CBG MEB

Public Assessment Report

Scientific discussion

Vecuronium SUN 10 mg powder for solution for injection/infusion

(vecuronium bromide)

NL/H/3632/001/DC

Date: 17 March 2017

This module reflects the scientific discussion for the approval of Vecuronium SUN 10 mg powder for solution for injection/infusion. The procedure was finalised on 1 September 2016. 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
OOS	Out of Specification
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 Vecuronium SUN 10 mg powder for solution for injection/infusion from Sun Pharmaceutical Industries Europe B.V.

The product is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery in adults, neonates, infants, children and adolescents.
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 Norcuron 10 mg powder for solution for injection (NL License RVG 11243), which was registered in the Netherlands by N.V. Organon on 30 March 1988. The product was withdrawn from the Dutch market in 2014 but is still available on the European market.

The concerned member states (CMS) involved in this procedure were Germany 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

Vecuronium SUN 10 mg is a white to off-white lyophilised powder.

The pH of the reconstituted solution is between 3.5 and 4.5, and osmolality is between 150 and 250 mOsm/kg.

The powder is packed in 10 ml colourless tubular glass vial with grey bromobutyl rubber stopper sealed with red flip off aluminium seal.

The excipients are citric acid anhydrous, disodium phosphate anhydrous, mannitol (E421), sodium hydroxide (for pH adjustment), phosphoric acid concentrated (for pH adjustment).

II.2 Drug Substance

The active substance is vecuronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.) and United States Pharmacopoeia (USP). Vecuronium bromide is a white or creamy white crystalline powder/crystals and slightly soluble in water and acetone, and sparingly soluble in alcohol. The drug substance is dissolved during manufacturing, hence polymorphic form and particle size are not considered relevant. Moreover, vecuronium bromide does not show polymorphism.

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
Vecuronium bromide is manufactured following a six step synthesis procedure. The final pharmacological activity is given in the sixth step of the synthesis process. The detailed manufacturing description is included in the ASMF. The choice of the starting material is justified.

Quality control of drug substance
The drug substance specification has been established by the ASMF-holder and was adopted by the MAH. The specification is based on the currently published Ph.Eur. and USP monographs, and additional in-house tests. Batch analytical data demonstrating compliance with the drug substance specification have been provided for three production scaled batches.

Stability of drug substance
Stability data on the active substance have been provided for multiple batches, manufactured using the regular process, as well as the second crop process. The batches were stored at 25°C/60%RH (up to 60 months) and at 40°C/75%RH (6 months). The batches were stored in the commercial packaging. Results of the accelerated and long term storage conditions showed no specific up or downward trends in any of the parameters tested. All results are within specification. The re-test period of 60 months with no specific storage restrictions is acceptable.

II.3 Medicinal Product

Pharmaceutical development
The development of the product has been described, the choice of excipients is justified and its functions explained. It was aimed to develop a product equivalent to the reference product Norcuron 10 mg. No bioequivalence studies have been performed; they are also not considered necessary. The drug product differs from the innovator product with respect to osmolality of the reconstituted solution. Osmolality of the reconstituted test product is below 250 mOsm/kg, which is hypo-osmolar (osmolality normal human serum = 289 mOsm/kg), while the reference product is isotonic. The MAH argued that vecuronium is mainly distributed in extracellular fluid compartment, and acts on nicotinic receptors expressed on the cell membrane. Therefore, the difference in the osmolality between the test and the reference product on permeability of vecuronium is not relevant. Differences in osmolality are acceptable from a quality, as well as a clinical point of view.
Manufacturing process development has been described. Based on the provided information, filtration in combination with aseptic processing is considered acceptable as the sterilisation method. Compatibility studies with diluents mentioned in the SmPC have been performed. Compatibility was demonstrated with water for injections, 5% glucose, 0.9% sodium chloride, lactated Ringer's solution, 5% glucose in 0.9% sodium chloride, 5% glucose in Ringer's lactate solution, haemaccel and 5% dextran-40 in 0.9% NaCl solution.

Manufacturing process
The manufacturing process consists of the following steps: sterilisation of the packaging materials and equipment, preparation of bulk solution, aseptic filtration and aseptic filling, followed by freeze drying and vial capping. Since the process is considered a non-standard manufacturing process, validation on full scale is necessary prior to approval. The manufacturing process has been adequately validated according to relevant European guidelines for two batch sizes.

Control of excipients
All excipients are tested in accordance with their respective Ph.Eur. monograph. These specifications are acceptable.

Quality control of drug product
The product specification includes tests for description, identification, identification by chemical test, water content, osmolality, clarity and completeness of solution, reconstitution time, pH of constituted solution, absorbance, transmittance, uniformity of dosage units, related substances, assay of vecuronium bromide, assay of mannitol, bacterial endotoxin, particulate contamination and sterility. Release and end-of-shelf-life specification are identical, except for related substances.
All limits are acceptable. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site have been provided on three exhibit batches and on three full scale batches, demonstrating compliance with the release specification.

Stability of drug product
Stability data on the product have been provided for three pilot scale batches and three commercial scale batches stored at 25°C/60%RH (24 months) and 40°C/75%RH (6 months). The conditions used in the stability studies are according to the ICH stability guideline. The batches were stored in glass vial type 1 with grey rubber stopper.
Due to some fluctuations in assay values, no clear trend can be observed under long-term storage conditions but one out of specification (OOS) result is observed at 18 months. As this batch tests within specification at 24 months, and as five other batches test within specification at 18 months, the OOS result is considered an outlier. Under accelerated conditions out of specification results are obtained due to an increase in a related compound, and hence total impurities. In view of the results, the product should not be stored above 25°C. Photostability studies in line with the NfG on Photostability testing have been performed. The product is not susceptible to light.
In view of the provided stability results, a shelf-life of 18 months can be accepted.

In-use stability testing showed that all tested parameters remained stable after dilution with the diluents as mentioned in the SmPC to a solution of 1.0 mg/ml upon 24 hours of storage at 2-8°C and 15-25°C. The reconstituted vecuronium bromide solution, when injected in the line of running infusions was found to be stable and compatible with the IV set over a period of 2 hours.

Specific measures for 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 Vecuronium SUN 10 mg powder for solution for injection/infusion 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 Vecuronium SUN 10 mg 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 Norcuron, 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

Vecuronium 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

Vecuronium SUN 10 mg is a parenteral formulation, a lyophilized powder for solution for intravenous administration, 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 composition of Vecuronium SUN qualitatively identical with the innovator, and the used excipients do not interact with vecuronium. 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 Vecuronium SUN.

- Summary table of safety concerns as approved in RMP

Important identified risks	• Hypersensitivity/anaphylactic reactions Prolonged/residual Neuromuscular block • Altered neuromuscular block • Local injection site reactions
Important potential risks	• Cardiovascular events • Rhabdomyolysis
Missing information	• Use in pregnancy • Use in lactation • Use in preterm newborn infants • Continuous infusion in paediatric patients

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 Norcuron. No new clinical studies were conducted. The MAH demonstrated equivalence based on comparative chemical-pharmaceutical data. Risk management is adequately addressed. This generic medicinal product can be used instead of the reference product.

V. USER CONSULTATION

The package leaflet 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 two rounds. Overall, each and every question meets criterion of 81% correct answers. The results show that the package leaflet 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

Vecuronium SUN 10 mg powder for solution for injection/infusion has a proven chemical-pharmaceutical quality and is a generic form of Norcuron 10 mg powder for solution for injection. Norcuron 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 Vecuronium SUN with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finalised with a positive outcome on 1 September 2016.

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached