Public Assessment Report

Decentralised Procedure

Vecuronium bromide 10mg, powder for solution for injection

(Vecuronium bromide)

Procedure No: UK/H/5693/001/DC

UK Licence No: PL 43946/0002

BRADEX S.A.
LAY SUMMARY

Vecuronium bromide 10mg, powder for solution for injection
(vecuronium bromide, powder for solution for injection, 10mg)

This is a summary of the Public Assessment Report (PAR) for Vecuronium bromide 10mg, powder for solution for injection (PL 43946/0002; UK/H/5693/001/DC). It explains how Vecuronium bromide 10mg, powder for solution for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Vecuronium bromide 10mg, powder for solution for injection.

For practical information about using Vecuronium bromide 10mg, powder for solution for injection patients should read the package leaflet or contact their doctor or pharmacist.

The product will be referred to as Vecuronium bromide throughout the remainder of this public assessment report.

What is Vecuronium bromide and what is it used for?
Vecuronium bromide is a ‘generic medicine’. This means that Vecuronium bromide is similar to a ‘reference medicine’ already authorised in the European Union (EU) called Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands).

Vecuronium bromide is one of a group of drugs called muscle relaxants. Muscle relaxants are used during an operation as part of a general anaesthetic. When the patient has an operation their muscles must be completely relaxed. This makes it easier for the surgeon to perform the operation.

How does Vecuronium bromide work?
Normally, the body’s nerves send messages called impulses to the muscles. Vecuronium bromide acts by blocking these impulses so that the body’s muscles relax. Because the body’s breathing muscles also relax, the patient will need help to breathe (artificial ventilation) during and after their operation until the patient can breathe on their own again.

During the operation the patient’s anaesthetist will keep a check on the effect of the muscle relaxant, and if necessary will give the patient some more. At the end of surgery, the effects of the drug are allowed to wear off and the patient will start breathing on their own. Sometimes the anaesthetist will give the patient another drug to help speed this up.

How is Vecuronium bromide used?
The pharmaceutical form of this medicine is a powder for solution for injection. The route of administration of this medicine is into the patient’s vein (intravenously), either as single injections or as a continuous infusion (a drip).

Vecuronium bromide will be given to the patient by the patient’s anaesthetist.

Vecuronium bromide can be used in adults and children of all ages including infants and newborns. The patient’s anaesthetist will work out the dose of Vecuronium bromide they need based on:
• the type of anaesthetic
• the expected length of the operation
• other drugs the patient is taking
• the patient’s state of health
• the patient’s age.
The normal dose is 80 – 100 micrograms per kg body weight and the effect will last 24 – 60 minutes. During the procedure it will be checked whether Vecuronium bromide is still working. The patient may be given additional doses if they are needed.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

**What benefits of Vecuronium bromide have been shown in studies?**
No additional studies were needed as Vecuronium bromide is a generic medicine that is given intravenously and contains the same active substance as the reference medicine, Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands).

**What are the possible side effects of Vecuronium bromide?**
Because Vecuronium bromide is a generic medicine, its benefits and possible side effects are taken as being the same as the reference medicine.

For the full list of restrictions, see the package leaflet.

For the full list of all side effects reported with Vecuronium bromide, see section 4 of the package leaflet available on the MHRA website.

**Why was Vecuronium bromide approved?**
It was concluded that, in accordance with EU requirements, Vecuronium bromide has been shown to have comparable quality and to be comparable to Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands). Therefore, the MHRA decided that, as for Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands), the benefits are greater than its risk and recommended that it can be approved for use.

**What measures are being taken to ensure the safe and effective use of Vecuronium bromide?**
A risk management plan (RMP) has been developed to ensure that Vecuronium bromide is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Vecuronium bromide including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

**Other information about Vecuronium bromide**
Germany, Portugal and the UK agreed to grant a Marketing Authorisation for Vecuronium bromide on 06 January 2016. A Marketing Authorisation was granted in the UK on 03 February 2016.

The full PAR for Vecuronium bromide follows this summary.

For more information about treatment with Vecuronium bromide, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in March 2016.
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I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Vecuronium bromide (PL 43946/0002; UK/H/5693/001/DC) could be approved. The product is a prescription-only medicine (POM) and 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.

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Germany and Portugal as Concerned Member States (CMS). The application was submitted under Article 10.1 of Directive 2001/83/EC, as amended, as a generic application. The reference medicinal product for this application is Norcuron 10 mg, powder for solution for injection (PL 05003/0044; N. V Organon, The Netherlands) which has been registered in the UK since 04 October 1991.

Vecuronium bromide (vecuronium bromide) is a non-depolarising neuromuscular blocking agent, chemically designated as the aminosteroid 1-(3α,17β-diacetoxy-2β piperidino-5α-androstan-16β-yl)-1 methylpiperidinium bromide.

Vecuronium bromide blocks the transmission process between the motor nerve-ending and striated muscle by binding competitively with acetylcholine to the nicotinic receptors located in the motor end-plate region of striated muscle.

Unlike depolarising neuromuscular blocking agents, such as suxamethonium, vecuronium bromide does not cause muscle fasciculations.

Within the clinical dosage range, vecuronium does not block the sympathetic nicotinic receptors, and thus exerts no ganglion blocking activity. In addition, in this dose range vecuronium does not block the parasympathetic muscarinic receptors, and thus exerts no vagolytic activity.

No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of an originator product that has been licensed for over 10 years.

No new clinical data have been submitted and none are required for applications of this type. A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 209) on 06 January 2016. After a subsequent national phase, a licence was granted in the UK on 03 February 2016.
II QUALITY ASPECTS

II.1 Introduction

One vial contains 10 mg vecuronium bromide (as a freeze dried powder), which on reconstitution as recommended in 5ml of water for injections corresponds to 2 mg vecuronium bromide per ml.

Other ingredients consist of the pharmaceutical excipients citric acid monohydrate, disodium phosphate dihydrate, mannitol, sodium hydroxide (for pH correction) and phosphoric acid (for pH correction). The finished product is packed into clear, colourless glass (Type I) vials closed with a rubber closure and sealed with an aluminium cap and is available in pack sizes of 1, 10, 20, 20 (2x10) and 100 vials. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Vecuronium bromide

Chemical name: Piperidinium, 1-{(2β,3α,5α,16β,17β)-3,17-bis(acetyloxy)-2-(1-piperidinyl) androstan-16-yl}-1-methyl-,bromide

Structural formula:

![Structural formula of vecuronium bromide]

Molecular formula: \( C_{34}H_{57}BrN_2O_4 \)
Molecular mass: 637.75
Appearance: White or cream white crystals, or a crystalline powder.
Solubility: Freely soluble in alcohol and chloroform, slightly soluble in acetone, forms a gel with water which at 1% concentration is fluid.

Vecuronium bromide is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory certificates of analysis have been provided for all working standards. Batch analysis data are provided that comply with the proposed specification.
Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product
Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, powder for solution for injection containing 10 mg vecuronium bromide (as a freeze dried powder) which on reconstitution in 5ml of water for injections (as recommended) corresponds to 2 mg vecuronium bromide per ml, that was comparable to the originator product Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands). A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale batch size and shown satisfactory results.

Finished Product Specification
The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 2 years for the unopened vial with no special storage conditions.

Chemical and physical in-use (i.e. following reconstitution) stability has been demonstrated for 24 hours at 25°C.

From a microbiological point of view, unless the method of reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Do not use Vecuronium bromide when the solution after reconstitution contains particles or is not clear.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.
II.4 Discussion on chemical, pharmaceutical and biological aspects
There are no objections to the approval of this application from a pharmaceutical viewpoint.

III NON-CLINICAL ASPECTS

III.1 Introduction
As the pharmacodynamic, pharmacokinetic and toxicological properties of vecuronium bromide are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The Applicant’s non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

III.2 Pharmacology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.3 Pharmacokinetics
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.4 Toxicology
Not applicable for this product type. Refer to section ‘III.1; Introduction’ detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)
Since Vecuronium bromide 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.6 Discussion on the non-clinical aspects
No new non-clinical studies were conducted, which is acceptable given that the application was based on being a generic medicinal product of a reference product that has been licensed for over 10 years.

There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction
The Applicant has provided a justification for not submitting new clinical data. The proposed product is intended for intravenous administration. It contains the same active substance as the reference product. According to the current ‘Guideline on the Investigation of Bioequivalence’ (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. There are no excipient interactions which might affect the pharmacokinetics of the active substance.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of vecuronium bromide.

Based on the data provided, Vecuronium bromide can be considered a generic of Norcuron 10 mg, powder for solution for injection (N. V Organon, The Netherlands).
IV.2 Pharmacokinetics
In line with the guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/Corr**), the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. No bioequivalence study has been submitted with this application and none is required.

IV.3 Pharmacodynamics
No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy
No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety
No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), 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 bromide.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary table of safety concerns:

| Important identified risks | - Residual neuromuscular block
|                           | - Hypersensitivity reactions (including anaphylaxis)
|                           | - Prolonged paralysis with long term use of neuromuscular blocking agents in the Intensive Care Unit
|                           | - Myopathy after long term administration of non-depolarizing neuromuscular blocking agents in the Intensive Care Unit in combination with corticosteroid therapy
|                           | - Altered responses in patients with: neuromuscular diseases, including previous poliomyelitis and neuromuscular junction disorders; obesity; burns; hypothermia; electrolyte and metabolic disturbances; prolonged circulation time; dehydration
| Important potential risks  | - Safety in hepatic disease
|                           | - Safety in renal disease
|                           | - Drug interactions
| Missing information       | - Safety in pregnancy and lactation
|                           | - Safety in preterm newborn infants

Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

IV.7 Discussion on the clinical aspects
No new clinical studies were conducted, which is acceptable given that the application was based on
being a generic medicinal product of a reference product that has been licensed for over 10 years.

A bioequivalence study was not necessary to support this application as both test and reference products are aqueous intravenous solutions at the time of administration.

The grant of a marketing authorisation is recommended for this application.

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 language used for the purpose of user testing the PIL was English.

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
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with vecuronium bromide is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Vecuronium bromide is presented below: