Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocuronium bromide 10 mg/ml solution for injection/infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection or infusion contains 10 mg rocuronium bromide. Each vial with 5 ml contains 50 mg rocuronium bromide.

Excipient with known effect
Each vial contains 8.18 mg (0.35 mmol) sodium (as sodium chloride and sodium acetate trihydrate).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection / infusion
Clear colourless to yellow or orange solution.
pH of the solution: 3.8 to 4.2

Osmolality: between 250 and 300 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

As with other neuromuscular blocking agents, Rocuronium bromide may only be administered by, or under the supervision of, an experienced doctor who is familiar with the method of action and use of these medicinal products.

Posology
As with other neuromuscular blocking agents, the dosage of Rocuronium bromide should be individualised in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicinal products that are administered concomitantly and the condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of the neuromuscular block and recovery.

Inhalational anaesthetics potentiate the neuromuscular blocking effects of Rocuronium bromide. This potentiation will only become clinically relevant during anaesthesia when the inhalational anaesthetics have attained the tissue concentrations necessary for interaction. As a result, in the case of operations under inhalational anaesthesia lasting longer than 1 hour, lower maintenance doses of Rocuronium bromide should be administrated at less frequent intervals or the infusion rate should be reduced (see section 4.5).
In adult patients the following dosage recommendations may serve as a general guidance for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical Procedures
Tracheal intubation:

The standard intubating dose during routine anaesthesia is 0.6 mg/kg rocuronium bromide, which results in adequate intubation conditions within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation

conditions are also established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

Caesarean section:
Posologies of 0.6 mg/kg rocuronium bromide do not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation. In blood samples from the umbilical cord, it has been shown that only limited quantities of rocuronium bromide cross the placenta, which do not lead to any clinical adverse reactions in the neonate.

Posologies of 1.0 mg/kg have been investigated during rapid sequence induction, but not in patients undergoing caesarean section.

Higher posologies:
If there is reason to administer a higher posology, initial posologies of up to 2 mg/kg rocuronium bromide have been administered without adverse cardiovascular reactions being observed. The use of higher doses shortens the onset time and prolongs the duration of effect (see section 5.1).

Maintenance dosage:
The recommended maintenance dose is 0.15 mg/kg rocuronium bromide. In case of long- term inhalational anaesthesia it should be reduced to 0.075-0.1 mg/kg of rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train-of-four stimulation (TOF) are present.

Continuous infusion:
If Rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when the neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train-of-four stimulation.

In adults under intravenous anaesthesia, the infusion rate required to maintain the neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h. Under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h.

Continuous monitoring of the neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric Population:
For neonates (0-27 days), infants (28 days to ≤ 3 months), toddlers (> 3 months to ≤ 2 years), children (2-11 years) and adolescents (12 to ≤ 17 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

However, the duration of action of the single intubating dose will be longer in neonates and infants than in children (see Section 5.1).

For continuous infusion in paediatrics, the infusion rates, with exception of children, are the same as for adults. For children, higher infusion rates might be necessary.

Thus, for children the same initial infusion rates as for adults are recommended and then this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure.

The experience with rocuronium bromide in rapid sequence induction in paediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure:
The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine induction of anaesthesia is 0.6 mg/kg rocuronium bromide. In patients for whom a prolonged duration of effect is anticipated, a posology of 0.6 mg/kg rocuronium bromide should be considered for rapid sequence induction. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see also 'Continuous infusion' and section 4.4).

Overweight and obese patients:
When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account a lean body mass.

Intensive Care Procedures

Tracheal intubation
For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance dosing
The use of an initial loading dose of 0.6 mg/kg rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response.

Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Special populations
Rocuronium bromide is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and elderly patients due to a lack of data on safety and efficacy.

Method of administration
Intravenous use
Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium or the bromide ion, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Since Rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this active substance until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. In the event of intubation difficulties resulting in a clinical need for immediate reversal of neuromuscular blockage induced by rocuronium bromide, the use of sugammadex should be considered.

As with other neuromuscular blocking agents, residual curarization has been reported for Rocuronium. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Elderly patients (65 years or older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent (such as sugammadex or acetylcholinesterase inhibitors) should be considered, especially in those cases where residual curarization is more likely to occur.

Anaphylactic reactions can occur following administration of neuromuscular blocking agents. Precautions should always be taken for the treatment of such reactions. Extreme caution is required in the case of previous anaphylactic reactions to neuromuscular blocking agents, as there have been reports of allergic cross-reactivity between neuromuscular blocking agents. As neuromuscular blocking agents are known to cause histamine release, both locally at the injection site and systemically, attention should be paid to the possible occurrence of itching and erythema at the injection site and/or systemic histaminoid (anaphylactoid) reactions when administering these medicinal products. In clinical studies, only a slight increase has been

observed in mean plasma histamine levels following rapid administration of a bolus dose of 0.3–0.9 mg/kg rocuronium bromide.

In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular blockage and/or overdose, it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to the effect in the individual patient. This should be done by or under the supervision of experienced clinicians who are familiar with the effects and with appropriate neuromuscular monitoring techniques.

Myopathy has frequently been reported in intensive care after long-term concurrent use of non-depolarising neuromuscular blockers and corticosteroids. The period of use of muscle relaxants should therefore be kept as short as possible in patients receiving both muscle relaxants and corticosteroids.
If suxamethonium is used for intubation, it is recommended that rocuronium bromide be administered only if the patient is recovered from the neuromuscular blockade caused by suxamethonium.

As rocuronium bromide is always used with other medicinal products and because of the risk of malignant hyperthermia during anaesthesia, even in the absence of known triggering factors, physicians must be aware of the early symptoms, confirming diagnosis and treatment of malignant hyperthermia prior to the anaesthesia. Animal studies show that rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with Rocuronium bromide have been reported during post-marketing surveillance, but the causal connection has not been proven.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuroniumbromide:

Hepaticand/or biliary tract disease and renal failure
Rocuronium bromide is excreted in urine and bile. Therefore, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of the effect has been observed with doses of 0.6 mg/kg rocuronium bromide.

Prolonged circulation time
Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and an oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of the effect. The duration of action may also be prolonged by reduced plasma clearance.

Neuromuscular disease
Like other neuromuscular blocking agents, rocuronium bromide should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of rocuronium bromide may have profound effects and rocuronium bromide should be titrated to the response.

Hypothermia
In surgery under hypothermic conditions, the neuromuscular blocking effect of rocuronium bromide is increased and the duration prolonged.

Obesity
Like other neuromuscular blocking agents, rocuronium bromide may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight.

Burns
Patients with burns are known to develop resistance to non-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to the response.

Treatment with magnesium salts for pre-eclampsia
As magnesium salts enhance neuromuscular blockade, reversal of the neuromuscular block after the administration of neuromuscular blocking agents may be delayed or insufficient in patients treated with magnesium salts for pre-eclampsia. The posology of rocuronium bromide in such patients should be reduced and titrated based on the muscle response obtained.

Conditions which may increase the effects of Rocuronium bromide

Hypokalaemia (e.g. after severe vomiting, diarrhoea or diuretic therapy), hypermagnesemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia.

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interactions

The following medicinal products have been shown to influence the magnitude and/or duration of the effect of non-depolarising neuromuscular blocking agents:

Increased effect
- Halogenated volatile anaesthetics enhance the neuromuscular blockade of rocuronium bromide. The effect only becomes evident with maintenance dosing (see section 4.2). Reversal of the block using acetylcholinesterase inhibitors may also be inhibited
- Following intubation using suxamethonium (see section 4.4).
- Long term use of corticosteroids and rocuronium in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).

Other medicinal products:
- antibiotics: aminoglycosides and polypeptide antibiotics, lincosamides and acylamino-penicillin antibiotics.
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium antagonists, lithium salts, local anaesthetics (lidocaine i.v., bupivacaine epidural) and acute administration of phenytoin or beta-blocking agents.

Recurarisation has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4).

Decreased effect
- Prior chronic administration of corticosteroids, phenytoin or carbamazepine
- Protease inhibitors (gabexate, ulinastatin).

Variable effect
- Administration of other non-depolarising neuromuscular blocking agents in combination with rocuronium bromide may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
- Suxamethonium given after the administration of rocuronium bromide may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

Effect of rocuronium on other medicinal products
When combined with lidocaine, rocuronium bromide could result in a more instant effect of lidocaine.

Paediatric population
Interaction studies have only been performed in adults. The above mentioned interactions for adults and the special warnings and precautions for use of these medicines (see section 4.4) should also be taken into account for paediatric population.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no clinical data on the use of rocuronium bromide in pregnant women. Animal studies do not indicate direct or indirect undesirable effect on pregnancy, embryonal/foetal development, birth or postnatal development (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Rocuronium bromide during pregnancy.

Caesarean section
Rocuronium bromide may be used for a rapid sequence induction in patients undergoing caesarean section, provided no intubation difficulties are anticipated and an adequate posology of the anaesthetic is administered or suxamethonium has been used for the intubation. It has been demonstrated that posologies of 0.6 mg/kg rocuronium bromide can be safely used for caesarean section. Rocuronium bromide does not affect Apgar score, foetal muscle tone nor cardiorespiratory adaptation.

In blood samples from the umbilical cord, it has been shown that only limited quantities of rocuronium bromide pass the placenta, which do not lead to any clinical adverse reactions in the neonate.
Note 1: doses of 1.0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg/kg is recommended in this patient group.

Note 2: As magnesium salts enhance the neuromuscular blockade, reversal of the neuromuscular blockade after administration of neuromuscular blocking agents may be delayed or insufficient in patients treated with magnesium salts for pre-eclampsia. The posology of rocuronium bromide in such patients should therefore be reduced and titrated based on the muscle response obtained.

Breast-feeding
It is unknown whether rocuronium bromide/metabolites are excreted in human milk. Other medicinal products of this class show little excretion into breast milk and low resorption by the suckling child. Available data in rats have shown excretion of insignificant levels of rocuronium bromide in milk. Rocuronium bromide should only be administered to women who are breast-feeding if the treating doctor decides that the benefits outweigh the potential risks. It is recommended not to breast-feed after the administration of a single dose during five elimination half-lives of rocuronium, which is about 6 hours.

Fertility
There are no data with regard to effects of rocuronium bromide on fertility.

4.7 Effects on ability to drive and use machines

As rocuronium bromide is used as a general anaesthetic adjunct, the normal precautionary measures after general anaesthesia should be taken for outpatients.

4.8 Undesirable effects

Summary of the safety profile
The most common undesirable effects are pain/reaction around injection site, changes in vital functions and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

Tabulated Summaries of adverse reactions:

MedDRA SOC	**MedDRA preferred term[1]**		
	Uncommon/rare[2] (≥1/1,000 to <1/100 / ≥1/10,000 to <1/1,000)	**Very rare[2]** (<1/10 000)	**Not known** (cannot be estimated from the available data)
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Cardiac disorders	Tachycardia		Kounis syndrome
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and		Bronchospasm	Apnoea Respiratory failure

mediastinal disorders			
Skin and subcutaneous tissue disorders		Angioneurotic oedema Urticaria Skin rash Erythematous rash	
Musculoskeletal and connective tissue disorders		Muscular weakness[3] Steroid myopathy[3]	
General disorders and administration site conditions	Medicinal product ineffective Reduced medicinal product effect/therapeutic response Increased medicinal product effect/increased therapeutic response Pain at site of injection Reaction at site of injection	Face oedema	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Complication in respiratory tract from anaesthesia	

[1] Frequencies are estimated on the basis of post-marketing monitoring reports and data from the general literature.
[2] Exact frequencies cannot be obtained from post-marketing monitoring data and therefore the reporting frequency is divided into 2 categories rather than 5.
[3] Following prolonged use in intensive care.

Description of selected adverse reactions

Anaphylactic reaction

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide, have been reported. Anaphylactic/anaphylactoid reactions include symptoms such as bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse – shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, they should always be taken into account and the necessary precautions should be taken (see section 4.4).

Histamine release and histaminoid reactions

Since neuromuscular blocking agents are known to be capable of inducing histamine release, both locally at the injection site and systemically, it is important to always watch out for the occurrence of itching and erythema at the site of injection and/or systemic histaminoid (anaphylactoid) reactions (see also under "Anaphylactic reactions" above) when administering these medicinal products.

In clinical studies only a slight increase in mean plasma histamine level has been observed following rapid bolus administration of 0.3-0.9 mg/kg rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarising blocking agents as a class consists of an extension of the agent's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea.

Myopathy
Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see also section 4.4 and 4.5).

Local injection site reactions
During rapid sequence induction of anaesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Paediatric population
A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide (up to 1mg/kg) showed that tachycardia was identified as adverse drug reaction with a frequency of 1.4%.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system:
HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. There are two options for the reversal of neuromuscular block:
(1) In adults, sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block.
(2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of rocuronium bromide, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED_{90} (135 mg/kg) was administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents, other quaternary ammonium compounds.

ATC code: M03AC09

Mechanism of action
Rocuronium bromide is an intermediate acting non-depolarising neuromuscular blocking agent with a fast onset possessing all of the characteristic pharmacological actions of this class of medicinal products (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic properties
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/kg. The ED_{95} in newborn infants and infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively).

The clinical duration of action (the duration from the moment of administration to the recovery of the muscle response to 25% of the control value) at a posology of 0.6 mg/kg rocuronium bromide is 3040 minutes. The total duration of action (time until spontaneous recovery of the muscle response to 90% of control value) is 50 minutes. The mean time to spontaneous recovery of muscle response 25 to 75% of the control value after a bolus posology of 0.6 mg/kg rocuronium bromide is 14 minutes. With a lower posology of 0.3-0.45 mg/kg rocuronium bromide (1-1.5 x ED_{90}), onset is later and duration of action is shorter. With a higher posology of 2 mg/kg, the duration of action is 110 minutes.

Clinical efficacy and safety

Intubation during routine anaesthesia

Within 60 seconds after intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED_{90} under balanced anaesthesia), adequate intubation conditions can be achieved in nearly all patients. In 80% of these patients intubation conditions are rated excellent. Within 2 minutes general muscle paralysis adequate for any type of procedure is established. After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are reached after 90 seconds.

Rapid sequence induction

During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, after administration of a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. After administration of a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Paediatric population

Mean onset time in infants, toddlers and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. Comparison within paediatric age groups showed that the mean onset time in neonates and adolescents (1 min) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min, respectively).

The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. Comparing within paediatric age groups demonstrated that mean time to reappearance of T3 was prolonged in neonates and infants (56.7 and 60.7 min, respectively) when compared to toddlers, children and adolescents (45.3, 37.6 and 42.9 min, respectively).

Mean (SD) time to onset and clinical duration following 0.6 mg/kg rocuronium initial intubating dose during sevoflurane/nitrous oxide and isoflurane/nitrous oxide (maintenance) anaesthesia (Paediatric patients) PP group*

	Time to maximum block ** (min)	Time to reappearance of T3 ** (min)
Neonates (0-27 days) n=10	0.98 (0.62)	56.69 (37.04) n=9
Infants (28 days-≤3 months) n=11	0.44 (0.19) n=10	60.71 (16.52) n=11
Toddler (>3 months-23 months) n=30	0.59 (0.27) n=28	45.46 (12.94) n=27
Children (2-11 years) n=34	0.84 (0.29) n=34	37.58 (11.82)
Adolescents (11-17 years) n=31	0.98 (0.38)	42.90 (15.83) n=30

* Dose of rocuronium administered within 5 seconds.

**[2] Calculated from the end of administration of the rocuronium intubating dose

Elderly patients and patients with hepatic and/or biliary tract disorders and/or renal insufficiency

The duration of the effect of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes) (see section 4.2). No cumulation of effect (progressive increase in duration of action) with repetitive maintenance doses at the recommended level has been observed.

Intensive Care

Following prolonged continuous infusion in intensive care, the time to recovery of the TOF ratio to 0.7 depends on the depth of the neuromuscular block at the end of the infusion. After continuous infusion for 20 hours or more, the median (range) time

between the return of T2 to TOF stimulation and recovery of a TOF ratio of 0.7 is approximately 1.5 (1 – 5) hours in patients without multiple organ failure and 4 (1–25) hours in patients with multiple organ failure.

Cardiovascular surgery
In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum blockage after receiving a dose of 0.6-0.9 mg/kg rocuronium bromide are a slight and clinically insignificant increase in heart rate up to 9% and an increase in mean arterial blood pressure up to 16% from the control values.

Antagonism of the muscle relaxant effect
Administration of sugammadex or acetylcholinesterase inhibitors such as neostigmine, pyridostigmine or edrophonium, antagonises the action of rocuronium bromide. Sugammadex can be given for standard reversal (at 12 post tetanic counts (PTC) to the return of T_2), or for immediate reversal (3 minutes after administration of rocuronium bromide).

Acetylcholinesterase inhibitors can be administered upon return of T_2 or the first signs of clinical recovery.

5.2 Pharmacokinetic properties

Absorption, distribution and elimination

After intravenous administration of a single bolus dose of Rocuronium bromide solution for injection, the time course of the plasma concentration runs in three exponential phases. In normal adults, the mean (95%CI) elimination half-life is 73 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193-214) ml/kg and the plasma clearance is 3.7 (3.5-3.9) ml/kg/min.

Rocuronium bromide is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabelled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as rocuronium bromide.

Biotransformation
No metabolites are detected in the plasma.

Paediatric population
Pharmacokinetics of rocuronium bromide in paediatric patients (n=146) with ages ranging from 0 to 17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance (l/kg/h). The volume of distribution (l/kg) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarized below:

Estimated PK parameters of rocuronium bromide in typical paediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/Nitrous oxide (maintenance anaesthesia)

PK Parameters	Patient age range				
	Term newborn infants (0-27 days)	Infants (28 days to 2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (11-17 years)
CL (l/kg/h)	0.31 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of distribution (l/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
$t_{½\beta}$ (h)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

Elderly patients and patients with hepatic and/or biliary tract disorders and/or renal failure
In controlled studies, the plasma clearance in geriatric patients and in patients with renal dysfunction was reduced, however, this was reaching the threshold of statistical significance in most studies. In patients with hepatic failure, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min (see also section 4.2).

Intensive care
When administered as a continuous infusion to facilitate mechanical ventilation for a time period of 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A high variability between patients was found in controlled clinical studies, related to the nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (±SD) elimination half-life of 21.5 (±3.3) hours, an (apparent) volume of distribution at steady state of 1.5 (±0.8) l/kg and a plasma clearance of 2.1 (±0.8) ml/kg/min were found.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of rocuronium bromide when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on results obtained in clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate
Acetic acid, glacial (for pH adjustment)
Sodium chloride
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substance: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin.

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6

6.3 Shelf life

Unopened vial: 2 years
After dilution:
Chemical and physical in-use stability has been demonstrated for 72 hours at 30°C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator 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.

6.4 Special precautions for storage

Before opening: Store in a refrigerator (2–8°C).

Storage out of the refrigerator:
Rocuronium bromide solution for injection may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks, after which it should be discarded. The product should not be placed back into the refrigerator, once it has been kept outside. The storage period must not exceed the shelf-life.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear glass vial (Type I) with stopper (bromobutyl rubber) and yellow flip off aluminium seal.

Pack size: 10 x 5ml

6.6 Special precautions for disposal and other handling

For single use only.
Any unused solutions should be discarded.

The solution is to be visually inspected prior to use. Only clear solutions free from particles should be used.

Rocuronium bromide solution for injection has been shown to be compatible with: sodium chloride 9 mg/ml (0.9%), glucose 50 mg/ml (5%), glucose 50 mg/ml (5%) in sodium chloride 9 mg/ml (0.9%), water for injections, Lactated Ringers solution and Haemaccel for in-use concentrations of 0.5 mg/ml and 2 mg/ml.

If Rocuronium bromide solution for injection is administered via the same infusion line with other medicinal products, it is important that the infusion line is adequately flushed (e.g. with sodium chloride 9 mg/ml (0.9 %) solution for infusion) between administration of Rocuronium bromide solution for injection and medicinal products for which incompatibility with rocuronium bromide has been demonstrated or for which compatibility with rocuronium bromide has not been established.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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