COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sugagelan 100 mg/ml solution for injection

(sugammadex)

NL/H/5555/001/MR

Date: 30 November 2022

This module reflects the scientific discussion for the approval of Sugagelan 100 mg/ml solution for injection. The procedure was finalised on 9 May 2022. 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 medicinal 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 Sugagelan 100 mg/ml solution for injection, from G.L. Pharma GmbH.

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.

The innovator product is Bridion 100 mg/ml solution for injection, which has been registered in the EEA by Merck Sharp & Dohme B.V. since 25 July 2008 via a centralised procedure.

This current product has been approved via a mutual recognition procedure (MRP). The national marketing authorisation for Sugagelan (RVG 128235) was granted in the Netherlands on 13 July 2021.

The concerned member state (CMS) involved in this procedure was Austria.

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

II. QUALITY ASPECTS

II.1 Introduction

Sugagelan is a clear, colourless to slightly yellow brown solution for injection, practically free from particles. The pH is between 7 and 8 and osmolality is between 300 and 500 mOsm/kg. 1 ml contains sugammadex sodium equivalent to 100 mg sugammadex.

The solution for injection is packed in colourless type I glass vial closed with a bromobutyl rubber stopper and aluminium cap with a coloured flip-top.

The excipients are: sodium hydroxide (to adjust pH) and/or hydrochloric acid (to adjust pH) and water for injection.

II.2 Drug Substance

The active substance is sugammadex, an established active substance but not described in the European Pharmacopoeia (Ph.Eur.). Sugammadex octasodium is a white to off-white powder, freely soluble in water and very slightly to slightly soluble in polar organic solvents. It is a chiral compound and possesses 40 asymmetric carbons, resulting form 8 linked glucose units. No information on polymorphism of the drug substance is provided. However, as the drug product is a solution for injection, this is not considered to be of relevance.

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 comprises of two consecutive 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. Batch analytical data demonstrating compliance with this specification have been provided for a sufficient amount of batches.

Stability of drug substance

Sugammadex octasodium is generally very stable at accelerated and long-term conditions and no specific degradational trends are being observed. Based on the provided stability data, the re-test period of 24 months with the storage condition "Store in its original packaging under inert atmosphere" is acceptable.

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 product was developed as a generic equivalent to Bridion. The drug product manufacturer applied quality by design concepts to develop a generic drug product that is therapeutically/pharmaceutically equivalent to the reference medicinal product. The quality target product profile was defined based on characterisation of the reference product, the properties of the drug substance and the intended patient population. Risk assessment was used throughout development to identify potentially high risk formulation and process variables, and to

determine which studies were necessary to achieve product and process understanding in order to develop a control strategy. Each risk assessment was then updated during or after development to capture the reduced level of risk based on knowledge gained through development. However, no design-space is claimed. The developed product is qualitatively and quantitatively identical to the reference product Bridion.

Manufacturing process

The manufacturing process has been validated according to relevant European guidelines. It is considered a standard process. The manufacturing process has been described in sufficient detail and adequate information on the sterilisation and depyrogenation of the packaging components is provided. Process validation data on the product have been presented for three batches in accordance with the relevant European guidelines.

Control of excipients

All excipients are commonly used in medicinal products and comply with their respective monographs in the Ph.Eur. 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, colour of solution, clarity of solution, pH of solution, osmolarity, extractable volume, particulate matter, identification, assay, impurities, 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 of six 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 six batches stored at 25°C/ 60% RH (12 months) and 40°C/75% RH (6 months). The batches were stored in accordance with the ICH guideline. In view of the provided stability data, the MAH proposed a 24 month shelf-life with the special storage condition “Keep the vial in the outer carton in order to protect from light.” for the drug product in the proposed container closure system. This is acceptable. After first opening and dilution chemical and physical in-use stability has been demonstrated for 48 hours at 2°C to 25°C. From a 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 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.

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 Sugagelan 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 Sugagelan 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 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

Sugagelan 100 mg/ml solution for injection is a parenteral formulation and therefore fulfils the exemption mentioned in the Guideline on the investigation of bioequivalence, 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 (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **). The quantitative composition of Sugagelan 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 Sugagelan.

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

Important identified risks	- Delayed onset time or insufficient neuromuscular blockade at re-treatment with steroidal neuromuscular blocking agent - Neuromuscular block prolonged (Delayed recovery) - Re-occurrence of neuromuscular blockade - Anaesthetic complication/ Light anaesthesia - Use 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 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. Risk management is adequately addressed. This generic 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 Bridion 100 mg/ml solution

for injection. 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

Sugagelan 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. 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 Sugagelan with the reference product, and have therefore granted a marketing authorisation. The mutual recognition procedure was finalised with a positive outcome on 9 May 2022.

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
NL/H/5555/1/IB/001	To extend the shelf-life of the finished product - As packaged for sale	Yes	30-9-2022	Approved	N/A