Medicines & Healthcare products
Regulatory Agency

Public Assessment Report

National Procedure

Vecuronium bromide 10 mg powder for solution for injection/infusion

vecuronium bromide

PL 13621/0085

Flynn Pharma Limited

LAY SUMMARY

Vecuronium bromide 10 mg powder for solution for injection/infusion vecuronium bromide

This is a summary of the Public Assessment Report (PAR) for Vecuronium bromide 10 mg powder for solution for injection/infusion. It explains how this product 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 this product.

This product will be referred to as Vecuronium in this lay summary for ease of reading.

For practical information about using Vecuronium, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Vecuronium and what is it used for?
This application is for a medicine that has a well-established use. This means that the use of the active substance in this medicine has been well-established in the UK/European Union for at least 10 years, with recognised efficacy and an acceptable level of safety.

Vecuronium is used as a muscle relaxant during surgery in adults, newborn babies (0-27 days), infants (28 days-23 months), children (2-11 years) and adolescents (12-17 years).

Muscle relaxants are used during an operation as part of a general anaesthetic. When a patient has an operation, their muscles must be completely relaxed. This makes it easier for the surgeon to perform the operation.

How does Vecuronium work?
Vecuronium contains the active substance vecuronium bromide, which belongs to the group of medicines that relax the muscles (muscle relaxant). Normally, nerves send messages called impulses to the muscles. Vecuronium bromide acts by blocking these impulses so that the muscles relax.

How is Vecuronium used?
The pharmaceutical form of this medicine is a powder for solution for injection/infusion and the route of administration is intravenous (into a vein) use.

Vecuronium will be given to the patient by their anaesthetist. The drug is given into a vein (intravenous), as a single injection or continuous infusion (drip).

Vecuronium is used in adults and children of all ages. The dose will be determined by the patient's anaesthetist. They will receive Vecuronium before or during the operation.

The usual starting dose is 0.08 to 0.1 mg per kg of body weight, and the effect lasts from 24 to 60 minutes. During the procedure it will be checked whether the medicine is still working. The patient may be given additional doses if they are needed. The dose they receive will depend on different factors. These include the possibility of interactions with other medicines they have been given, the expected duration of the operation, their age and general health.

For further information on how Vecuronium is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning the medicine.

What benefits of Vecuronium have been shown in studies?
As the active substance, vecuronium bromide has been in clinical use for over 10 years, data were provided in the form of literature references to show that Vecuronium is a safe and efficacious for use as a muscle relaxant during surgery in adults and children of all ages.

What are the possible side effects of Vecuronium?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on behalf of someone else they care for, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Vecuronium approved?
It was concluded that the data provided from literature references had shown that Vecuronium is effective for use as a muscle relaxant during surgery in adults and children of all ages. Furthermore, the well-established use of the active substance vecuronium has shown that it has a recognised efficacy and an acceptable level of safety. Therefore, the MHRA decided that the benefits are greater than the risks and recommended that it can be approved for use.

What measures are being taken to ensure the safe and effective use of Vecuronium?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Vecuronium. The RMP details the important risks of Vecuronium, how these risks can be minimised, any uncertainties about Vecuronium (missing information), and how more information will be obtained about the important risks and uncertainties.

There are no safety concerns associated with use of Vecuronium.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by the healthcare professionals and patients. Side effects of Vecuronium are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Vecuronium
A Marketing Authorisation for Vecuronium was granted in the United Kingdom (UK) on 09 May 2024.

The full PAR for Vecuronium follows this summary.

This summary was last updated in July 2024.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Vecuronium bromide 10 mg powder for solution for injection/infusion (PL 13621/0085) could be approved.

The product is approved for the following indication:
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.

Vecuronium (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 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 does not cause muscle fasciculations.

This application was approved under Regulation 54 of The Human Medicines Regulation 2012, as amended (previously Article 10a of Directive 2001/83/EC, as amended), as a well-established use application. No new non-clinical or clinical studies were submitted, as the data submitted for these applications is in the form of literature references.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A national marketing authorisation was granted in the United Kingdom (UK) on 09 May 2024.

II QUALITY ASPECTS

II.1 Introduction

The active substance is vecuronium bromide.
Each vial contains 10 mg of vecuronium bromide.

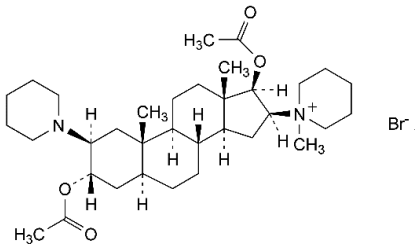
In addition to vecuronium bromide, this product also contains the following excipients: citric acid monohydrate and L-alanine.

The finished product is packaged in clear, colourless type I glass vials closed with grey bromobutyl rubber stoppers, and flanged aluminium caps covered by a thin coloured plastic disc and is available in packs of 10 vials.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current regulations concerning materials in contact with food.

II.2 ACTIVE SUBSTANCE

rINN: Vecuronium bromide
Chemical Name: 1-[3α,17β-Bis(acetyloxy)-2β-(piperidin-1-yl)-5α-androstan-16β-yl]-1-methylpiperidin-1-ium bromide.
Molecular Formula: $C_{34}H_{57}BrN_2O_4$
Chemical Structure:



Molecular Weight: 638
Appearance: White or almost white crystals or crystalline powder.
Solubility: Slightly soluble in water, freely soluble in methylene chloride, sparingly soluble in acetonitrile and in anhydrous ethanol.

The information related to the active substance was provided in an ASMF. The Active substance is the subject of a Ph.Eur. 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 specifications are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

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. Batch analysis data are provided and comply with the proposed specification. Satisfactory certificates of analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current regulations concerning materials in contact with food.

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

II.3 DRUG PRODUCT

Pharmaceutical development

A satisfactory account of the pharmaceutical development has been provided.

All excipients comply with either their respective European/national monographs, or a suitable in-house specification. Satisfactory Certificates of Analysis have been provided for all excipients.

No excipients of animal or human origin are used in the finished product.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacture of the product

A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulation data have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results.

Finished Product Specification

The finished product specifications at release and shelf-life are satisfactory. The test methods have been described and adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability

Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished product stored in the packaging proposed for marketing. Based on the results, a shelf-life of 30 months for the unopened vial, with the storage conditions ‘Keep in the original container to protect from light’, ‘Do not store above 25 °C’, is acceptable.

After first opening and following reconstitution, chemical and physical stability for 24 hours at a temperature up to 25 °C has been demonstrated. From a microbiological point of view, 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 and would normally not be longer than 24 hours at 2 to 8 °C, unless dilution has taken place in controlled and validated aseptic conditions.

The solution should not be used if it contains particles after preparation/reconstitution.

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

The grant of a marketing authorisation was recommended.

III NON-CLINICAL ASPECTS

III.1 Introduction

This application was submitted under Regulation 54 of The Human Medicines Regulation 2012, as amended, as a well-established use application. No new non-clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

III.2 Pharmacology

The non-clinical overview provides an adequate review of the available published data on the non-clinical pharmacology of vecuronium bromide.

The primary pharmacodynamics of vecuronium has been comprehensively evaluated. The effects of vecuronium on the neuromuscular system have been elaborated in various animal models. The principal pharmacodynamic effect of vecuronium relevant to the neuromuscular system is its muscle relaxant action. Neuromuscular blocking effects have been directly demonstrated *in vivo* in numerous experiments in different rat, dog, cat and monkey models. Overall, the results of these numerous *in vivo* and *in vitro* studies demonstrate that vecuronium exhibits effective neuromuscular blockade in various animal species.

Results of few *in vivo* studies performed in rats, dogs and cats demonstrate that vecuronium has minimal effects on the cardiovascular system in these species. Results obtained in anaesthetized rats, dogs and cats have demonstrated that, in contrast to other neuromuscular blocking drugs, vecuronium, even in doses up to 21 times the ED_{90} dose for the neuromuscular blocking effect of vecuronium, has no effects on heart rate, arterial pressure, cardiac output, or renal sympathetic nerve activity. *In vitro*, in the isolated rat atria, vecuronium had no significant effects on the heart rate but produced positive inotropic effects. In isolated spontaneously beating guinea pig hearts, during perfusion with vecuronium no significant effects on cardiac conduction and pacemaker activity could be observed. In the isolated, cross-circulated right atrial and left ventricular preparations of the dog, vecuronium, injected into the external jugular vein of the support dog, induced dose-dependent decreases in heart rate and arterial blood pressure, and increased atrial contractile force. Overall, these results suggest that vecuronium possesses significant advantages over other non-depolarizing neuromuscular blocking drugs, since its clinical use should not be associated with clinically significant effects on the cardiovascular system.

The results of these few studies in the rat, rabbit, guinea pig and dog suggest that vecuronium exhibits no detrimental effects on the respiratory system of these species.

Results of limited studies obtained in the rat and dog indicate that vecuronium exhibits no detrimental effects on the nervous system of these species.

The results of few studies indicate a low potential of vecuronium to induce histamine release. In addition, these results suggest that vecuronium may exert radical-scavenging effects and thus may exhibit protective effects against free-radical injury of the endothelium of blood vessels.

Pharmacodynamic drug interactions of vecuronium in animals were found with numerous drugs, including adenosine, aminopyridines, anaesthetics, benzodiazepines, calcium antagonists, corticosteroids, ethanol, magnesium, medetomidine, metronidazole, neuromuscular blocking drugs (NMBDs), pantoprazole, and succinylcholine. Coadministration of these drugs produced either an enhancement or a reduction of the vecuronium-induced neuromuscular blockade. Numerous pharmacodynamic drug interactions of vecuronium with other drugs were also observed in man.

III.3 Pharmacokinetics

The non-clinical overview provides an adequate review of the available published data on the non-clinical pharmacokinetics of vecuronium bromide.

The pharmacokinetics of vecuronium have been evaluated in various species (mouse, rat, dog, and cat) using different routes of administration (intravenous, intramuscular, intratracheal) and doses covering a wide range, thus giving a detailed literature survey on the relevant features of its disposition.

III.4 Toxicology

The non-clinical overview provides an adequate review of the available published data on the non-clinical toxicology of vecuronium bromide.

The lack of primary repeat-dose toxicity data can be accepted based on the wealth of clinical data and on consideration of the indication (single-occasion administration during surgery).

In addition, based on the presented information, it could be accepted that vecuronium bromide is not genotoxic.

The lack of carcinogenicity data can be accepted based on the lack of evidence of mutagenicity, that no cause for concern has been identified in the limited repeat-dose toxicity studies, and on consideration of the indication (single-occasion administration during surgery).

Likewise, the lack of reproductive, developmental and juvenile data can be accepted based on the wealth of clinical data, that no cause for concern has been identified in the limited repeat-dose toxicity studies and on consideration of the indication (single-occasion administration during surgery).

III.5 Ecotoxicity/Environmental Risk Assessment

Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is for a product containing an active substance of well-established use that will be used in place of existing products, an increase in environmental exposure is not anticipated following approval of the Marketing Authorisation for the proposed product.

III.6 Discussion on the non-clinical aspects

The grant of a marketing authorisation was recommended.

IV CLINICAL ASPECTS

IV.1 Introduction

No new clinical studies were submitted, as the data submitted for this application is in the form of literature references. The literature review provided is satisfactory.

IV. 2 Pharmacokinetics

Absorption

The pharmacokinetics of vecuronium fits the three-compartment pharmacokinetic model. In a study in thirty patients undergoing elective plastic surgery who received vecuronium (0.1 mg/kg, i.v.) the area under the plasma concentration curve (AUC) was 29.5 μg/ml/min in men compared with 33.3 μg/ml/min in women. Following administration of vecuronium (60 μg/kg bolus; 1 μg/kg/min infusion) to twenty adult surgical patients who were anaesthetised with either halothane or fentanyl, the plasma vecuronium concentrations were 0.34 μg/ml for the halothane group and 0.32 μg/ml for the fentanyl group associated with 93 and 88% twitch depression, respectively.

Distribution

Vecuronium is rapidly distributed into the extracellular space. Following intravenous administration of 0.05 and 0.2 mg/kg of vecuronium to surgical patients, distribution half-life ($t_{1/2\alpha}$) was 2.9 min and 2.8 min in the low and high dose group, respectively. Volume of distribution at steady-state (Vdss) was 148 and 124 ml/kg, respectively. Plasma protein binding of vecuronium occurs to the extent of 30%. Vecuronium is ionised and water-soluble prohibiting passage through the blood brain barrier.

Metabolism

Most of the drug excreted in the urine and bile is unchanged. About 30-40% of vecuronium is metabolised mainly in the liver by deacetylation at the 3- and 17-positions to three alcohol metabolites, i.e., 3-desacetylvecuronium, 17-desacetylvecuronium and 3,17-desacetylvecuronium. Only a small fraction of the drug undergoes hepatic metabolism to 3-hydroxyvecuronium, which is active at the neuromuscular junction.
3-desacetylvecuronium is a potent (80% of vecuronium) neuromuscular blocking drug, which has a lower clearance rate and longer duration of action than vecuronium. The 3-desacetylvecuronium metabolite is rapidly converted to 3,17-desacetylvecuronium which is only 2% as potent as the parent drug.

Excretion

Vecuronium mainly undergoes biliary elimination with about 30-80% of the dose excreted via the bile unchanged and about 1.5-12% as the 3-hydroxy metabolite. Renal elimination of vecuronium is relatively low with up to 30% of the administered drug excreted in the urine. Clearance of vecuronium was 4.35 ml/kg/min. In a study in thirty patients undergoing elective plastic surgery who received vecuronium (0.1 mg/kg, i.v.), the elimination half-life ($t_{1/2\beta}$) and plasma clearance (Cl) were not different between men (49.8 min and 235.8 ml/min, respectively) and women (52.3 min and 208.6 ml/min, respectively).

Special populations

Paediatrics

A study in five infants (3 to 11 months old) and five children (1 to 5 years old) undergoing elective surgery and given vecuronium (2.5 μg/kg/min) showed age-related changes in the pharmacokinetics of vecuronium. In this study, Vdss was larger in infants than in children (357 vs. 204 ml/kg). Vdss in children was slightly smaller than in adult historical control (269 ml/kg). Cl was of the same order for infants and children (5.6 vs. 5.9 ml/kg/min).

In twelve children (aged 1-8 years) and 12 adults (aged 18-54 years) undergoing elective plastic surgery, the Vdss was greater in children than in adults by direct comparison (198.2 vs. 166.5 ml/kg). The other pharmacokinetic variables were not significantly different between the two age groups. In the children, AUC, MRT, Vc, $t_{1/2\beta}$, and Cl were 33.3 µg/ml/min, 60.9 min, 62.7 ml/kg, 53.7 min, and 4.4 ml/kg/min, respectively. The corresponding figures in adults were 30.8 µg/ml/min, 56.3 min, 40.3 ml/kg, 48.3 min, and 3.2 ml/kg/min, respectively.

Elderly
In a study of the pharmacokinetics of vecuronium (2.5 µg/kg/min) in twelve healthy elderly subjects (70-84 years) and twelve young adults (30-57 years) plasma clearance (3.7 and 5.2 ml/kg/min, respectively) and Vdss (179 and 244 ml/kg, respectively) were lower in the elderly than in young adults. However, the values for $t_{1/2\alpha}$ and $t_{1/2\beta}$ were similar for the two age groups. In another study of the pharmacokinetics of vecuronium (0.1 mg/kg) in eight elderly patients aged 72-86 years and eight younger adults aged 26-48 years undergoing elective surgical procedures, compared to the younger adults, $t_{1/2\beta}$ of vecuronium was significantly prolonged (125 vs. 78 min) and plasma clearance reduced (2.6 vs. 5.6 ml/kg/min) in elderly.

Pregnancy
Despite an increased in bodyweight, plasma volume by 45% and blood volume by 35% that might influence the volume of distribution of polar drugs, the apparent volume of distribution at steady state, volume of distribution and the apparent volume of the central compartment of vecuronium are unchanged during pregnancy. It is not known whether vecuronium is distributed into milk. Studies in pregnant women showed that there is only minimal placental transfer of intravenously administered vecuronium, and the drug does not reach the foetus in clinically important concentrations.

Renal impairment
In general, the pharmacokinetics of vecuronium was found to differ little when studied in patients with normal renal function and those with renal failure. However, results of few studies indicated that in patients with renal failure, clearance may be reduced, and terminal elimination half-life may be increased. In a comparative study in twelve patients with renal failure who were to receive kidney transplants and 8 patients with normal renal function who received vecuronium (0.1 mg/kg), a significantly decreased plasma clearance (3.0 vs. 5.29 ml/kg/min) and a prolonged elimination half-life of vecuronium (83.1 vs. 52.57 min) was noted in the renal failure group as compared with controls. Distribution half-life was significantly prolonged in patients with renal failure compared with controls (11.3 vs. 7.53 min). Vdss did not differ significantly between patients with renal failure and those with normal renal function (0.241 vs. 0.199 l/kg). The duration of neuromuscular blockade was longer in patients with renal failure than in those with normal renal function (98.6 vs. 54.1 min). Onset time did not differ significantly between patients with renal failure and those with normal renal function (1.9 vs. 1.8 min). Overall, these data show that the pharmacokinetics of vecuronium differ little when studied in patients with normal renal function and those with renal failure. There are currently insufficient data available to allow specific dosage recommendations for patients with renal insufficiency.

Hepatic impairment
A study in nine surgical patients with cholestasis, and in fourteen patients without hepatic or renal disease given vecuronium (0.2 mg/kg), showed that the plasma clearance of vecuronium is significantly decreased (2.36 vs. 4.30 ml/min/kg), and elimination-half-life is significantly prolonged (98 vs. 58 min) in patients with cholestasis compared with controls.

$T_{1/2\alpha}$ and Vdss in patients with cholestasis (11.8 min and 0.206 l/kg, respectively) did not significantly differ from those in the control patients (7.4 min and 0.247 l/kg). In a study on the effect of liver cirrhosis on the pharmacodynamics and pharmacokinetics of vecuronium in twelve patients with cirrhosis and fourteen control patients undergoing elective surgery, cirrhosis caused a reduction of plasma clearance and prolongation of elimination half-life. Vecuronium plasma clearance was reduced significantly from 4.26 ml/min/kg in the controls to 2.73 ml/min/kg in the patients with cirrhosis. The elimination half-life was 58 min in the controls and was prolonged significantly to 84 min in the patients with cirrhosis. The total apparent volume of distribution was unchanged in patients with cirrhosis (0.253 l/kg vs. 0.246 l/kg in the controls). These data show that, due to the hepatic metabolism of the drug, hepatic insufficiency may cause a reduction of plasma clearance and prolongation of elimination half-life of vecuronium. Therefore, hepatic impairment may require a dose adjustment. There are currently insufficient data available to allow specific dosage recommendations for patients with hepatic impairment or cholepathia.

Obesity
A study in seven obese patients and seven control patients of ideal body weight who received vecuronium (0.1 mg/kg) showed that obesity does not alter the distribution or elimination of vecuronium, with similar pharmacokinetics of the drug for both groups. When the data were calculated on the basis of ideal body weight (IBW) for obese and control patients, total volume of distribution (791 vs. 919 ml/kg IBW), plasma clearance (4.65 vs. 5.02 ml/min/kg IBW), and elimination half-life (119 vs. 133 min) were not different between groups.

Interactions
In a study in ten epileptic patients, coadministration of carbamazepine (1.2-1.6 g/d) and vecuronium (0.1 mg/kg) resulted in a 2-fold increase in clearance of vecuronium compared with untreated controls (9.0 vs. 3.8 ml/kg/min), whereas no changes in volumes of distribution at steady-state were observed. The mean residence time was halved (17.8 vs. 31.9 min). In a study in twenty epileptic and ten non-epileptic children and adolescents (4-22 years) treated with vecuronium (0.15 mg/kg), coadministration of carbamazepine or phenytoin increased clearance and reduced the elimination half-life of vecuronium. $T_{1/2\beta}$ was significantly reduced in both anticonvulsant groups compared with control (18.4 vs. 23.5 vs. 48.2 min). Vecuronium clearance was increased in both anticonvulsant groups [18.8 vs. 15.1 vs. 9.0 ml/kg/min).

IV.3 Pharmacodynamics

Pharmacodynamic studies
In a controlled, randomized randomised study on the neuromuscular blocking (NMB) effect of vecuronium (0.1 mg/kg) on the orbicularis occuli and adductor pollicis muscle in fifty patients (30-75 years) undergoing elective peripheral limb surgery, 100% neuromuscular block was attained both in the orbicularis occuli and adductor pollicis muscle within 174 s and 148 s, respectively. Recovery to 90% of control value of the first evoked response of train-of-four (TOF) stimulation was noted after 82 min in both muscles.

A pharmacodynamic study in forty subjects who received either vecuronium or pancuronium, single and cumulative dose-response curves using the adductor pollicis muscle indicated that vecuronium bromide was slightly more potent than pancuronium bromide with ED_{50} of 28 vs. 42 μg/kg, respectively. After a 36 mg/kg vecuronium dose, time to onset was 4.5 min. No cumulation was seen after seven repeated doses of the two NMBDs. Time taken for recovery to 25% of control twitch height was shorter in the vecuronium group than in the pancuronium group (15 vs. 32 min).

Dose effect relationships
Clinical studies showed that administration of higher dosages of vecuronium shortens onset time to maximal blockade and prolongs the duration of action. Results of a randomised study performed to determine the onset time and duration of high doses of vecuronium (100, 200, 300 and 400 μg/kg) in forty patients scheduled for elective surgery showed there was a dose-dependent decrease in onset of neuromuscular blockade and a dose-dependent increase in duration of NMB. 100% NMB was reached in all patients and endotracheal intubating conditions were good or excellent in all patients in all dose groups. Onset time decreased from 208 to 106 s as the vecuronium dose was increased from 100 to 400 μg/kg. Corresponding times to endotracheal intubation also decreased from 183 to 96 s with increasing doses. Recovery time (T1 = 25%) increased from 37 to 138 min with increasing doses.

Effects on respiratory system
In an open-label, controlled study in 150 patients (18-60 years) undergoing elective surgeries and who were randomised to receive vecuronium (0.1-0.15 mg/kg), atracurium (0.5 mg/kg), or rocuronium (0.6-0.8 mg/kg), residual NMB resulted in reductions in forced vital capacity (FVC) and peak expiratory flow (PEF) in the immediate postoperative period indicating impaired respiratory muscle function. There was no statistically significant difference in the postoperative reductions in pulmonary function test parameters in patients with residual NMB among the different neuromuscular blocking agents tested.

Effects on cardiovascular system
In a randomised, controlled study of the effects of vecuronium (0.08 mg/kg) and pancuronium (0.1 mg/kg) on the left ventricular function of 20 adult surgical patients (mean age 39.8 years) using transesophageal echocardiography under clinical conditions, vecuronium did not cause any significant changes in hemodynamic performance, whereas pancuronium caused a significant increase in the heart rate, mean arterial pressure and cardiac index.

In a randomised, controlled double-blind study in 20 patients scheduled for elective coronary artery bypass surgery who received either vecuronium (0.12 mg/kg) or atracurium (0.5 mg/kg), vecuronium produced no statistically significant changes in any hemodynamic variable measured other than a decrease in pulmonary capillary wedge pressure ten minutes after the drug was administered. Atracurium produced a statistically significant decrease in blood pressure at two minutes and a statistically significant increase in cardiac output and decrease in systemic vascular resistance at 2, 5, and 10 minutes.

In a comparative study of the effect of rocuronium (20 mg) and vecuronium (4 mg) on intra-operative heart rate in 116 fit, out-patients undergoing gynaecological laparoscopic procedures, patients given rocuronium had significantly fewer episodes of bradycardia (heart rate < 50 beat/min) than patients given vecuronium. Profound bradycardias (heart rate < 30 beat/min) did not occur in any of the patients in the rocuronium study group, whereas 5% of patients receiving vecuronium had a period of transient asystole.

Results of double-blind, placebo-controlled, randomised, 6-period cross-over thorough QTc study with 84 healthy volunteers showed that treatment with single i.v. doses of sugammadex at therapeutic and supra-therapeutic levels either with or without vecuronium (0.1 mg/kg) or rocuronium was not associated with QTc prolongation based on the ICH-E14 guideline.

Pharmacodynamic drug-drug interactions

Acetylcholinesterase inhibitors

Administration of acetylcholinesterase inhibitors such as neostigmine, pyridostigmine or edrophonium, antagonises the effect of vecuronium.

Anaesthetics

Halogenated volatile anaesthetics potentiate the neuromuscular blocking effects of vecuronium probably due to increased neuromuscular sensitivity.

Antibiotics

The concomitant use of antibiotics such as aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, clindamycin, bacitracin, and polymixin B may intensify the neuromuscular blockade produced by vecuronium.

Anticonvulsants

Anticonvulsant therapy with carbamazepine or phenytoin has been associated with accelerated recovery from NMBs. A study in 100 neurosurgical patients receiving chronic phenytoin therapy and who received vecuronium showed that patients receiving chronic phenytoin therapy were resistant to vecuronium-induced neuromuscular blockade.

In a study in 20 epileptic and 10 non-epileptic children and adolescents (4-22 years) treated with vecuronium (0.15 mg/kg) and coadministered carbamazepine or phenytoin, both anticonvulsant drugs induced resistance to vecuronium.

In contrast, administration of phenytoin produced significant augmentation of neuromuscular blockade ($P<0.001$) when administered intravenously at a dose of 10 mg/kg in comparison to 0.9% saline (control) to a group of 10 patients in whom steady state neuromuscular blockade had been established with an infusion of vecuronium.

Calcium antagonists

Administration of diltiazem prior to tracheal intubation reduces time to onset of vecuronium-induced neuromuscular blockade and attenuates changes in blood pressure caused by tracheal intubation.

Dantrolene

Prolonged vecuronium neuromuscular blockade was reported in a patient receiving orally administered dantrolene. Depth of block and 90% recovery time were 100% and 47 min in the dantrolene-treated patients compared with 79% and 22 min in untreated patients.

Ephedrine

In a study in 120 patients, a small dose of ephedrine (70 μg/kg) given before induction of anaesthesia decreased the onset time of vecuronium and improved intubating conditions at 2 min after vecuronium, probably by increased cardiac output.

Magnesium

A study observed increases in magnesium potentiate the activity of non-depolarizing NMBDs.

A significantly prolonged action of vecuronium from magnesium treatment after general anaesthesia for urgent caesarean section was reported in two cases.

Neuromuscular blocking agents
Dose-response studies with pancuronium, vecuronium and their combination found no interactions between the two drugs.

A study in 60 children on potential interactions of vecuronium and atracurium during halothane anaesthesia showed that the neuromuscular effects of vecuronium and atracurium are neither additive nor synergistic.

A study on the interactions between vecuronium, mivacurium or rocuronium in seventy healthy women showed that the clinical duration of maintenance doses of vecuronium and rocuronium were significantly shorter after an intubating dose of mivacurium than that after an intubating dose of vecuronium or rocuronium, respectively.

Salbutamol
Potentiation of vecuronium-induced neuromuscular blockade by intravenous salbutamol was described in a case report.

Sugammadex
This selective relaxant binding agent rapidly reverses profound vecuronium-induced neuromuscular block.

IV.4 Clinical efficacy

The applicant has submitted clinical efficacy data from 129 clinical studies with a total of 6,639 infants, children and adults.

Table 1: Tabulated summary of clinical trials performed with intravenously administered vecuronium bromide

Indication	Clinical studies (patients)		Total
	Controlled	Non-controlled	
General anaesthesia to facilitate endotracheal intubation in adults	38 (2,423)	11 (865)	49 (3,288)
General anaesthesia to facilitate endotracheal intubation in infants and children	8 (400)	14 (453)	22 (853)
General anaesthesia to facilitate endotracheal intubation in elderly	5 (594)	4 (184)	9 (778)
General anaesthesia to facilitate endotracheal intubation in renal insufficiency	2 (146)	11 (408)	13 (554)
General anaesthesia to facilitate endotracheal intubation in hepatic insufficiency	-	6 (164)	6 (164)
General anaesthesia to facilitate endotracheal intubation in pregnancy	3 (120)	6 (161)	9 (281)
General anaesthesia to facilitate endotracheal intubation in various clinical conditions	8 (211)	13 (510)	21 (721)
Total	64 (3,894)	65 (2,745)	129 (6,639)

Adults
The applicant has submitted data from 38 controlled studies including 2423 patients. A few key examples are discussed below.

Intubation
In a randomised, controlled study in 60 patients (16-70 years) scheduled to undergo elective surgery under general anaesthesia, i.v. vecuronium bromide (0.1 mg/kg) and i.v. rocuronium (0.6 mg/kg) provided good to excellent intubating conditions at 168 s and 95 s, respectively. Intubating conditions with vecuronium were excellent in 60% and good in 36.7% of patients while in the rocuronium group, intubating condition were excellent in 63.3% and good in 30% of patients. None of the patient in either group had impossible intubation.

In a randomised study in 50 patients (18-70 years) conducted to compare the effects vecuronium (0.1 mg/kg), three doses of rocuronium (0.6, 0.9, and 1.2 mg/kg), or succinylcholine (1.0 mg/kg) intubating conditions did not differ significantly in the five groups. Excellent or good intubating conditions were achieved in 90%, 100%, and 100% of patients in the vecuronium, rocuronium and succinylcholine groups, respectively. Vecuronium onset time (144 s) was longer than that in the rocuronium 0.6, 0.9 and 1.2 mg/kg groups (89 s, 75 s, 55 s) and succinylcholine group (50 s).

Skeletal muscle relaxation
A randomised study in 60 patients (17-51 years) scheduled for elective plastic surgery who received either vecuronium or rocuronium showed that the neuromuscular blocking potency of rocuronium is approximately 15% that of vecuronium. All patients had 100% T1 response depression after administration of 0.08 mg/kg of vecuronium or 0.6 mg/kg of rocuronium. After administration of equipotent doses of both drugs, the duration of peak effect, clinical duration, recovery index, and total duration were not significantly different between the two drugs.

In a multicentre, randomised, controlled study in 93 patients (mean age 49.5 years) scheduled for a surgical procedure under sevoflurane/opioid anaesthesia, an intubating dose of vecuronium (0.1 mg/kg) and maintenance doses of 0.02-0.03 mg/kg resulted in effective neuromuscular blockade that was reversed by administration of both sugammadex and neostigmine.

In a randomised, controlled study in 62 patients (18-60 years) scheduled for laparotomies and pelvic surgeries under general anaesthesia who received either vecuronium infusion (63.2 μg/kg/h) or atracurium infusion (478 μg/kg/h), 84.4% of patients in the vecuronium group fell within good to very good category of muscle relaxation as compared to 63.3% in atracurium group. Spontaneous recovery was faster with vecuronium as compared to atracurium (541 vs. 596 s).

After intubation with suxamethonium
Twenty-five healthy adult patients undergoing general anaesthesia for elective surgery were randomly allocated to five groups (n = 5), and their mechanical isometric adductor pollicis activity (twitch height, TH), was monitored. The patients in groups I, II and III received succinylcholine 1 mg/kg followed by 0.04 mg/kg vecuronium 5 min (group I), 15 min (group II) or 30 min (group III) after complete recovery from muscle paralysis. The patients in groups IV and V received only vecuronium 0.045 and 0.080 mg/kg, respectively. Mean maximum TH depression (about 42% of initial value in group IV and 5% in group V) decreased to less than 4% in groups I, II and III regardless of the time interval between the injections of succinylcholine and vecuronium. Mean duration to 90% recovery of vecuronium

induced blockade was prolonged in patients in groups I, II and III when compared with the patients in group IV (28 min vs 12 min).

Moreover, the possible interactions between residual succinylcholine and vecuronium was evaluated, by measuring the amount of vecuronium required to maintain the TH at 10% of its initial value over a 90-min period by the on-demand infusion method in two series of 15 adult patients (ASA class I-II). One group, the vecuronium treatment (V) group, received 0.07 mg/kg of vecuronium and the on-demand infusion; the second group, the succinylcholine-vecuronium treatment group (SV), was given 0.03 mg/kg of vecuronium and on-demand infusion 5 min after the complete recovery of TH after administration of 1 mg/kg of succinylcholine. In this study, after a vecuronium on-demand infusion of long duration (lasting more than 90 min), previous succinylcholine administration does not interfere with late vecuronium requirements and the spontaneous rate of recovery of TH.

Effect of gender
In a study of 40 patients undergoing routine surgery, females were more sensitive to vecuronium than males, requiring 22% less drug to achieve the same degree of neuromuscular block. Similarly, in another study in 60 patients (18-51 years) undergoing elective plastic surgery, the mean percentage depression of T_1 (using TOF monitoring) was 43% greater for females at each dose of vecuronium. The dose-response curve for females was shifted to the left with ED_{50} and ED_{90} of 18.4 and 33.5 μg/kg, respectively, in females, and 23.9 and 45.4 μg/kg, respectively, in males. Moreover, the duration of peak effect, clinical duration, and the total duration differed significantly between men and women. They were 18.7, 26.6 and 50.6 min respectively in men and 26.0, 37.1 and 65.9 min in women.

Elderly patients
In a controlled, randomised study in 40 patients aged 18-50 years and 40 elderly patients (>65 years) who received vecuronium (0.1 mg/kg), the initial dose of vecuronium caused a significantly longer period of clinical relaxation in the elderly group compared with the controls (50 vs. 36 min), and the duration of action of repeated doses was longer in the elderly group.

A randomised, controlled double-blind study on the spontaneous recovery profiles of vecuronium (bolus: 0.1 mg/kg; maintenance 0.02 mg/kg) and cisatracurium in 136 adult (18-64 years) and 141 elderly (≥65 years) patients receiving anaesthesia showed the duration of action and duration of spontaneous recovery of vecuronium, but not of cisatracurium, to be significantly prolonged in the elderly. The clinically effective duration of the initial bolus dose, defined as the meantime to 25% T_1 recovery, for the adult and elderly patients was 34.1 and 47.5 min for vecuronium. The duration of spontaneous sufficient recovery, defined as the meantime interval from 25% T_1 recovery to a T_4:T_1 ratio ≥0.8 after the last bolus dose, for the adult, respectively, elderly patients was 38.5 and 60.3 min for vecuronium.

Overall, these data indicate that there is a risk of prolonged effect of vecuronium in the elderly, and monitoring of neuromuscular function is recommended in this group. The prolonged duration of action in the elderly is thought to be secondary to altered pharmacokinetics consistent with age-related deterioration in renal and hepatic function.

Paediatric population
In a randomised, double-blind, controlled study in 53 children (1-13 years) scheduled for elective surgery who received vecuronium (0.1 mg/kg) or pancuronium (0.1 mg/kg), vecuronium produced a significantly greater number of acceptable intubations than pancuronium (93 vs. 72%). The onset of complete block was quicker after vecuronium (186

vs. 220 s) and the duration to 25% recovery was significantly shorter with vecuronium compared with pancuronium (20 vs. 48 min).

In a randomised, controlled study in 90 children (aged 6 months to 12 years) who underwent elective surgery who received vecuronium (0.1 mg/kg), fazadinium (1 mg/kg) or pancuronium (0.1 mg/kg) satisfactory or excellent intubating conditions were noted in 70%, 70% and 57% of patients, respectively. Time to maximum NMB effect was shorter in the vecuronium group (3.6 min) than in the fazadinium (6.1 min) and pancuronium group (6.9 min). The mean time to the first sign of recovery was the shortest in the vecuronium group (13.0 min) compared with the fazadinium (26.7 min) and pancuronium group (27.0 min).
In a randomised, controlled double-blind study in 23 critically ill patients aged younger than 2 years undergoing congenital heart surgery showed a markedly shorter recovery of neuromuscular transmission after postoperative administration of cisatracurium (2.7 μg/kg/min) compared with vecuronium (1.1 μg/kg/min) (i.e., 30 vs. 180 min). However, there was no evidence that this observed difference in neuromuscular recovery affects outcomes.

In a study in 12 critically ill neonates/infants (median age 4 months) and 18 children (2-10 years) who were admitted to an ICU and required tracheal intubation, there was an age-dependent statistically significant difference in vecuronium requirements and in recovery times between the two age groups. Neonates/infants less than 1 year required 45% less vecuronium (54.7 μg/kg/h) than older children (98.7 μg/kg/h) and had faster recovery to 70% T_4/T_1 (45 vs. 65 min), with no evidence of prolonged weakness. There was no evidence of cumulation.

Age-dependent dose requirement was also observed in a study in 81 paediatric patients scheduled to elective surgical procedure. Results of the study showed that neonates (12-27 days) and infants (mean age 6.2 months) had a mean requirement of vecuronium 105 μg/kg during the first 1 h of anaesthesia, to establish and maintain 90-98% neuromuscular blockade, compared with a mean requirement of 217 μg/kg for children aged 3-10 years. Duration of >90% NMB achieved with 150 μg/kg of vecuronium was prolonged in neonates and infants (110 min) as compared with children (38 min) and adolescents (68 min).

Efficacy in special populations

Renal impairment

In general, vecuronium is considered a suitable muscle relaxant for patients with renal failure because its elimination depends mainly on metabolism by the liver.

A meta-analysis including eight trials comparing the effects of vecuronium (0.05 to 0.14 mg/kg) in patients with either normal renal function or renal failure found no differences were either in onset time, or in recovery index between the two groups, whereas the duration of action was longer in the renal failure group than in the control group (46.4 vs. 31.6 min).

Results of a study in 20 patients undergoing renal transplantation who received either vecuronium (0.05 mg/kg) or atracurium (0.25 mg/kg) indicated that vecuronium may accumulate in renal transplant patients. Time to 90% recovery was comparable in the vecuronium and atracurium group after the initial dose (75.78 vs. 71.98 min). However, after a second dose of vecuronium time to 90% recovery was significantly longer than after a second dose of atracurium (89.23 vs. 57.99 min).

In a study performed with 24 adult patients in end-stage renal failure and 21 normal patients the effective doses required to produce 50, 90 and 95% neuromuscular blockade in patients with renal failure were not significantly different from the doses in the normal patients.

In a study in critically ill neonates/infants and children who were admitted to an ICU and required tracheal intubation, 4 patients requiring peritoneal dialysis for renal failure did not have prolonged recovery, but rather, in infants at least, needed smaller doses.

Hepatic impairment
Vecuronium requirements have been reported to be reduced among recipients of liver transplantations, as the drug is eliminated principally by the liver.

Results of a study in 30 patients undergoing biliary surgery including ten patients with biliary obstruction and twenty patients without biliary obstruction indicate that the neuromuscular blocking effect of vecuronium is significantly prolonged in patients with biliary obstruction. The mean time until injection of the second dose of vecuronium was significantly longer in patients with biliary obstruction (46 min) than in the elderly patients (31 min) and young patients (29 min) without biliary obstruction. The mean total dose of vecuronium was lower in the patients with biliary obstruction (1.2 μg/kg/min) than in the elderly patients (1.7 μg/kg/min) and young patients (2.0 μg/kg/min) without biliary obstruction.

Results of a study in 10 surgical patients with alcoholic liver disease and 10 healthy surgical patients with a mean age of 49 years who received vecuronium (0.1 mg/kg) showed that alcoholic liver disease does not affect the duration of action of vecuronium. The time required to achieve 100% twitch depression was significantly prolonged in patients with liver disease (2.8 ± 0.7 min) compared with controls (1.9 ± 0.4 min). The time to 50% recovery was 59.8 min for liver disease patients and 66.1 min for controls (NS).

Pregnancy
Results of a comparative study on the onset of vecuronium (0.1 mg/kg) neuromuscular block and the conditions of tracheal intubation in 10 patients (mean age 30 years) undergoing elective caesarean section and 10 non-pregnant females (mean age 28 years) showed that administration of vecuronium according to body weight results in a more rapid onset and delayed recovery of neuromuscular block in pregnant women undergoing caesarean section than in the non-pregnant control patients. In patients undergoing caesarean section, the onset time (50% NMB) was shorter than that observed in the control non-pregnant women (80 vs. 144 s). The time of recovery to T_1/control ratio of 25% was longer in the pregnant patients than in the non-pregnant patients (46 vs. 28 min). The conditions for tracheal intubation at 50% neuromuscular block were excellent or good in 90% of the patients in both groups.

In a study on the time-course of action of vecuronium (0.1 mg/kg) in 30 non-pregnant and in 30 postpartum patients within four days after delivery, the clinical duration of vecuronium was significantly prolonged in postpartum patients as compared with non-pregnant subjects (49 vs. 32 min).

In a study in 27 patients undergoing elective caesarean section under general anaesthesia who received vecuronium (initial dose: 0.05 mg/kg; maintenance dose: 0.01 mg/kg) complete neuromuscular block resulted in all cases and lasted for a mean duration of 19.3 min. Nine infants were delivered before the injection of vecuronium and 19 infants were delivered after its injection. There was no significant difference between the Apgar scores in the two groups, suggesting that vecuronium does not cross the placenta in concentrations that affect the newborn.

Neuromuscular disease
Patients with myasthenia gravis are more sensitive to vecuronium bromide due to a reduced number of functioning acetylcholine receptors (AChR) at the neuromuscular junction, resulting in prolonged neuromuscular effects at usual therapeutic doses of vecuronium. In a controlled study in eleven myasthenia gravis patients (mean age 34 years) and seven healthy anaesthetised patients (mean age 39 years) the average ED95 value obtained using electromyographic recordings was 250% greater in control than in myasthenic patients (59 vs. 17 μg/kg). The hourly requirement of vecuronium to maintain an 80-90% neuromuscular blockade was 38 μg/kg in myasthenic and 120 μg/kg in control patients. The ED95 of vecuronium in patients with myasthenia gravis was significantly related to patient's acetylcholine receptor antibody titer.

In a report on the use of vecuronium in three anaesthetised patients with dystrophia myotonica, two patients showed a normal sensitivity to vecuronium, whereas the third patient showed a markedly increased sensitivity. His ED95 was 50% less than the others.

A study compared the effects of d-tubocurarine, pancuronium, and gallamine on two paediatric surgical patient groups: one with a previous history of polio occurring 6 to 12 years prior admission (n=30), and another without history of this disease (n=51). Following uniform premedication, thiopental, N_2O/O_2 + narcotic (fentanyl) anaesthesia was given for reconstructive surgeries; for orotracheal intubation the patients were briefly paralysed with 0.7 mg/kg succinylcholine. After full recovery from the effect of succinylcholine, cumulative ED_{50} values and the recovery index (minutes elapsed from 90% to 50% block of the twitch response) of the three non-depolarising muscle relaxants were determined. The ED50 of d-tubocurarine and pancuronium were significantly lower with both neuromuscular responses in the post-polio groups as compared to the controls. A tendency toward lower ED50 values in the polio group was also observed with gallamine ($P<0.2$). Recovery times were identical in the polio versus non-polio groups.

Obesity
Results of a study on the effect of obesity on the duration of action of vecuronium (0.1 mg/kg) in 28 neurosurgical patients, the time for recovery of twitch response from 5 to 25% was significantly longer in obese patients (14.6 min) than it was in non-obese control patients (6.9 min).

In a study in seven obese patients and seven control patients of ideal body weight who received vecuronium (0.1 mg/kg), recovery was prolonged in obese patients. Times to 50% recovery of twitch were longer in the obese than in the control patients (75 vs. 46 min) as were 5%-25% recovery times (14.9 vs. 10.0 min) and 25%-75% recovery times (38.4 vs. 16.7 min).

Hypothermia
A study in 10 normothermic and 10 mildly hypothermic (34.5°C) patients who received vecuronium (0.1 mg/kg) showed that mild hypothermia significantly increases the duration of action of and time for spontaneous recovery from vecuronium-induced neuromuscular blockade. Duration of action of vecuronium was 28 min during normothermia compared with 62 min during hypothermia, respectively. The corresponding values for spontaneous recovery from T_1 = 10% to TOF ratio >75% were 37 and 80 min.

Burns
In a comparative study in 20 adults with 27-81% total body surface area burn and non-burn controls, burn patients showed enhanced distributional clearance at the terminal phase (0.12

vs 0.095 l/min), which yielded shorter elimination half-life for vecuronium (5.5 vs 6.6 h). This may partially contribute to the known resistance to vecuronium in patients with major burns.

Conclusion on clinical efficacy
The applicant has submitted adequate bibliographic evidence to support the clinical efficacy of vecuronium 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.

IV.5 Clinical safety
The safety data from clinical studies of vecuronium to facilitate tracheal intubation and provide skeletal muscle relaxation during surgery at relevant doses are summarised below. No drug-related deaths were reported in the clinical studies performed with the recommended therapeutic doses of vecuronium.

Adults
In the majority of the clinical studies reviewed by the applicant, vecuronium bromide was reported as well-tolerated and no adverse events were reported.

In a randomised study comparing priming infusion (5 μg/kg/min for 2 and 3 min) regimen of vecuronium using patient controlled analgesia (PCA) pump with the usual bolus (10 μg/kg) priming in 112 patients (34-54 years) scheduled for cholecystectomy and abdominal surgeries, adverse effects observed in patients who received the usual bolus dose were blurring of vision (50%), difficulty in opening eye (33%), heaviness over the chest (4%) and difficulty in head lift (4%). No adverse effects were observed in the groups with 10 μg/kg/min and 15 μg/kg priming dose. In the group with a 20 μg/kg priming dose, 7% patients complained of blurring of vision and diplopia.

In a randomised, comparative study in 40 outpatients who underwent arthroscopy of the knee under anaesthesia and who received either vecuronium (0.1 mg/kg) or atracurium (0.5 mg/kg) side effects reported in the vecuronium group were nausea/vomiting (n=2) and dizziness/headache (n=1). In the atracurium group two patients reported nausea/vomiting and three reported dizziness/headache.

In a double-blind, prospective, randomised trial in 30 women (mean age 31.6 years) undergoing laparoscopy, who received vecuronium or atracurium in equipotent doses (0.1 and 0.4 mg/kg, respectively), mild intraoperative hypotension was equally common (n= 6 and 5, respectively) in both groups as was sinus bradycardia (n=1 each).

In a comparative study in 64 patients (18-65 years) scheduled to undergo surgery who received vecuronium (up to 0.129 mg/kg) or atracurium (up to 0.564 mg/kg), there was no clinical evidence of histamine release during the study. No clinically significant changes in arterial pressure or heart rate were seen after the injection of either drug, although vecuronium caused a statistically significant decrease in heart rate (approximately 5%) at 5 and 10 min after administration.

In a comparative study in 40 elderly patients (mean age 73.1 years) given vecuronium (0.1 mg/kg) or cisatracurium (0.15 mg/kg), no adverse effects were noted in either group.

In a randomised, controlled study on the spontaneous recovery profiles of vecuronium (bolus: 0.1 mg/kg; maintenance 0.02 mg/kg) and cisatracurium in 136 adult (18-64 years) and 141 elderly (≥65 years), in the vecuronium group 3 patients experienced hypotension or bradycardia and two patient's bronchospasms. Nausea (15.7%) and vomiting (4.3%) comprised the most frequent postoperative adverse events (AEs) and occurred almost equally in both young and elderly patients.

Paediatrics
In the majority of the clinical studies reviewed by the applicant, vecuronium bromide was reported as well-tolerated and no adverse events were reported.

In a randomised, double-blind study in 37 critically ill children (aged 3 months to 16 years) requiring mechanical ventilation who received either vecuronium (2.6 μg/kg/min) or cisatracurium (3.9 μg/kg/min) no adverse effects other than prolonged recovery from NMB for vecuronium were observed. No clinically important changes in haemodynamic variables and vital signs were attributed to either drug.

In a randomised, controlled study in 90 children (aged 6 months to 12 years) who underwent elective surgery treatment with vecuronium (0.1 mg/kg), fazadinium (1 mg/kg) or pancuronium (0.1 mg/kg) was well tolerated. The only AEs observed were skin eruptions on the face, neck and upper chest area in two cases each in the vecuronium and fazadinium group and one in the pancuronium group, disappearing within five minutes without treatment.

In a randomised controlled study in 30 children (3-9 years) undergoing elective tonsillectomy who received equipotent doses of vecuronium (0.14 mg/kg) or mivacurium (0.2 mg/kg), mild cutaneous flush of the injection side or the thorax immediately after induction were noticed in two children in the vecuronium group and one child in the mivacurium group. No cardiovascular side effects were observed.

Adverse events by body system
Nervous system disorders
Prolonged neuromuscular blockade lasting up to seven days may occur after the termination of long-term administration (i.e., more than two days) of vecuronium in critically ill patients. There is no significant relation between the presence of prolonged blockade and the total dose of vecuronium, the rate of administration, or the duration of treatment.

In a study in 16 critically ill adult patients who had received vecuronium to facilitate mechanical ventilation for at least two consecutive days, 7 of the 16 patients had prolonged neuromuscular blockade, lasting from six hours to more than seven days, after the termination of vecuronium therapy. All of these 7 patients had renal failure, and no patient without renal failure had prolonged NMB. These seven patients, six of whom were women, had had higher plasma concentrations of 3-desacetylvecuronium, higher plasma magnesium concentrations and lower arterial blood pH values than the nine patients without prolonged neuromuscular blockade. The median total dose of vecuronium was similar in the patients with prolonged blockade and those without prolonged blockade. The median duration of treatment was also similar in the two groups.

Cardiac disorders
A case report described a 14-year-old male that experienced sinus node exit block twice approximately 5 minutes after receiving a 0.08 μg/kg intravenous dose of vecuronium. The block resolved spontaneously without sequelae.

Results of an estimation of the rate of anaphylaxis to NMBDs by analysing cases of NMBD anaphylaxis referred to the only specialised diagnostic centre in Western Australia over a 10-year period revealed 80 patients diagnosed with life-threatening anaphylaxis to an NMBD. Rocuronium was responsible for 56% of cases of NMBD anaphylaxis, succinylcholine for 21%, and vecuronium for 11%. There was no difference in the severity of reactions for different NMBDs. The calculated rate of anaphylaxis of vecuronium was 2.8 per 1000 000 administrations.

Skin and subcutaneous disorders

Results of a 12-year survey at a French paediatric centre conducted to assess hypersensitivity reactions to general anaesthesia in 68 children (mean age 8 years) showed IgE-mediated anaphylaxis in 51 children among them 31 (60.8%) for NMBDs, with vecuronium as the NMBD causing the largest number of reactions (n=24).

A case of anaphylaxis within 1 min of giving vecuronium bromide (4mg) was described in a 48-year-old obese and hypertensive woman who presented with a blood pressure of 74/32 mmHg, a heart rate of 52/min and saturation of 89%. Rashes appeared on the chest and the upper arms. Intradermal testing identified vecuronium bromide to be the offending agent.

In a retrospective observational study, the incidences of intraoperative anaphylaxis to neuromuscular blocking agents (NMBAs) using electronic medical records were determined. Over 9 years, 729 429 patients were exposed to NMBAs, the most frequently used being rocuronium [425 047 (58.3%)] and vecuronium [274 801 (37.7%)]. The overall incidence of intraoperative anaphylaxis was 2.6 per 100 000 (19 cases), and was higher with rocuronium (16 cases, 3.8 per 100 000) than with vecuronium (two cases, 0.7 cases per 100 000), P = 0.014. Comparing the first 3 years with the last 6 years of the observational period, the incidence of intraoperative rocuronium anaphylaxis appeared to increase 1.4-fold (P = 0.006).

Musculoskeletal and connective tissue disorders
In a study on the effects of priming doses of vecuronium and rocuronium on muscular weaknesses and pulmonary function tests in 10 young (25-35 years) and 10 elderly (65-73 years) patients, elderly patients showed more signs of muscle weakness and greater decreases in oxygen saturation and pulmonary function in both groups.

Pregnancy
Studies in pregnant women showed that there is only minimal placental transfer of i.v. vecuronium, and the drug does not reach the foetus in clinically important concentrations. Foetal concentrations of vecuronium are proportional to the maternal dose injected. Compared with its concentration in maternal blood, the concentration of vecuronium in the umbilical vein is low and did not appear to affect the newborn adversely.

A study in 20 pregnant women undergoing general anaesthesia for caesarean section and who received vecuronium (60-80 μg/kg) showed that the drug crosses the human placental barrier to a very limited extent and that its use is safe for the newborn. The mean venous cord concentration of vecuronium was 40 ng/ml and was much lower than the maternal concentration (390 ng/ml). The maternal concentration ratio averaged 11% and was not influenced by the interval between induction and delivery. Apgar scores at 1 and 5 min averaged 9.1 and 9.9.

In a study on the placental transfer and neonatal effects of vecuronium (0.04 mg/kg) in 18 women at term undergoing caesarean section, vecuronium crossed the placenta, as

demonstrated by low concentrations of vecuronium (8.5-26.4 ng/ml) found in umbilical venous blood. At delivery, mean concentrations of vecuronium in maternal vein, umbilical vein and umbilical artery were 162, 17.9 and 9.1 ng/ml, respectively. The ratio of the drug concentration in umbilical venous blood to that in maternal venous blood was 0.11. Clearance and elimination half-life of vecuronium were 6.4 ml/kg/min and 36 min, respectively. Neonatal outcome was not affected adversely by vecuronium, as assessed by Apgar scores and Adaptive Capacity Score (NACS).

Overdose
An accidental overdose of vecuronium at a 50-fold dose of recommended infusion rate (0.5-0.8 mg/kg/h) was given to a haemodynamically unstable 23-month-old child with no adverse effects reported. An incorrect rate was set after a change of infusion pump, which delivered 37 mg (3.83 mg/kg/h) of vecuronium intravenously over one hour. All haemodynamic variables remained virtually unchanged during the infusion and over the next 24 hours.

Conclusion on clinical safety
The applicant has submitted adequate bibliographic evidence to support the clinical safety of vecuronium 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.

IV.6 Risk Management Plan (RMP)
The Applicant has submitted a RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. The Applicant proposes only routine pharmacovigilance and routine risk minimisation measures for all safety concerns. This is acceptable.

IV.7 Discussion on the clinical aspects
The grant of a marketing authorisation was recommended for this application.

V USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) was provided with the application in accordance with legal requirements, including user consultation.

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 from the literature. 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.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory, and in line with current guidelines.

In accordance with legal requirements, the current approved UK versions of the SmPC and PIL for this product are available on the MHRA website.

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations where significant changes are made are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**