Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocuronium 10 mg/ml solution for injection / infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of solution for injection / infusion contains 10 mg rocuronium bromide.

Each vial with 2.5 ml contains 25 mg rocuronium bromide.

Each vial with 5 ml contains 50 mg rocuronium bromide.

Each vial with 10 ml contains 100 mg rocuronium bromide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection / infusion

Clear, colourless to pale brownish-yellow solution
pH of the solution: 3.8 to 4.2
Osmolality: 270– 310 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rocuronium is indicated in adult 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 is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjunct in the intensive care unit (ICU) (e.g. to facilitate intubation), for short term use.

4.2 Posology and method of administration

Rocuronium bromide should be administered only by an experienced staff familiar with the use of neuromuscular blocking agents. Adequate facilities and staff for endotracheal intubation and artificial ventilation have to be available for immediate use.

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 becomes clinically relevant during the course of anaesthesia when a certain tissue concentration of the volatile agents is reached. Consequently, adjustments should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of rocuronium bromide during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (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 rocuronium bromide per kg body weight, which results in adequate intubation conditions within 60 seconds in nearly all patients. A dose of 1.0 mg rocuronium bromide per kg body weight 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 rocuronium bromide per kg body weight is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

Higher doses
Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dosage:
The recommended maintenance dose is 0.15 mg rocuronium bromide per kg body weight. In case of long-term inhalational anaesthesia it should be reduced to 0.075 - 0.1 mg of rocuronium bromide per kg body weight.

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 rocuronium bromide per kg body weight 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.

Dosage in pregnant patients:
In patients undergoing Caesarean section, it is recommended to only use a dose of 0.6 mg rocuronium bromide per kg body weight, since a 1.0 mg/kg dose has not been investigated in this patient group.

Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium should be reduced and be titrated to twitch response.

For further information see also section 4.6.

Paediatric population
For neonates (0-27 days), infants (28 days to 2 months), toddlers (3 months to 23 months), 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 (2-11 years), are the same as for adults. For children aged 2-11 years higher infusion rates might be necessary.

Thus, for children (2-11 years) the same initial infusion rates as for adults are recommended and 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 facilitation tracheal intubation conditions during rapid sequence induction in paediatric patients.

Dosage in geriatric 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 anaesthesia is 0.6 mg rocuronium bromide per kg body weight. A dose of 0.6 mg per kg body weight should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected however adequate conditions for intubation may not be established for 90 seconds after administration of rocuronium bromide. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075 - 0.1 mg rocuronium bromide per kg body weight, and the recommended infusion rate is 0.3 - 0.4 mg/kg/h (see Continuous infusion) (see also section 4.4)

Dosage in 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 ideal body weight.

Intensive care procedures

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

Administration
Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion (for further information see also section 6.6). This medicinal product is for single use only.

4.3 Contraindications

Rocuronium bromide is contra-indicated in patients with hypersensitivity to rocuronium bromide or to 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 medicinal product 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.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for Rocuronium. In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Geriatric 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 reversal agent (such as sugammadex or acetylcholinesterase inhibitors) should be considered, especially in those cases where residual curarization is more likely to occur.

It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering Rocuronium, hypersensitivity to other neuromuscular blocking agents should be excluded. Rocuronium should only be used when absolutely essential insusceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

Dose levels higher than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation.

In general, following long term use of neuromuscular blocking agents 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 neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to 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.

Because rocuronium bromide is always used with other drugs and because of the risk of malignant hyperthermia during anaesthesia, even in the absence of known triggering factors, physicians should be aware of the early symptoms, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of anaesthesia. Animal studies have shown that rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with rocuronium bromide have been observed through post-marketing surveillance; however, the casual association has not been proven.

Myopathy after long term administration of other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

Rocuronium should only be administered after full recovery from the neuromuscular blockade caused by suxamethonium.

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

Hepatic and/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 rocuronium bromide per kg body weight.

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

Neuromuscular disease
Like other neuromuscular blocking agents, rocuronium bromide should be used with extreme caution in patients with 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-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of rocuronium bromide
Hypokalaemia (e.g. after severe vomiting, diarrhoea or diuretic therapy), hypermagnesaemia, 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 medicinal product contains less than 1 mmol sodium (23 mg) per vial (2.5ml, 5ml, 10ml) i.e. 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-depolarizing neuromuscular blocking agents:

Effect of other medicinal products on rocuronium bromide

Increased effect:
- Halogenated volatile anaesthetics potentiate the neuromuscular block of rocuronium bromide. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.4).
- High doses of: thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate and propofol
- Other non-depolarizing neuromuscular blocking agents.
- Prior administration of suxamethonium (see section 4.4).
- Long-term concomitant use of corticosteroids and rocuronium bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other medicinal products:
- antibiotics: aminoglycosides, lincosamides (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, high doses of metronidazole.
- diuretics, thiamine, MAO inhibiting agents, quinidineand its isomer quinine, protamine, adrenergic blocking
- agents, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v., bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents.

Recurarization 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:
- Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives
- Prior chronic administration of corticosteroids, phenytoin or carbamazepine
- Noradrenaline, azathioprine (only transient and limited effect), theophylline, calcium chloride, potassium chloride
- Protease inhibitors (gabexate, ulinastatin).

Variable effect:
- Administration of other non-depolarizing 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 bromide on other medicinal products
Rocuronium bromide combined with lidocaine may result in a quicker onset of action of lidocaine.

Paediatric patients
No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use (see section 4.4) should also be taken into account for paediatric patients.

4.6 Fertility, pregnancy and lactation

Pregnancy
For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. Caution should be exercised when prescribing rocuronium bromide to pregnant women.

Caesarean section

In patients undergoing Caesarean section, rocuronium bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. Rocuronium bromide, administered in doses of 0.6 mg/kg, has been shown to be safe in parturients undergoing Caesarean section. Rocuronium bromide does not affect Apgar score, foetal muscle tone nor cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the newborn infant.

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: reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium bromide should be reduced and be titrated to twitch response.

Breast-feeding

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk. Rocuronium bromide should be given to lactating women only when the attending physician decides that the benefits outweigh the risks. After the administration of a single dose, it is recommended to abstain from next breastfeeding for five elimination half-lives of rocuronium, i.e. for about 6 hours.

4.7 Effects on ability to drive and use machines

Since rocuronium bromide is used as an adjunct to general anesthesia, the usual precautionary measures after a general anesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs 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.

MedDRA SOC	**Preferred term[1]**		
	Uncommon/rare[2] (<1/100,>1/10000)	**Very rare (<1/10 000)**	**Not known**
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 mediastinal disorders		Bronchospasm	Apnoea Respiratory failure
Skin and subcutaneous tissue disorders		Angioedema	

		Urticaria	
		Rash	
		Erythematous rash	
		Itching	
		Exanthema	
Musculoskeletal and connective tissue disorders		Muscular weakness[3]	
		Steroid myopathy[3]	
General disorders and administration site conditions	Drug ineffective	Face oedema	
	Drug effect/ therapeutic response decreased		
	Drug effect/ therapeutic response increased		
	Injection site pain		
	Injection site reaction		
Injury, poisoning and procedural complications	Prolonged neuromuscular block	Airway complication of anaesthesia	
	Delayed recovery from anesthesia		

Anaphylactic reaction
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide, have been reported. Anaphylactic/anaphylactoid reactions are: 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, one should always assume they may occur and take the necessary precautions.

[1]Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
[2] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over two rather than five categories.
[3]after long-term use in the ICU

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.

Increased histamine level
Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these drugs.

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 rocuronium bromide per kg body weight.

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug'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 section 4.4).

Paediatric population
A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide (up to 1 mg/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 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 can be used 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 ventilation must be continued until spontaneous breathing is restored. Repeated dosage 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 per kg body weight) 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-depolarizing neuromuscular blocking agent with a fast onset, possessing all of the characteristic pharmacological actions of this class of medicinal products (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects
The ED_{90} (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0.3 mg per kg bodyweight. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg,respectively).

Routine practice
Within 60 seconds after intravenous administration of a dose of 0.6 mg rocuronium bromide per kg body weight (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.

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with this dose is 30 - 40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75 % (recovery index) after a bolus dose of 0.6 mg rocuronium bromide per kg body weight is 14 minutes.

With lower dosages of 0.3 - 0.45 mg rocuronium bromide per kg body weight (1 - 1 ½ x ED_{90}), the onset of the effect is slower and the duration of action is shorter. After administration of 0.45 mg rocuronium bromide per kg body weight, acceptable intubation conditions are reached after 90 seconds. With high doses of 2mg/kg, clinical duration is 110 minutes.

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 rocuronium bromide per kg body weight. 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 rocuronium bromide per kg body weight, 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.

Intensive Care
The use of rocuronium in the Intensive Care Unit was studied in two open-label trials. A total of 95 adult patients were treated with an initial dose of 0.6 mg rocuronium bromide per kg body weight, followed by a continuous infusion of 0.2 - 0.5 mg/kg/h during the first hour of administration as soon as twitch height recovers to 10 % or upon reappearance of 1 to 2 twitches to train-of-four (TOF) stimulation. The dosages were individually titrated. In the following hours, doses were decreased under regular monitoring of the TOF stimulation. Administration for a time period of up to 7 days has been investigated.

Adequate neuromuscular blockade was achieved, but a high variability in hourly infusion rates between patients and a prolonged recovery from neuromuscular blockade was observed.

The time to recover of the train of four ratio to 0.7 is not significantly correlated to the total duration of rocuronium infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T2 to train of four stimulation and recovery of the train of four ratio to 0.7 varied between 0.8 and 12.5 hours in patients without multiple organ failure and 1.2 – 25.5 hours in patients with multiple organ failure.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The duration of the effect of maintenance doses of 0.15 mg rocuronium bromide per kg body weight 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 accumulation of effect (progressive increase in duration of action) with repetitive maintenance doses at the recommended level has been observed.

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 (56.7and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 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=28	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 (12-17 years) n=31	0.98 (0.38)	42.90 (15.83) n=30

* Dose of rocuronium administered within 5 seconds.
** Calculated from the end of administration of the rocuronium intubating dose

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 rocuronium bromide per kg body weight 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.

Reversal ofmusclerelaxation
Administration of either sugammadex or acetylcholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium, antagonises the action of rocuronium bromide.

5.2 Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide, 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.

The plasma clearance in geriatric patients and in patients with renal dysfunction is slightly reduced compared to younger patients with normal renal function. In patients with hepatic diseases, 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).

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.

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. No metabolites are detected in the plasma.

Paediatric patients
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.hr-1kg-1). The volume of distribution (l.kg-1) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarised 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 (12-17 years)
CL (L/kg/hr)	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)
T1/2β (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction and genotoxicity.

Carcinogenicity studies have not been performed with rocuronium bromide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections

Acetic acid, glacial (for pH-adjustment)

Sodium chloride

Sodium acetate trihydrate

6.2 Incompatibilities

Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substances: 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: 3 years

Opened vial: The product should be used immediately after opening the vial.

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

From the 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.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Storage out of the refrigerator:

Rocuronium may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum of 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

Colourless glass vials (type I) with chlorobutyl rubber stopper and aluminium cap. Content of the vials: 2.5 ml, 5 ml or 10 ml.

Package sizes:
Packaging of 5 and 10 vials each containing 2.5 ml.
Packaging of 5 and 10 vials each containing 5 ml.
Packaging of 5 and 10 vials each containing 10 ml.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused solutions should be discarded.

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

Rocuronium name has shown to be compatible with: sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5%) solution for infusion.

If rocuronium bromide 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 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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