CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Rocuroniumbromide B.Braun 10 mg/ml solution for injection or infusion
B. Braun Melsungen AG, Germany

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/1073/001/DC
Registration number in the Netherlands: RVG 100155

9 September 2009

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, to provide skeletal muscle relaxation; adjunct in the intensive care unit (ICU) for short term use
Prescription status:	prescription only
Date of authorisation in NL:	23 July 2009
Concerned Member States:	Decentralised procedure with AT, BE, CZ, DE, EL, ES, FI, IE, IT, LU, PL, PT, SE, SK, 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 Rocuroniumbromide B.Braun 10 mg/ml solution for injection or infusion, from B. Braun Melsungen AG. The date of authorisation was on 23 July 2009 in the Netherlands.

The product is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction, to provide skeletal muscle relaxation, during surgery. It is also indicated as an adjunct in the intensive care unit (ICU) (e.g. to facilitate intubation), for short term use.

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

Rocuronium bromide is an intermediate acting, non-depolarizing 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 cholinergic receptors at the motor end-plate. This action is also antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.
The ED_{90} (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 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 10(1) 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 Rocuroniumbromide B.Braun 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.

No paediatric development programme has been submitted.

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.*). It is an almost white to slightly yellow powder, and is very soluble in water. Rocuronium bromide contains 10 chiral centres and complies to the criteria of specific optical rotation as described in the Ph.Eur.

Manufacture
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/EMEA 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.

Rocuronium bromide is prepared in a five-stage synthesis. Acetyl chloride and allyl bromide are used as alkylating substances. The potential genotoxicity of these substances have been adequately discussed and an appropriate limit for allyl bromide is included in the drug substance specification. The manufacturing process has been adequately described.

Specification
The drug substance specification is in line with the Ph.Eur. with adequate additional specifications for bromide content, acetic acid content, residual allyl bromide, residual solvents, microbiological purity, and endotoxins. The proposed set of specifications is regarded to be sufficient. Batch analysis results of 6 batches have been provided. All 6 batches comply with the specifications.

Stability
Stability data have been obtained for three pilot scale batches during storage at 25°C/60%RH and 5°C±3°C. The batches stored under the accelerated condition show unacceptable signs of instability within the first month. When stored under the long term conditions, with the exception of the total impurities that show a slight increase, all parameters remain stable. In view of the stability data the claimed re-test period of 9 months and storage conditions 5°C ± 3°C was granted.
The MAH committed to perform long term stability studies for three batches manufactured at a commercial scale batch size and to provide the results when available.

** 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
Rocuroniumbromide B.Braun contains as active substance 10 mg/ml of rocuronium bromide and is a clear, colourless to pale brownish-yellow solution.

The solution for injection or infusion is packed in colourless glass vials (type I) with chlorobutyl rubber stopper and aluminium cap. The vials contain 2.5 ml, 5 ml or 10 ml of solution.

The excipients are: water for injections, glacial acetic acid (for pH-adjustment), sodium chloride, sodium acetate trihydrate. All specifications comply with the respective Ph.Eur. monographs.

Pharmaceutical development
The development of the product is satisfactorily performed and explained. All components of the drug product are simple and commonly used, the submitted data provided is sufficient. The primary packaging materials are used routinely for parenteral preparations. All excipients comply with the Ph.Eur.

Manufacturing process
The manufacture of Rocuronium bromide 10 mg/ml is performed by dissolving the ingredients in the solvent, after which the pH is adjusted. After addition of the API, the pH of the solution is readjusted and the solution is filtrated and filled in vials. The filled vials are sterilised by steam.
Three validation batches were produced for the lower (2.5 ml) and the upper (10 ml) filling volume, in order to qualify the processing, filtration, filling and testing stages of Rocuronium bromide (bracketing). All

batches complied with the proposed release limits. Given the relative simplicity of the manufacturing process, the process can be regarded as sufficiently validated.

Product specification
The product specification includes tests for appearance, extractable volume, pH, sterility, endotoxins, sub-visible particles, osmolality, identity, assay rocuronium bromide and related substances. With the exception of the method used for the determination of the identity, the assay and the related substances, the methods used are identical to the standard Ph.Eur. methods. An adequate description of the in-house method is included in the dossier. Satisfactory validation data for the analytical methods have been provided. Batch analysis results for 7 batches have been submitted. All 7 batches comply with the proposed specifications. The release and shelf-life specifications were found acceptable. The proposed set of specifications is regarded to be sufficient.

Stability tests on the finished product
Eleven non-commercial scale batches were stored at 25°C/60%RH and 5°C±3°C. Accelerated stability studies at 25°C/60% RH ± 5%RH show a significant increase of impurity C where levels up to 1.9% are observed (0.6% initial value). However, since this impurity is the main metabolite the proposed end of shelf-life limits are acceptable. The unknown other impurities remain at levels of 0.1-0.2%.
When stored at 5 ± 3°C impurity C shows an increase but less pronounced than when stored at 25°C.
On the basis of the submitted data the claimed shelf-life of 24 months when stored at 2 – 8°C was granted.
The MAH committed to submit further stability data of the ongoing studies, at least covering the claimed storage period, when available.

Chemical and physical in-use stability of a 5.0 mg/ml and 0.1 mg/ml (diluted with sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5%) solution for infusion) has been demonstrated for 24 hours at room temperature exposed to room light in glass, PE and PVC.

Compatibility
The compatibility with isotonic solutions of glucose and sodium chloride was examined in PE and PVC bags over the period of 24 hours. After dilution of rocuronium bromide 10 mg/ml with sodium chloride 0.9% and glucose 5% infusion solution (both diluted 1:2 and 1:100), the solutions were shown to be stable for 24 hours at room temperature. The appearance of the prepared rocuronium bromide infusion solutions did not change during 24 hours. The number of the particulate matter was below the limit and no increase was observed. The pH-value remained nearly unchanged. The content of rocuronium bromide was stable, i.e. a degradation of the active substance or an increase of the related substances was not noted.

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. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

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.

Rocuroniumbromide B.Braun 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 Rocuroniumbromide B.Braun 10 mg/ml solution for injection or 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.

Pharmacovigilance

The MAH has a pharmacovigilance system at their disposal, which is based on the current European legislation. All comments raised during the DCP have been addressed satisfactorily. There are two remaining points for clarification, which can be solved post-approval. See post-approval commitments on page 6.

Risk management plan

Rocuronium bromide was first approved in March 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 postauthorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC

All comments concerning the SPC raised by the member states have been resolved. To resolve the comment raised by two CMSs concerning the use of rocuronium in intensive care unit ("It is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation".), this indication has been limited to short term use only.

Labelling

All comments raised by the member states have been addressed adequately. To meet with comments raised by some concerned member states the pharmaceutical form was changed into "Solution for injection/infusion". Additionally, in response to the comment from the UK that "IV" on the labelling of the vial should be changed into "for intravenous use" or other suitable statement, the MAH responded as follows: "Due to the fact that for Belgium three different languages need to fit on the labelling, we would prefer to leave the abbreviation "IV" on the labelling. Furthermore, we think that the medicinal staff is sufficiently familiar with the abbreviation "IV". However, we would agree to change the method of administration to "For intravenous use" on the English national labelling.". This was agreed upon by all member states.

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.
After a pre-round with 2 participants, two cohorts of 10 participants were interviewed. Resulting from the preround, the following revisions were made before testing:

- In section 2 *Before you use Rocurium Bromide* some key words were changed into bold and a new subheading *Please note* was created.
- The subsection *Important information about some of the ingredients* and *Possible side effects* were rewritten.

After the first round of 10 participants, no amendments were made.

Diagnostic testing was performed. Questions (15 in total: 6 general questions and 9 applicability questions) were asked about all parts of the leaflet. The report is of good quality and the results show that the PIL fulfils the criteria as set in the readability guideline.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Rocuroniumbromide B.Braun 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. There are two remaining points for clarification, which can be resolved post-approval (see below).

The SPC, package leaflet and labelling are in the agreed templates and are in agreement with other rocuronium bromide containing products.

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 B.Braun 10 mg/ml with the reference product, and have therefore granted a marketing authorisation. The decentralised procedure was finished on 16 July 2008. Rocuroniumbromide B.Braun 10 mg/ml was authorised in the Netherlands on 23 July 2009.

A European harmonised birth date has been allocated (17 March 1994) and subsequently the first data lock point for rocuronium bromide is February 2011. The first PSUR will cover the period from July 2008 to February 2011, after which the PSUR submission cyclus is 3 years.

The date for the first renewal will be: 1 November 2011.

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

<u>Quality - active substance</u>

- The MAH committed to perform long term stability studies for three batches manufactured at a commercial scale batch size and to submit the results when available.

<u>Quality - medicinal product</u>

- The MAH committed to submit further stability data of the ongoing studies, at least covering the claimed storage period, when available.

<u>Pharmacovigilance</u>

- The MAH committed to provide a written procedure regarding ‘interaction between safety issues and product defects’ before the product is marketed.
- The MAH committed to identify its license partners before the product is marketed.

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
Addition of a new manufacturer for the active substance rocuronium bromide	NL/H/1073/ 001/II/001	II	7-1-2009	17-6-2009	Approval	N
Addition of a CEP of a new manufacturer for the active substance rocuronium bromide	NL/H/1073/ 001/IA/002	IA	5-5-2009	19-5-2009	Approval	N