COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rocuroniumbromide Aguettant 10 mg/ml, solution for injection in pre-filled syringe (rocuronium bromide)

NL/H/5559/001/DC

Date: 28 February 2025

This module reflects the scientific discussion for the approval of Rocuroniumbromide Aguettant 10 mg/ml, solution for injection in pre-filled syringe. The procedure was finalised on 17 May 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 Rocuroniumbromide Aguettant 10 mg/ml, solution for injection in pre-filled syringe, from Laboratoire Aguettant.

The product is indicated:

- for use in adult and children from 2 years of age, as an adjunct to general anaesthesia, to facilitate tracheal intubation during routine induction and to achieve general muscle relaxation during surgical procedures.
- for use in adults to facilitate tracheal intubation during rapid induction and as an adjunct in intensive care to facilitate tracheal intubation and mechanical ventilation, for short term use.

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.

This decentralised procedure concerns a hybrid application claiming essential similarity with the innovator product Esmeron 10 mg/ml solution for injection from Merck Sharp Dohme B.V., which has been registered in the Netherlands by the national procedure RVG 16946 since 06 April 1994. The current Reference Member State (RMS) of the reference is the Netherlands, justification to use this reference is based on RMS's own files. The reference information was circulated during the validation period. The proposed product differs from the reference medicinal product in the pharmaceutical form (a solution for injection in a pre-filled syringe instead of solution for injection (glass vial)).

The drug product is an integral drug-device combination which is administered intravenously. Rocuronium bromide is a non-depolarising neuromuscular blocking agent with a short onset time. It has all pharmacological properties characteristic of this class of medicines (curariform). It competitively blocks the cholinergic nicotinic receptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine. Rocuronium should only be administered by, or under supervision of, an experienced physician familiar with the action and use of these agents. The dosage should be determined individually for each patient. The method of anaesthesia used and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicinal products administered concomitantly and the patient's condition must be taken into account when determining the dose.

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

II. QUALITY ASPECTS

II.1 Introduction

Rocuroniumbromide Aguettant 10 mg/ml a clear colourless to pale brown-yellowish solution for injection with a pH value between 3.8 and 4.2 and an osmolality value between 270 and 330 mOsm/kg. 1 mL of the solution contains 10 mg rocuronium bromide as active substance. The product is presented in a 5 mL pre-filled syringe, each syringe contains 50 mg rocuronium bromide.

The excipients are sodium acetate trihydrate (E262), sodium chloride, glacial acetic acid (for pH adjustment) (E260) and water for injection.

The drug product is an integral drug-device combination. 5 mL of the injection solution is presented in a pre-filled syringe (polypropylene), with plunger stopper (chlorobutyl), without needle, with a graduated self-adhesive transparent label (sub graduations of 0.2 mL, from 0 to 5 mL). An endcap (polypropylene) protects the syringe tip. The pre-filled syringe is individually packed in a transparent blister packed in a cardboard box.

II.2 Drug Substance

The active substance is rocuronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). The active substance is a slightly hygroscopic powder and is freely soluble in water and anhydrous ethanol. Rocuronium bromide exhibits isomerism. However, the manufacturing process applied by the drug substance manufacturer does not allow the formation of stereoisomers. Because the drug product is a solution, polymorphism of rocuronium bromide is not relevant.

The CEP procedure is used for the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the Ph.Eur.

<u>Manufacturing process</u>
A CEP has been submitted; therefore no details on the manufacturing process have been included.

<u>Quality control of drug substance</u>
The active substance specification is in line with the Ph. Eur. monograph and the CEP, with additional requirements for microbial contamination and bacterial endotoxins. The drug substance specification is acceptable in view of the route of synthesis and the various

European guidelines. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance
The retest period for the active substance is 5 years, when stored under the stated conditions. Assessment thereof was part of granting the CEP (and has been granted by the EDQM).

II.3 Medicinal Product

Pharmaceutical development
The drug product is an integral Drug Device Combination product (DDC), a pre-filled syringe (PFS) or the delivery system which is administered intravenously. This integral DDC is composed of the following elements:

- The medicinal product part of the DDC: the solution for injection of Rocuronium bromide 10 mg/mL
- The device constituent of the DDC: the 5 mL syringe composed of a barrel and a cap, a plunger stopper, a plunger rod, a barrel lubricant and a syringe label.

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 explained. The excipients and packaging are usual for this type of dosage form. The aim of the development was to develop a drug product solution similar to the reference product but in a different pharmaceutical form (a solution for injection in a pre-filled syringe instead of a solution for injection in glass vial). As the product is intended for parenteral use, the finished product is sterile and meets the usual Ph. Eur. for sterility and bacterial endotoxins. Sufficient information is provided on biocompatibility of the pre-filled syringe, extractables and leachables studies. The pre-filled syringe includes a graduation marking therefore, requirements of the EMA Q&A on graduation of measuring devices for liquid dosage forms are applicable. The data submitted on these aspects meets the requirements and demonstrates the suitability of the graduation of the pre-filled syringe for the intended use, the effectiveness of the adhesive / label system under normal conditions of storage and the dose accuracy. Overall, the pharmaceutical development of the product has been adequately performed.

Manufacturing process
The manufacturing process is a standard process. Details on the in-process controls and process parameters have been provided. During the process validation, the durations of holding times/processing times were also validated on three validation batches. The proposed holding times have been found acceptable. The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product has been presented for three production scale batches of the lower industrial batch size. A process validation scheme is provided for the upper batch size.

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

Microbiological attributes

The drug product is intended to be administered as parenteral (intravenous) solution for injection. It is a sterile product and does not contain any preservative system. The drug product meets the usual Pharmacopoeia requirements for sterility and bacterial endotoxins. The suitability of the sterilisation method used and the integrity of the syringe and blister were adequately demonstrated.

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 drug product description, appearance of solution, identification, clarity, colour, extractable volume, pH, osmolality, (sub)visible particles, assay, impurities, plunger activation and gliding force, syringe integrity, delivered dose accuracy, blister integrity, readability of the label, sterility solution, external sterility of the syringe and endotoxins. The release and shelf-life limits are identical except for 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 from three production scale batches of the lower batch size from the proposed production site(s) have been provided, demonstrating compliance with the specification.

Stability of drug product

Stability data on the product have been provided for three production scale batches, stored at 5°C ± 3°C (18 months), 25°C ± 2°C / 60% ± 5% RH (6 months) and after 12 weeks exposure at 30°C ± 2°C / 35% ± 5% RH. The stability was tested in accordance with ICH stability guideline. The batches were stored in the proposed packaging. Photostability studies were performed in accordance with ICH recommendations and showed that the product is stable when exposed to light. All stability results comply with the proposed specifications. A clear increase in one impurity (and correspondingly total impurities) was observed for all tested conditions except during photostability testing, although all results were still compliant with the specification. Exceptional storage out of the fridge stability studies were performed. On basis of the data submitted, a shelf life was granted of 3 years. The labelled storage conditions are:

- After opening, the medicinal product must be used immediately.
- This medicinal product may be stored for a short period at temperatures not exceeding 30°C for a period of maximum 12 weeks. In all cases, once initially removed from refrigerated storage, the medicinal product should be discarded after 12 weeks. The product should not be placed back into the refrigerator once it has been kept outside. The storage period must not exceed the shelf-life.
- Store in a refrigerator (2°C - 8°C). Do not freeze. For storage conditions after first opening of the medicinal product, see section 6.3.

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 Rocuroniumbromide Aguettant 10 mg/ml 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 Rocuroniumbromide Aguettant 10 mg/ml 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

As rocuronium bromide is a widely used, well-known active substance with known pharmacodynamic, pharmacokinetic and toxicological properties, the MAH has not provided additional studies. Instead, an adequate 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

Rocuroniumbromide Aguettant 10 mg/ml 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

The pharmacokinetics of Rocuronium 10 mg/ml solution for injection is well known. Referring to the Note for Guidance on the investigation of bioequivalence CPMP/QWP/EWP/1401/98 Rev. 1, no clinical studies are needed to support this application.

IV.3 Pharmacodynamics/ Clinical efficacy / Clinical safety

The application contains an adequate review of published clinical data. The reference formulation Esmeron 10 mg/ml and the test formulation of the Rocuronium Aguettant 10 mg/ml solution for injection are aqueous solutions and excipients are not expected to affect the distribution of rocuronium. Therefore, no bioequivalence studies are required.

IV.4 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 Rocuroniumbromide Aguettant 10 mg/ml. At the time of approval, the most recent version of the RMP was version 03 dated 10 March 2023.

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.5 Discussion on the clinical aspects

The application contains an adequate review of published clinical data. No bioequivalence study has been performed. The MAH has adequately justified why there is no need to generate additional clinical data. Based on the submitted data, therapeutic equivalence between the product and the reference was demonstrated. Risk management is adequately addressed. This hybrid medicinal product can be used instead of the reference product. The clinical aspects of this product are approvable.

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

Rocuroniumbromide Aguettant 10 mg/ml, solution for injection in pre-filled syringe has a proven chemical-pharmaceutical quality and is a hybrid form of Esmeron 10 mg/ml solution for injection. Esmeron is a well-known medicinal product with an established favourable efficacy and safety profile. Rocuroniumbromide Aguettant differs from Esmeron in the pharmaceutical form (a solution for injection in a pre-filled syringe instead of solution for injection (glass vial). The suitability of the pre-filled syringe for his product has been adequately demonstrated.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary. A biowaiver has been granted.

The application was discussed at the Board meeting 1027 held on 4 May 2023, the following was discussed:

On day 180 of the application, it had not yet been demonstrated that the analytical methods used for the quality control of the final product and therefore also the stability, are suitable and adequately validated. The data submitted on these aspects was not considered acceptable and a justification, supplemented with additional data, was required. As requested, the additional data was submitted by the MAH. Based on the data, the major objection was considered resolved.

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 Rocuroniumbromide Aguettant 10 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 17 May 2023.

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/5559/001 /IB/001	Change in the (invented) name of the medicinal product: - For Nationally Authorised Products.	Yes	13-12-2023	Approved	N.A.
NL/H/5559/001 /P/001	Art. 61(3): review of the clusters of multilingual packaging due to space constraint on the label.	Yes	21-12-2023	Approved	N.A.
NL/H/5559/001 /IB/002	Change in the shelf-life or storage conditions of the finished product: - Extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	3-4-2024	Approved	N.A.
NL/H/5559/001 /IB/003	Change in the shelf-life or storage conditions of the finished product: - Extension of the shelf life of the finished product. As packaged for sale (supported by real time data).	Yes	19-9-2024	Approved	N.A.
NL/H/5559/001 /IA/004	Change to in-process tests or limits applied during the manufacture of the finished product: - Tightening of in-process limits.	No	21-10-2024	Approved	N.A.

NL/H/5559/001 /IA/006	Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient: European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. - Updated certificate from an already approved manufacturer.	No	15-01-2025	Approved	N.A.
NL/H/5559/001 /IA/008	Change to importer, batch release arrangements and quality control testing of the finished product: Replacement or addition of a manufacturer responsible for importation and/or batch release. - Not including batch control/testing.	Yes	20-2-2025	Approved	N.A.