Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocuronium Bromide 10mg/ml Solution for Injection/Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of Rocuronium Bromide contains 10mg of rocuronium bromide.

Each 5ml vial contains 50 mg rocuronium bromide.
Each 10ml vial contains 100 mg rocuronium bromide.

Excipient(s) with known effect:
Each 5 ml of Rocuronium Bromide contains 7.8 mg of sodium.
Each 10 ml of Rocuronium Bromide contains 15.6 mg of sodium.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection/Infusion.
Clear, colourless to yellow-orange solution
pH of the solution: 3.8 to 4.2
Osmolality: 256-312 mOsmol/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rocuronium Bromide is indicated in adult and paediatric patients (from term neonates to adolescents [aged 0 to 18 years]) as an adjunct to general anaesthesia to facilitate tracheal intubation during routine 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 tracheal intubation and mechanical ventilation for short term use (See also sections 4.2 and 5.1).

4.2 Posology and method of administration

Posology
Like other neuromuscular blocking agents, Rocuronium Bromide should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.

Like other neuromuscular blocking agents, the dosage of Rocuronium Bromide should be individualized for 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 drugs 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 neuromuscular block and recovery.

Surgical procedures

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Rocuronium Bromide. This potentiation becomes clinically relevant during the course of anaesthesia when the volatile agents have reached the tissue concentrations required for this interaction. Therefore, during surgery under inhalation anaesthesia lasting longer than 1 hour, lower maintenance doses of Rocuronium Bromide at less frequent intervals should be given or the infusion rate should be reduced (see section 4.5).

Adults

In adult patients, the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the ICU.

Tracheal intubation

The standard intubation dose during routine induction of anaesthesia is 0.6 mg/kg Rocuronium Bromide, after which adequate intubation conditions are established 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 established within 60 seconds in nearly all patients. When a dose of 0.6 mg/kg of Rocuronium Bromideis used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of Rocuronium Bromide.

For use of Rocuronium Bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 4.6.

Maintenance dosing

The recommended maintenance dose is 0.15 mg/kg Rocuronium Bromide; in the case of long-term inhalational anaesthesia this should be reduced to 0.075-0.1 mg/kg Rocuronium Bromide. The maintenance doses should best be administered when the twitch height has recovered to 25% of the control twitch height, or when 2 to 3 responses to 'train of four '(TOF)-stimulation 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 neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of the control twitch height or to maintain 1 to 2 responses to TOF stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3 to 0.6 mg/kg/h and under inhalation anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

The dose is individual and monitoring is therefore essential. The above mentioned doses are to be seen as guidance.

Paediatric population

For neonates (0-27 days), infants (28 days-2 months), toddlers (3-23 months), children (2-11 years) and adolescents (12-17 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 paediatric patients, the infusion rate, with the exception of children (2-11 years), is the same as for adults. For children aged 2-11 years, higher infusion rates might be necessary.

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 to 2 twitches to train of four (TOF) stimulation during the procedure.

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

Geriatric patients and patients with hepatic and /or biliary tract disease and /or renal insufficiency

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. A dose of 0.6 mg/kg should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected.

Regardless of the anaesthetic technique, the recommended maintenance dose for these patients is 0.075 to 0.1 mg/kg Rocuronium Bromide, and the recommended infusion rate is 0.3 to 0.4 mg/kg/h (see 'Continuous infusion').

Overweight and obese patients

When used in overweight and obese patients (defined as patients with a body weight of 30% or more above the ideal body weight), doses should be reduced taking into account the 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 the twitch height has recovered to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. The 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) is 0.3 to 0.6 mg/kg/h during the first hour of administration which will need to be decreased over the following 6 to 12 hours, depending on the individual response. Thereafter, individual dose requirements remain relatively constant.

A large variability in infusion rates were seen in clinical trials. The average infusion rates ranging from 0.2 to 0.5 mg/kg/h, depending on the 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 for up to 7 days has been investigated.

Special Populations

Rocuronium Bromide is not recommended for the facilitation of mechanical ventilation in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Method of administration

Rocuronium Bromide is administered intravenously as a bolus injection or continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium 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 drug 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 case of intubation difficulties resulting in a clinical need for immediate reversal of a rocuronium induced neuromuscular block, the use of sugammadex should be considered.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for Rocuronium Bromide. 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. Elderly patients (65 years or older) may be at increased risk of residual neuromuscular blockade. Other factors which could cause residual neuromuscular blockade 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 should be considered (such as sugammadex or acetylcholinesterase inhibitors), especially in those cases where residual neuromuscular blockade 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. Anaphylactic reactions may occur after administration of neuromuscular blocking agents. Precautions for treating

such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

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 block and/or overdosage 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 patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long term administration of other non-depolarising 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.

If suxamethonium is used for intubation, the administration of Rocuronium Bromide should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

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

Hepatic and / or biliary tract disease and renal failure

Because rocuronium is excreted in the urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary disorders and/or renal failure. In these patient groups prolongation of the duration of action has been observed with doses of 0.6 mg/kg rocuronium bromide.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, advanced 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 disorders

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-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Treatment with magnesium salts for toxaemia

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.

Conditions which may increase the effects of Rocuronium Bromide

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

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

Each ml contains 1.56 mg sodium. This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially “sodium- free”.

4.5 Interaction with other medicinal products and other forms of interactions

The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

Effect of other medicinal products on Rocuronium Bromide

Increased effect

- Halogenated volatile anaesthetics (eg, halothane, enflurane and methoxyflurane) 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, propofol.
- Other non-depolarising neuromuscular blocking agents.
- 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: aminoglycoside, lincosamide (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics , tetracyclines, high doses metronidazole.
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or ß-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 phenytoin or carbamazepine.
- Protease inhibitors (gabexate, ulinastatin).
- Calcium chloride, potassium chloride

- Noradrenaline, azathioprine (only transient and limited effect), theophylline
- Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives

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 Bromide on other drugs

Combined use with lidocaine may result in a faster 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-1, has been shown to be safe in parturients undergoing Caesarean section. Rocuronium Bromide does not affect Apgar score, foetal muscle tone or cardio respiratory 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.

Note: 1 - doses of 1.0 mg/kghave 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.

Lactation

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.

Fertility

There are no data with regard to effects of Rocuronium Bromide on fertility.

4.7 Effects on ability to drive and use machines

Rocuronium Bromide has major influence on the ability to drive and use machines**.** It is not recommended to use potentially dangerous machinery or to drive a car during the first 24 hours after the full recovery from the neuromuscular blocking action of Rocuronium Bromide.

Since Rocuronium Bromide is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

The frequency of undesirable effects is classified into the following categories: uncommon/rare (≥1/10,000 to <1/100); very rare (<1/10,000); not known (cannot be estimated from the available data).

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 System Organ Class	**MedDRA Preferred Term[1]**	
	Uncommon/ Rare[2] (≥1/10,000 to <1/100)	**Very rare (<1/10,000)**
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm
Skin and subcutaneous tissue disorders		Angioneurotic oedema Urticaria Rash Erythematous skin rash
Musculoskeletal and connective tissue disorders		Muscular weakness[3] Steroid myopathy[3]
General disorders and administration site conditions	Drug ineffective Drug effect/ therapeutic response decreased Drug effect/ therapeutic response increased Injection site reaction Injection site	Face oedema

	pain	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia

[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

Myopathy

Myopathy has been reported after use of various neuromuscular blocking agents in combination with corticosteroids in the ICU (see also sections 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 an induction agent. In clinical studies, pain on injection was observed in 16% of patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0.5% of patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Class effects

Anaphylactic reactions

Although very rare, severe anaphylactic/anaphylactoid reactions to neuromuscular blocking agents, including Rocuronium Bromide were reported. The anaphylactic /anaphylactoid reactions are: bronchospasm, alteration at cardiovascular level (e.g., hypotension, tachycardia, circulatory collapse, shock), and cutaneous disorders (e.g., angioedema, urticaria).These reactions, in some cases, are fatal. Due to the potential severity of these reactions, one should always take into account the necessary precautions (see section 4.4).

Increased histamine level

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically, the possible occurrence of itching and

erythematous reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions such as bronchospasm and cardiovascular changes e.g. hypotension and tachycardia should always be taken into consideration when administering these drugs. Rash, exanthema, urticaria, bronchospasm and hypotension have been reported very rarely in patients given Rocuronium Bromide.

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 non depolarising 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 apnea.

Reporting of adverse side effects
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, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Paediatric patients

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%.

4.9 Overdose

In the event of overdosage 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. A dosage of 16 mg/kg is recommended. After administration of sugammadex, the patient should be carefully monitored for sustained return of neuromuscular function.
(2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) 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/kg rocuronium bromide) was administered.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group (ATC code): muscle relaxants, peripherally acting agents, ATC code: M03AC09

Mechanism of action

Rocuronium Bromide is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent. It has all the pharmacological properties characteristic to this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects

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

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) at a dose of 0.6 mg/kg Rocuronium Bromide is 30-40 minutes. The total duration (time until spontaneous recovery of twitch to 90% of control value) is 50 minutes. The mean time to spontaneous recovery of twitch response from 25% to 75% of control after a bolus dose of 0.6 mg/kgrocuronium bromide is 14 minutes. With a lower dose of 0.3 to 0.45 mg/kg rocuronium bromide (1-1.5 x ED_{90}), there is a later onset and shorter duration of action. With a higher dose of 2 mg/kg the duration of action is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds after intravenous administration of a dose of 0.6 mg/kg rocuronium (2 x ED_{90} of intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established

within 2 minutes. After administration of 0.45 mg/kg Rocuronium Bromide, acceptable intubation conditions are present 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. Within these groups, 70% of the cases were rated as excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following 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 patient

Mean onset time in infants, toddlers and children at an intubating dose of 0.6 mg/kg is slightly shorter than in adults. Comparison between the paediatric age groups showed that the average onset in neonates and adolescents (1.0 minute) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 minutes, respectively). The duration of action and time to recovery are usually shorter in children than in infants and adults. Comparison between the paediatric age groups showed that the average time to return of T_3 was prolonged in neonates and infants (56.7 and 60.7 minutes, respectively) compared with toddlers , children and adolescents (45.5, 37.6 and 42.9 minutes, 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)

	Time to maximum block** (min)	Time to reappearance of T_3** (min)
Neonates (0-27 days) n=10	0.98 (0.62)	56.69 (37.04) n=9
Infants (28 days-2 months) n=11	0.44 (0.19) n=10	60.71 (16.52)
Toddlers (3-23 months) n=28	0.59 (0.27)	45.46 (12.94) n=27
Children (2-11 years) n=34	0.84 (0.29)	37.58 (11.82)

Adolescents (12-17 years) n=31	0.98 (0.38)	42.90 (15.83) n=30

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

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal insufficiency

The duration of the effect of maintenance doses of 0.15 mg/kg of 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 continuous infusion in the ICU, the time of recovery 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 T_2 to TOF-stimulation and recovery of the TOF- ratio to 0.7 is 1.5 (1-5) hours in patients without failure of multiple organs (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 to 0.9 mg/kgrocuronium 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.

Reversal of the muscle relaxant effect

The action of rocuronium can be reversed by either sugammadex or by acetylcholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium). Sugammadex can be given for routine reversal (at 1-2 post-tetanic counts (PTC) for the return of T_2), or for immediate termination (3 minutes after administration of Rocuronium Bromide). Acetylcholinesterase inhibitors can be administered at reappearance of T_2 or the first signs of clinical recovery.

5.2 Pharmacokinetic properties

Distribution and elimination

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% Confidence Interval) 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.

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 is excreted via urine and bile. Excretion in urine approaches 40% within 12-24 hours. After administration of a radio-labelled dose of Rocuronium Bromide, the excretion of the radio-label after 9 days is on average 47% in urine and 43% in faeces. Approximately 50% is recovered as the parent compound.

Biotransformation

No metabolites are detected in the plasma.

Paediatric patients

The apparent volume of distribution in infants (3–12 months) is higher compared to older children (1–8 years) and adults. In children aged 3-8 years, clearance is higher and the elimination half-life is approximately 20 minutes shorter compared to adults and children < 3 years.

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/kg). The volume of distribution (l/kg) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of the typical paediatric patient with each age group are summarized below:

Estimated pharmacokinetic (PK) parameters (mean [SD]) characteristic of Rocuronium Bromide in paediatric patients during sevoflurane and nitrous oxide (induction), and isoflurane/nitrous oxide (maintenance) anaesthesia.

PK parameters	Age of patients				
	Term newborns (0-27 days)	Infants (28 days-2 months)	Infants (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)
Distribution volume (l/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
$t_{½}\beta$ (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal insufficiency

In controlled studies the plasma clearance in geriatric patients and in patients with renal failure was lowered, but in most studies without reaching the limit of statistical significance. In patients with liver failure, the mean elimination half-life extended by 30 minutes and the average plasma clearance is reduced by 1 ml/kg/min. (See section 4.2.)

5.3 Preclinical safety data

Effects in animal studies were observed only at exposures sufficiently in excess of the maximum human exposure levels. These effects are, therefore, of little relevance to clinical practice.

There is no proper animal model to mimic the usually extremely complex clinical situation of the Intensive Care Unit 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 anhydrous (E262)
- sodium chloride
- acetic acid, glacial (for pH adjustment) (E260)
- sodium hydroxide (for pH adjustment) (E524)
- water for injections

6.2 Incompatibilities

Rocuronium Bromide is physically incompatible with solutions of the following drugs: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednislone sodium succinate, thiopental, trimethoprim and vancomycin. Furthermore Rocuronium Bromide is incompatible with Intralipid.

Rocuronium Bromide should not be mixed with other drugs, except those listed in Section 6.6.

If Rocuronium Bromide is administered via the same infusion line that is used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Rocuronium Bromide and drugs for which incompatibility with Rocuronium Bromide has been demonstrated of for which compatibility with Rocuronium Bromide is not established.

6.3 Shelf life

Unopened bottle: 3 years

After first opening: Since Rocuronium Bromide does not contain preservative, the solution should be used immediately after opening the vial.

Diluted product: After dilution with infusion fluids (see section 6.6), chemical and physical in-use stability of the diluted product (see section 6.6) has been demonstrated for 72 hours at 30^{o}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 and would normally not be longer than 24 hours at 2 to 8^{o}C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2-8^{o}C).
Rocuronium Bromide can be stored outside of the refrigerator at a temperature of up to 30^{o}C for a maximum of 12 weeks. 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.

6.5 Nature and contents of container

Rocuronium Bromide 50mg/5ml presentation (10mg/ml)

5 ml glass vial (type I), bromobutyl rubber stopper and aluminium flip-off seal. The rubber stopper of the vial does not contain latex.

Each vial of the 50mg presentation contains 5ml of solution.

Rocuronium Bromide 100mg/10ml presentation (10mg/ml)

10 ml glass vial (type I), bromobutyl rubber stopper and aluminium flip-off seal. The rubber stopper of the vial does not contain latex.

Each vial of the 100mg presentation contains 10ml of solution.

Each carton contains 10 vials.

6.6 Special precautions for disposal and other handling

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

Compatibility studies have been conducted with the following infusion fluids listed below.

Rocuronium Bromide in nominal concentrations of 0.5 mg/ml and 2.0 mg/ml is compatible with:
0.9% NaCl, 5% dextrose, 5% dextrose in 0.9% NaCl, sterile water for injection and lactated Ringer's solution.

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

7 MARKETING AUTHORISATION HOLDER

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Honey Lane
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United Kingdom

8 MARKETING AUTHORISATION NUMBER

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