COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Sugammadex Aguettant 10 mg/mL and 50 mg/mL
solution for injection in pre-filled syringe
(sugammadex sodium)

NL/H/5597/001-002/DC

Date: 8 October 2024

This module reflects the scientific discussion for the approval of Sugammadex Aguettant 10 mg/mL and 50 mg/mL solution for injection in pre-filled syringe. The procedure was finalised on 2 August 2023. 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
EMA	European Medicines Agency
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
RMS	Reference Member State
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 Aguettant 10 mg/mL and 50 mg/mL solution for injection in pre-filled syringe from Laboratoire Aguettant.

The product is indicated for reversal of neuromuscular blockade induced by rocuronium or vecuronium in adults. For the paediatric population: the product is only recommended for routine reversal of rocuronium induced blockade in children and adolescents aged from 2 to 17 years.

A comprehensive description of the up-to-date indications and posology is given in the SmPC.

The marketing authorisation has been granted pursuant to Article 10(3) of Directive 2001/83/EC, which concerns a hybrid application, as the strength and pharmaceutical form of the new product and the reference product is different. The reference medicinal product is a solution for injection (glass vial) and contains 100 mg/mL of sugammadex in 2 and 5 mL vials while the drug product is a solution for injection in pre-filled syringe and contain respectively 10 mg/mL (prefilled syringe of 10 mL) and 50 mg/mL (prefilled syringe of 5 mL).

In this decentralised procedure, essential similarity is proven between the new product and the innovator product Bridion 100 mg/mL solution for injection, which has been registered in the EEA via a centralised procedure (EU/1/08/466) since 2008.

The concerned member states (CMS) involved in this procedure were Austria, Belgium, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Norway, Poland, Portugal, Romania, Spain and Sweden.

II. QUALITY ASPECTS

II.1 Introduction

Sugammadex Aguettant is a clear colourless to slightly yellow solution for injection, free from visible particles. It has a pH between 7.0 – 8.0 and an osmolality between 270 – 330 mOsm/kg.

The Sugammadex Aguettant 10 mg/mL pre-filled syringe contains 10 mL sugammadex sodium equivalent to 100 mg of sugammadex. Each mL of solution for injection contains sugammadex sodium equivalent to 10 mg sugammadex.

The Sugammadex Aguettant 50 mg/mL pre-filled syringe contains 5 mL sugammadex sodium equivalent to 250 mg of sugammadex. Each mL of solution for injection contains sugammadex sodium equivalent to 50 mg sugammadex.

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

10 mL of the Sugammadex Aguettant 10 mg/mL solution for injection is pre-filled in a 10 mL syringe (polypropylene), with plunger stopper (chlorobutyl) closed with a frangible obturator, without a needle, with a graduated self-adhesive transparent label (sub-graduations of 0.5 mL from 0 until 10 mL). An end-cap (polypropylene) protects the syringe tip.

50 mL of the Sugammadex Aguettant 50 mg/mL solution for injection is pre-filled in a 5 mL syringe (polypropylene), with plunger stopper (chlorobutyl) closed with a frangible obturator, without a needle, with a graduated self-adhesive transparent label (sub-graduations of 0.2 mL from 0 until 5 mL). An end-cap (polypropylene) protects the syringe tip.

The pre-filled syringe is individually packed in a transparent blister, in a cardboard box.

II.2 Drug Substance

The active substance is sugammadex sodium, an established active substance not described in the European Pharmacopoeia (Ph.Eur.). The active substance is a crystalline powder and is soluble in water. Polymorphism is not relevant as the drug product is a solution. The active substance has several stereogenic centres, all of which originate from the starting material.

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 three stages. Adequate specifications have been adopted for starting materials, solvents and reagents. The active substance has been adequately characterised and the manufacturing process is described in sufficient detail.

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. Batch analytical data demonstrating compliance with this specification have been provided for three full-scale batches.

Stability of drug substance

Stability data on the active substance have been provided for three production scale batches in accordance with applicable European guidelines. Based on the data submitted, a retest period could be granted of 12 months when stored under the stated conditions.

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 are explained. The pharmaceutical development of the product is acceptable.

Manufacturing process

The manufacturing process consists of bulk solution preparation, clarifying filtration, filling in syringes, blistering and terminal sterilisation. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for two full scale batches of each strength.

Control of excipients

The excipients comply with Ph. Eur. requirements. These specifications are acceptable.

Microbiological attributes

For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

In leachable studies, three leachables were found to be present above the Analytical Evaluation Threshold (AET). The maximum amount at which these leachables are present in the product are compared to the Permitted Daily Exposure (PDE) for the compounds, which results in sufficient safety margins. The PDE's are sufficiently high to provide an adequate safety margin.

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 identification, clarity, colour, extractable volume, pH, osmolality, sub-visible and visible particles, assay, related substances, functional tests for the syringe and microbiological controls. The release and shelf-life limits are identical, except for the total impurities. Limits in the specification have been justified and are considered appropriate for adequate quality control of the product. An adequate nitrosamines risk evaluation report has been provided. No risk for presence of nitrosamines in the drug product was identified.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data four full-scale 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 two production-scale batches of each strength stored at 25°C/ 40% RH (12 months) and 40°C/25% RH (6 months) in accordance with applicable European guidelines. Photostability studies were performed and showed that the product is not stable when exposed to light. On basis of the data submitted, a shelf life was

granted of two years. The labelled storage conditions are “Do not freeze. Keep the blister 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 Aguettant 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 Sugammadex Aguettant is intended for generic substitution, this will not lead to an increased exposure to the environment. An environmental risk assessment was therefore not deemed necessary.

III.2 Discussion on the non-clinical aspects

This product is a hybrid formulation of Bridion which is available on the European market. Reference was made to the preclinical data obtained with the innovator product. A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which was 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. No bioequivalence study was submitted by the MAH, since the proposed product

is an aqueous solution for intravenous injection, which is acceptable. A non-clinical and clinical overview was provided based on scientific literature.

IV.2 Pharmacokinetics

Pharmacodynamic, pharmacokinetic and toxicological properties of Sugammadex Aguettant are well known. As Sugammadex Aguettant is a widely used, well-known active substance, the MAH has not provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate. The non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is adequate.

Clinical Efficacy
The proposed indication in adults and paediatric subjects are in line with the reference product. The proposed recommended doses are also in line with the reference product and supported by the discussed literature. The MAH aligned the posology with that of Bridion.

Clinical Safety
The MAH discussed mainly data from Martindale 2022 and the Bridion SmPC, however additional and confirmative data is available in the literature studies submitted for efficacy. The main undesirable effects include cough, dysgeusia, nausea, vomiting, pain, hypotension, and headache. These are accurately described and included in the SmPC. Also use in special population is adequately covered in the SmPC in terms of safety

The proposed product are prefilled syringes with a 2x or 10x lower concentration than the reference product. Although, the product is administered by specialist in a controlled environment there is a risk of dosing errors as the strength of the proposed and reference products are not identical.

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 Aguettant.

The product is a prefilled syringe with a volume of 10mL or 5mL, corresponding to a max dose of 100 mg and 250 mg, whereas the reference product Bridion contains 200 and 500 mg per vial. Therefore, in certain case, two consecutive injections of Sugammadex Aguettant might be required. Given the PK/PD properties of Sugammadex and the fact that consecutive boluses can be administered shortly after each other with the ready to use prefilled syringes, a difference in efficacy between the originator product and Sugammadex Aguettant is not expected for both indications; routine as well as immediate reversal following rocuronium or vecuronium blockade.

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

Important identified risks	None
Important potential risks	None
Missing information	None

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

No bioequivalence study was submitted by the MAH, since the proposed product is an aqueous solution for intravenous injection, which is acceptable.

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 language used for the purpose of user testing the PL was English.
The test consisted of: a pilot test with 4 participants, followed by two rounds with 10 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 package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Sugammadex Aguettant 10 mg/mL and 50 mg/mL solution for injection in pre-filled syringe have a proven chemical-pharmaceutical quality and are hybrid forms 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 aqueous solutions for intravenous injection (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 Sugammadex Aguettant with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 2 August 2023.

Literature References

Martindale: Sugammadex. The Complete Drug Reference (online). Sweetman SC (ed), London: Pharmaceutical Press. 2021. [Accessed 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
-	-	-	-	-	-