CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rocuronium Strides 10 mg/ml, solution for injection or infusion
Strides Arcolab International Ltd., United Kingdom

rocuronium bromide

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/2432/001/DC
Registration number in the Netherlands: RVG 110257

17 October 2013

Pharmacotherapeutic group:	muscle relaxants, peripherally acting agents, other quaternary ammonium compounds
ATC code:	M03AC09
Route of administration:	intravenous
Therapeutic indication:	adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction, to provide skeletal muscle relaxation during surgery; adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation
Prescription status:	prescription only
Date of authorisation in NL:	23 September 2013
Concerned Member States:	Decentralised procedure with AT, DE, DK, FI, IT, PL, DE, UK
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Rocuronium Strides 10 mg/ml, solution for injection or infusion from Strides Arcolab International Ltd. The date of authorisation was on 23 September 2013 in the Netherlands.

The product is indicated in adults and paediatric patients (from term neonates to adolescents 0 to < 18 years) as an adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery. In adults, rocuronium bromide is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

A comprehensive description of the indications and posology is given in the SPC.

Rocuronium bromide is an intermediate acting non-depolarising neuromuscular blocking agent with a fast onset, possessing all of the characteristic pharmacological actions of this class of medicinal products (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.
The ED90 (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0.3 mg per kg body weight.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator product Esmeron (NL License RVG 16946) which has been registered in the Netherlands by N.V. Organon since 1994. In addition, reference is made to Esmeron authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article <NN nn> of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the ‘original’ authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Rocuronium Strides 10 mg/ml is an aqueous solution for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current product can be used instead of its reference product.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for this product type at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is rocuronium bromide, an established active substance described in the European Pharmacopoeia (Ph.Eur.*). The active substance is an almost white or pale yellow powder, and is freely soluble in water. Rocuronium bromide has ten chiral centres. The drug substance is not known to exhibit polymorphism.

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 European Pharmacopoeia.

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

Quality control of drug substance
The drug substance specification is in line with the CEP, with additional requirements for methanol, foreign matter, bacterial endotoxins and microbial limits. The specification is acceptable in view of the route of synthesis and the various European guidelines.
Batch analytical data demonstrating compliance with the drug substance specification have been provided for two full-scale batches. This is acceptable since batch analytical data demonstrating compliance to the requirements of the CEP have been provided for a further four full-scale batches.

Stability of drug substance
Stability data on the active substance have been provided for three full-scale batches stored at -25°C to -15°C (12-18 months) and at 2 - 8°C (6 months). At accelerated conditions increases in related substances were observed. At long term conditions no specific trends were observed and all results remained with in specification limits. The other parameters tested remained relatively stable and within the proposed specification limits.
Based on the stability data provided the proposed re-test period of 12 months when stored in original package at -25°C to -15°C was granted.

** Ph.Eur. is an official handbook (pharmacopoeia) in which methods of analysis with specifications for substances are laid down by the authorities of the EU.*

Medicinal Product

Composition
Rocuronium Strides 10 mg/ml is a clear, colorless to yellow or orange solution with pH 3.8 to 4.2 and osmolality between 250 and 300 mOsmol/kg. Each ml of solution for injection or infusion contains 10 mg rocuronium bromide.

The product is packed in clear glass vials (Type I) with stopper (bromobutyl rubber) and yellow flip off aluminium seal. Each vial contains 5 ml of solution with 50 mg rocuronium bromide.

The excipients are: sodium acetate trihydrate, glacial acetic acid (for pH adjustment), sodium chloride, sodium hydroxide (for pH adjustment), water for injections.

Pharmaceutical development

The development of the product has been described, the choice of excipients is justified and their functions explained. The formulation was based on the formulation of the innovator. Two batches of the generic product have been compared to a batch of the innovator (Esmeron) with respect to appearance, identification, colour, light transmittance, pH, osmolality, related substances, assay. Differences were observed in colour, pH, osmolality and one impurity. The observed differences are not considered essential.

The main development studies were manufacturing process development and compatibility studies.

An overfill of 0.1 ml is used. Based on the batch analytical data of these batches, this overfill leads to compliance to the Ph.Eur. requirements for extractable volume.

The choice of sterilization method was changed from aseptic filtration to terminal sterilization, which is considered appropriate. The pharmaceutical development of the product has been performed adequately.

Manufacturing process

The manufacturing process is divided into the following steps: preparation of the bulk solution, filtration, filling and sterilisation. No process validation data have been provided of the proposed manufacturing process. However, a satisfactory process validation protocol has been provided. The product is manufactured using conventional manufacturing techniques. Process validation for full-scale batches will be performed post authorisation.

Control of excipients

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

Microbiological attributes

The drug product contains no antimicrobial preservative. Sterility is tested according to the Ph.Eur. in the final primary packaging. Additionally bacterial endotoxins are monitored in the drug product at release and in stability studies. Container closure integrity testing was performed as a non-destructive test to determine seal integrity of the closure (leak testing). Based on the results it was concluded that the container closure system adequately protects the drug product from microbial contamination.

Quality control of drug product

The product specification includes tests for appearance, identification, extractable volume, particulate contamination, sterility, bacterial endotoxins, light transmission, colour of solution, foreign matter, osmolality, pH, related substance, assay and allyl bromide. The release and shelf life limits are identical, except for one specific impurity and total impurities. The drug product specification is acceptable. The analytical methods have been adequately described and validated.

Batch analytical data has been provided of three pilot-scale batches sterilised by moist heat, demonstrating compliance to the drug product specification.

Stability of drug product

Stability data on the product has been provided for three full-scale batches, sterilised by filtration, stored at 2 - 8°C (18 months) and at 25°C/60% RH (6 months) in inverted position. The batches were stored in the proposed marketing packaging.

At both conditions increases were observed in one specific impurity. All other parameters tested remained relatively stable throughout the test period at both conditions. All results remained within specification limits.

As the provided stability data are of batches which were aseptically filtrated, no extrapolation of the stability data is considered acceptable. Based on the stability data provided a shelf life of 18 months at 2-8°C can be granted. Subsequently a shelf life of 12 weeks outside of the refrigerator at a temperature of up to 25°C for a maximum 12 weeks is applicable.

Compatibility/In-use stability

Stability data has been provided demonstrating that the product remains stable for 72 hours following dilution with 0.9% sodium chloride, 5% dextrose, 0.9% sodium chloride and 5% dextrose, lactated ringer solution, water for injection and heamaccel (0.5 - 2.0 mg/ml), when stored at 30°C.

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.2 Non-clinical aspects

This product is a generic formulation of Esmeron, which is available on the European market. 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.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of rocuronium bromide released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

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.

Rocuronium Strides 10 mg/ml aqueous solution for injection or 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 qualitative composition of Rocuronium Strides 10 mg/ml solution for injection or infusion is comparable to 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.

Risk management plan
Rocuronium bromide was first approved in 1994, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of rocuronium bromide can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. A detailed European Risk Management Plan is not necessary for this product. The MAH will however closely monitor and review the following reactions, as agreed during the latest PSUR worksharing for rocuronium:

- Cardiac arrest
- Bradycardia
- Anaphylaxis
- Rhabdomyolysis.

The review will be included in next PSUR.

Product information

SPC

The content of the SPC approved during the decentralised procedure is in accordance with that accepted for the reference product Esmeron.

Readability test

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 a pilot test with 4 participants, followed by two rounds with 10 participants each. The developed questionnaire contained 16 questions specific to rocuronium and 3 specific to the format of the package leaflet. The questions addressed all the key safety issues and concerns. Based on quantitative and qualitative results from all 3 rounds, the participants were able to correctly answer over 90% of the question asked. No revisions were suggested to the PIL.

Overall, it can be concluded that the readability test itself and the evaluation report are of an acceptable quality. There were sufficient questions about the critical sections. In the test it was easy to determine which results are linked to which conclusions. The conclusions are clear, concise and clearly presented. Furthermore, the following areas have been sufficiently covered: traceability, comprehensibility and applicability.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

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

Since both the reference and current product are intended as an aqueous solution for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. The SPC, package leaflet and labelling are in the agreed templates.

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 Rocuronium Strides 10 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 29 May 2013.
Rocuronium Strides 10 mg/ml, solution for injection or infusion was authorised in the Netherlands on 23 September 2013.

The date for the first renewal will be: 29 May 2018.

According to the EURD list, after July 2012 PSURs should be submitted for rocuronium containing products authorised under the legal basis of article 10(1) of directive 2001/83/EC as amended (generic authorisations). The PSUR cycle is 3 years and the next data lock point is 28 February 2016.

The following post-approval commitments have been made during the procedure:

Quality - medicinal product

- The MAH committed to perform process validation on the first three commercial scale batches.
- The MAH committed to conduct physiological solution compatibility studies at the end of shelf life of commercial batches.
- The MAH committed to continue the first three commercial batches on stability under long term conditions 5°C ± 3 °C for the proposed shelf life.
- The MAH committed to perform stability studies for three commercial batches which are manufactured by the new manufacturing method.
- The MAH committed to include one batch under long term storage conditions annually if manufactured.
- The MAH committed to perform stability studies of two batches at 2-8°C for 21 months followed by 3 months at 30°C, in order to claim a sequential shelf life of 12 weeks at 30°C in line with the innovator.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States

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