been adequately addressed; no risks are identified.

Stability of drug product

Stability data on the product have been provided for six batches, three for each presentation stored at 40°C/75% RH (6 months), 30°C/75% RH (12 months) and 25°C/60% RH (12 months) in accordance with applicable European guidelines. On basis of the data submitted, a shelf

life was granted of 24 months. Photostability testing was performed in accordance to the recommendations of ICH guideline Q1B on the drug product outside secondary packaging. For samples exposed outside of secondary packaging, a significant increase in degradation products was observed. Total of impurities increased accordingly, but was still within specification limits. The labelled storage conditions are "Keep the vial in the outer carton in order to protect from light".

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 Sugammadex Sandoz has a proven chemical-pharmaceutical quality. Sufficient controls have been laid down for the active substance and finished product.

The following post-approval commitments were made:

- The MAH commits that the proposed shelf-life limits of identified impurities will be re-evaluated when more stability data will be available. A variation is only foreseen when the stability data warrants a change to the dossier
- The MAH commits that proposed shelf-life limit for total assay will be re-evaluated when more stability data will be available. A variation is only foreseen when the stability data warrants a change to the dossier.

III. NON-CLINICAL ASPECTS

III.1 Ecotoxicity/environmental risk assessment (ERA)

Since Sugammadex Sandoz 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 Bridion 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

Sugammadex sodium 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

Sugammadex Sandoz 100 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 authorised reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Sugammadex Sandoz 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 Sugammadex Sandoz.

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

Important identified risks	- Delayed onset time or inufficient neuromuscular blockade at re-treatment with steroidal neuromuscular blocking agent - Neuromuscular block prolonged (delayed recovery) - Re-occurrence of neuromuscular blockade

	- Anesthetic complication/Light anesthesia - Use of suggamadex in patients with renal impairment
Important potential risks	- Drug hypersensitivity - Capturing interactions - Displacement interactions
Missing information	- Effect on values for laboratory parameters of blood coagulation time (aPTT, PT(inr), PT) - Exposure in infants and neonates - Exposure in pregnancy - Excretion of sugammadex in human milk

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 Bridion. No new clinical studies were conducted. Bioequivalence studies were not required, as the proposed product is a aqueous solutions to be used for intravenous (parenteral) injection. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The MAH submitted a justification for not performing a user test: the wording will be identical to the originator's PL text , the quality of the innovator's Pl text and the lay out that will follow the known 'house-style' of Sandoz. The latter was approved in several readability tests. Further to the argumentation provided by the MAH, this product will used only in a hospital setting: performing a user test will not lead to any additional benefits. Considering the aforementioned aspects, the approach not to perform a user test, can be accepted.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sugammadex Sandoz 100 mg/ml solution for injection has a proven chemical-pharmaceutical quality and is a generic form of Bridion 100 mg/ml solution for injection. Bridion 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.

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 Sugammadex Sandoz with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 25 February 2021.

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