COLLEGE TER BEOORDELING VAN GENEESMIDDELEN

Public Assessment Report

Scientific discussion

Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion

(rocuronium bromide)

NL/H/4555/001/DC

Date: 20 February 2020

This module reflects the scientific discussion for the approval of Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion. The procedure was finalised at 18 December 2019. For information on changes after this date please refer to the 'steps taken after finalisation' at the end of this PAR.

List of abbreviations

CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CMS	Concerned Member State
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 Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion from Noridem Enterprises Limited.

The product is indicated for use in adult and paediatric patients (from term neonates to adolescents [0 up to 18 years]), as an adjunct to general anaesthesia to facilitate tracheal intubation during routine induction and to achieve general muscle relaxation during surgical procedures.
In adults, the product is also used 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 indications and posology is given in the SmPC.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Esmeron 10 mg/ml solution for injection (NL licence RVG 16946) which has been registered in the Netherlands by N.V. Organon since 6 April 1994.

The concerned member states (CMS) involved in this procedure were Belgium, Cyprus, Germany, Greece, France, Ireland, Italy, 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

Rocuroniumbromide Noridem is a solution for injection/infusion with pH 3.8 – 4.2.

Each ml of solution contains 10 mg rocuronium bromide.

The solution is packed in: 6 ml Type I glass vials (containing 5 ml of solution) with rubber stopper & aluminum flip off cap and Type I glass ampoules with capacity ≥ 5 ml (containing 5 ml of solution).

The excipients are: sodium acetate trihydrate, sodium chloride, acetic acid glacial, water for injections.

II.2 Drug Substance

The active substance is rocuronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.). It is an almost white or pale yellow, slightly hygroscopic powder. Rocuronium bromide is freely soluble in water, very soluble in methylene chloride, and freely soluble in anhydrous ethanol.

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.

Manufacturing process

A CEP has been submitted; therefore no details on the manufacturing process have been included.

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. supplemented with additional tests which are listed in the CEP. Batch analytical data demonstrating compliance with this specification have been provided for three batches.

Stability of drug substance

The active substance is stable for three 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 product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines. The main objective of the formulation development work was to develop a sterile solution for injection comparable in performance to the reference product. The proposed drug product has the same qualitative and quantitative composition as the reference product. The development of the manufacturing process for the finished product has been described. The MAH performs terminal sterilisation of the drug product. Compatibility with all proposed diluents has been demonstrated. Pharmaceutical development has been adequately performed.

Manufacturing process

The product is manufactured using conventional manufacturing techniques. Manufacturing of the solution for injection includes compounding, filtration, filling of solution in ampoules

and final sterilisation by moist heat. The manufacturing processes and in process controls testing have been described in sufficient details. The proposed controls are sufficiently described and suitable for monitoring critical steps of manufacture and quality of finished product.
The manufacturing process has been validated according to relevant European/ICH guidelines. Process validation data on the product have been presented for three batches packed into vials and three batches packed into ampoules in accordance with the relevant European guidelines. Process validation for full-scale batches will be performed post authorisation.

Control of excipients
All excipients comply with the requirements of their respective Ph.Eur. monographs. 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, pH, osmolality, extractable volume, assay, related substances, particulate contamination, bacterial endotoxins, sterility and uniformity of dosage units. 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 from the proposed production site have been provided, demonstrating compliance with the specification.

Stability of drug product
Stability studies (at 5°C, 25˚C/60% RH, and 30˚C/65% RH) have been conducted on six batches of the finished product (three batches in glass ampoules and three batches in glass vials). Based on the data submitted, a shelf-life was granted of 30 months for the glass ampoules and 24 months for the glass vials, when stored at 2°C – 8°C. Photostability studies show that the product is photostable.

From a microbiological point of view, the product should be used immediately after dilution. 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 – 8˚C, unless dilution has taken place in controlled and validated aseptic conditions.

Microbiological attributes
The finished product is a sterile preparation for parenteral use. The product is filled in sterilised glass vials which are closed with sterilised rubber closures and sealed with sterilised aluminium flip-off caps. At release, the drug product is tested to the requirement as laid down in the Ph.Eur. monograph for parenteral preparations (Ph.Eur. 2.6.1 – Sterility, Ph.Eur. 2.6.14 - Bacterial endotoxins).

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 Noridem 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 Noridem 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 Esmeron 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

Rocuronium bromide 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

Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion 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 authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion 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 Rocuroniumbromide Noridem.

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

Important identified risks	--
Important potential risks	--
Missing information	--

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 Esmeron. No new clinical studies were conducted. The MAH demonstrated that the pharmacokinetic profile of the product is similar to the pharmacokinetic profile of this reference product. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

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 test consisted of: a pilot test with two participants, followed by two rounds with ten 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 PL of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

Rocuroniumbromide Noridem 10 mg/ml solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Esmeron 10 mg/ml solution for injection. Esmeron is a well-known medicinal product with an established favourable efficacy and safety profile.

Therapeutic equivalence with the reference product has been shown by the comparison of the dosage form, qualitative and quantitative composition and the results of *in vitro* studies on the relevant quality attributes. 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 Rocuroniumbromide Noridem with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 18 December 2019.

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