

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 contains 10 mg rocuronium bromide.

5 mL of solution for injection / infusion contain 50 mg rocuronium bromide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection / infusion.

Clear colourless to pale yellow solution.

pH 3.8 – 4.2

Osmolality : 270 – 310 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocuronium bromide is indicated for use in adult and paediatric patients (from term neonates to adolescents [0 up to 18 years]), as an adjunct to general anaesthesia to facilitate tracheal intubation during routine induction and to achieve general muscle relaxation during surgical procedures. In adults, Rocuronium bromide is also used to facilitate tracheal intubation during rapid induction and as an adjunct in intensive care to facilitate tracheal intubation and mechanical ventilation, for short term use.

4.2 Posology and method of administration

Like other neuromuscular blocking agents, Rocuronium bromide should only be administered by, or under supervision of, an experienced physician familiar with the action and use of these agents.

As with other neuromuscular blocking agents, the dosage of Rocuronium bromide should be determined individually for each patient. The method of anaesthesia used and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicinal products administered concomitantly and the patient's condition must be taken into account when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for determining neuromuscular blockade and recovery of muscle function.

Inhalational anaesthetics potentiate the neuromuscular blocking effect of Rocuronium bromide. This potentiation only becomes clinically relevant in the course of anaesthesia when inhalational anaesthetics have reached the tissue concentrations required for interaction. Consequently, during procedures lasting longer than 1 hour under inhalational anaesthesia, lower maintenance doses of Rocuronium bromide should be administered at less frequent intervals or the infusion rate must be lowered (see section 4.5).

In adults, the following dosage recommendations serve as a general guideline for tracheal intubation and muscle relaxation in short- to long-lasting surgical procedures and for short term use in intensive care.

Surgical procedures

Tracheal intubation

The standard intubation dose during routine induction is 0.6 mg.kg^{-1} rocuronium bromide, after which adequate intubation conditions are reached within 60 seconds in nearly all patients. To facilitate tracheal intubation during rapid induction of anaesthesia, 1 mg.kg^{-1} rocuronium bromide is recommended, after which adequate intubation conditions are also reached within 60 seconds in nearly all patients. If a dosage of 0.6 mg.kg^{-1} rocuronium bromide is used for rapid induction of anaesthesia, it is advisable to intubate the patient only after 90 seconds after administration of rocuronium bromide.

Pregnancy and Caesarean section

Pregnancy: As magnesium salts enhance neuromuscular blockade, reversal of neuromuscular blockade after administration of neuromuscular blocking agents may be delayed or insufficient in patients treated with magnesium salts for toxemia of pregnancy. The dosage of rocuronium bromide in these patients should therefore be reduced and titrated to the twitch response obtained.

Dosages of 0.6 mg.kg^{-1} rocuronium bromide have no influence on the Apgar score, foetal muscle tone or cardiorespiratory adaptation. In umbilical cord blood samples, it has been demonstrated that only limited amounts of rocuronium bromide cross the placenta, which do not lead to clinical adverse effects in the neonate.

Dosages of 1 mg.kg^{-1} have been investigated during rapid induction of anaesthesia, but not in patients undergoing Caesarean section.

Higher dosages

If there is reason to select a higher dosage: patients have been given initial dosages of up to 2 mg.kg^{-1} rocuronium bromide without any adverse cardiovascular effects having been observed. The use of a higher dosage shortens the onset time and prolongs the duration of action (see section 5.1).

Maintenance dosage

The recommended maintenance dosage is 0.15 mg.kg^{-1} rocuronium bromide; in long-term inhalational anaesthesia, this should be reduced to $0.075 - 0.1 \text{ mg.kg}^{-1}$ rocuronium bromide. The maintenance doses should preferably be given when twitch height has recovered to 25 % of the control value, 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 start with an initial bolus dose of 0.6 mg.kg^{-1} rocuronium bromide. Administration by continuous infusion can be started when twitch height starts to recover. The infusion rate should be such that twitch response remains at 10 % of the control value and 1 to 2 responses to TOF stimulation remain present. In adults under intravenous anaesthesia, this equates to an infusion rate of $0.3 - 0.6 \text{ mg.kg}^{-1}.\text{h}^{-1}$ and for those under inhalational anaesthesia to an infusion rate of $0.3 - 0.4 \text{ mg.kg}^{-1}.\text{h}^{-1}$. Continuous monitoring of neuromuscular blockade is recommended, since the required amount varies from patient to patient and is dependent on the method of anaesthesia used.

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 the maintenance dosage are similar to those in adults.

However, in neonates and infants, the duration of action of the single intubation dose will be longer 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 to 11 years inclusive, a higher infusion rate may be necessary.

Thus, the initial dosage for children (2 – 11 years) is the same as for adults and must be subsequently adjusted, so that twitch response remains at 10 % of the control value or 1 or 2 responses to TOF stimulation remain present.

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

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 induction of anaesthesia is 0.6 mg.kg^{-1} rocuronium bromide. In patients in whom a prolonged duration of action is expected, a dosage of 0.6 mg.kg^{-1} rocuronium bromide should be considered for rapid induction of anaesthesia. If a dosage of 0.6 mg.kg^{-1} rocuronium bromide is used for rapid induction of anaesthesia, it is advisable to intubate the patient only after 90 seconds after administration of rocuronium bromide, however muscle relaxation may still not be sufficient for intubation after 90 seconds.

Regardless of the anaesthetic technique used, the recommended maintenance dosage for these patients is $0.075 - 0.1 \text{ mg.kg}^{-1}$ rocuronium bromide, and the recommended infusion rate is $0.3 - 0.4 \text{ mg.kg}^{-1}.\text{h}^{-1}$ (see 'Continuous infusion' and also 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 and calculated on the basis of ideal body weight.

Short term use in intensive care

Tracheal intubation

For tracheal intubation, the same dosage recommendations as for surgical procedures apply.

Maintenance dosage

The use of an initial bolus dose of 0.6 mg.kg^{-1} rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10 %, or when 1 to 2 twitches to TOF stimulation are present. The dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for adults to obtain 80 – 90 % neuromuscular blockade (1 to 2 twitches to TOF stimulation) is $0.3 - 0.6 \text{ mg.kg}^{-1}.\text{h}^{-1}$ during the first hour of administration. The infusion rate should be reduced during the subsequent 6 to 12 hours, depending on the individual response. Thereafter, individual dose requirements remain relatively constant. The use of Rocuronium bromide must be for short term; however the total duration must not exceed 7 days, due to the lack of sufficient long-term data.

Wide variability in infusion rates has been seen in clinical studies. The mean infusion rate ranged from $0.2 - 0.5 \text{ mg.kg}^{-1}.\text{h}^{-1}$, depending on the nature and extent of organ failure, concomitant medication and the individual patient's condition. To meet the needs of the individual patient as far as possible, monitoring of neuromuscular transmission is highly recommended. Administration for a maximum of 7 days has been investigated.

Special populations

Rocuronium bromide is not recommended for facilitating 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 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, patients receiving this agent must be mechanically ventilated until spontaneous breathing has been adequately restored. As with all muscle relaxants, a pre-assessment should be made to establish whether intubation difficulties may be anticipated, particularly when used for rapid induction of anaesthesia. In the event of intubation difficulties resulting in a clinical need for immediate reversal of rocuronium-induced neuromuscular blockade, the use of sugammadex should be considered.

As with other neuromuscular blocking agents, residual curarisation has been reported with use of rocuronium bromide. In order to prevent complications resulting from residual curarisation, 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 curarisation after extubation in the post-operative phase (such as drug interactions or the patient's condition) should also be considered. If sugammadex or another antagonist (e.g. an

acetylcholinesterase inhibitor) is not routinely applied, their use should be considered, especially in those cases where it is likely that residual curarisation will occur.

Anaphylactic reactions can 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, extreme caution should be exercised, since allergic cross-hypersensitivity between neuromuscular blocking agents has been reported. As it is known that neuromuscular blocking agents can cause the release of histamine, both locally at the site of injection and systemically, onset of injection site pruritus and erythema and/or systemic histaminoid (anaphylactoid) reactions should always be considered when administering these medicinal products. In clinical studies, only a slight increase in mean histamine plasma levels has been observed following rapid administration of a bolus dose of 0.3 – 0.9 mg.kg⁻¹ rocuronium bromide.

In general, prolonged paralysis and/or muscle weakness have been reported after long-term use of muscle relaxants in intensive care. In order to help prevent possible prolongation of neuromuscular blockade and/or overdose, monitoring of neuromuscular blockade is highly recommended during the use of muscle relaxants. It is also essential that patients are administered adequate analgesia and sedation during neuromuscular blockade. Furthermore, dosages should be titrated to effect in the individual patient by or under the supervision of an experienced physician familiar with the action of muscle relaxants and appropriate neuromuscular monitoring techniques.

After long-term use of other non-depolarising neuromuscular blocking agents in combination with corticosteroids in intensive care, myopathy has been frequently reported. Therefore, the period of use of muscle relaxants must be limited as much as possible in patients receiving both muscle relaxants and corticosteroids.

If suxamethonium is used for intubation, it is advisable not to administer rocuronium bromide until the patient has recovered from the neuromuscular blockade caused by suxamethonium.

As rocuronium bromide is always used together with other medicinal products and due to 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 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 observed during post-marketing surveillance; however, the causal association has not been proven.

Hypertensive crisis in patients with phaeochromocytoma

Postmarketing data have identified cases of hypertensive crisis temporally related to administration of rocuronium in patients with diagnosed or latent phaeochromocytoma. Rocuronium should therefore be used with caution in such patients.

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

Hepatic and/or biliary tract disease and renal failure

As rocuronium is excreted in the urine and bile, it should be used with caution in patients with clinically relevant hepatic and/or biliary tract disease and/or renal failure. In these patient groups, prolongation of the duration of action has been observed at doses of 0.6 mg.kg⁻¹ rocuronium bromide.

Prolonged circulation time

Conditions in which prolonged circulation time occurs, such as cardiovascular disorders, advanced age and oedema formation associated with an increased volume of distribution, may cause a delayed onset of action. The duration of action may also be prolonged due to reduced plasma clearance.

Neuromuscular disorders

Like other neuromuscular blocking agents, rocuronium bromide should be used with extreme caution in patients with a neuromuscular disorder or after poliomyelitis, since the response to neuromuscular blocking agents may be considerably altered in these cases. The extent and nature of this alteration may vary greatly. In patients with myasthenia gravis or with myasthenic (Eaton-Lambert) syndrome, low doses of rocuronium bromide may have profound effects. In these conditions, 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 of action prolonged.

Obesity

Like other neuromuscular blocking agents, rocuronium bromide may show a prolonged duration of action and a prolonged spontaneous recovery time in obese patients, when doses are calculated on actual body weight.

Burns

Patients with burns are known to develop resistance to non-depolarising muscle relaxants. It is recommended that the dose be titrated to the effect.

Treatment with magnesium salts in toxæmia of pregnancy

As magnesium salts enhance neuromuscular blockade, reversal of neuromuscular blockade after administration of neuromuscular blocking agents may be delayed or insufficient in patients treated with magnesium salts for toxæmia of pregnancy. The dosage of rocuronium bromide in these patients should therefore be reduced and titrated to the twitch response obtained.

Conditions which may increase the effects of rocuronium bromide

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

Severe electrolyte imbalances, altered blood pH or dehydration must therefore be corrected, where possible, prior to administration of rocuronium bromide.

Sodium

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

4.5 Interaction with other medicinal products and other forms of interaction

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

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 may also be inhibited
- after intubation with use of suxamethonium (see section 4.4)
- long-term use of corticosteroids and rocuronium bromide in intensive care may result in prolonged neuromuscular block or myopathy (see sections 4.4 and 4.8)

Other medicinal products

- antibiotics: aminoglycoside and polypeptide antibiotics, lincosamide and acylamino-penicillin antibiotics
- diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (intravenous lidocaine and epidural bupivacaine) and acute administration of phenytoin and β -receptor 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 result in potentiation or attenuation of the neuromuscular block, depending on the sequence of administration and the neuromuscular blocking agent used
- suxamethonium, given after the administration of rocuronium bromide, may cause potentiation or attenuation of the neuromuscular blocking effect.

Effect of rocuronium bromide on other medicinal products

- rocuronium bromide in combination with lidocaine may result in a more rapid onset of action of lidocaine.

Paediatric population

No formal interaction studies have been performed. In paediatric patients, the above-mentioned interactions for adults should also be taken into account, as well as the special warnings and precautions for use of these agents (see section 4.4).

4.6 Fertility, pregnancy and lactationFertility

There is no data available regarding the effect of rocuronium bromide on the fertility.

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 using rocuronium bromide in 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 anesthetic 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, fetal 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.

Note 1: doses of 1.0 mg.kg^{-1} have been investigated during rapid sequence induction of anesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg.kg^{-1} 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 toxemia 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 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

As rocuronium bromide is used in general anaesthesia, the usual precautionary measures after general anaesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

The most commonly occurring adverse reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse reaction during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations beneath the table.

MedDRA System Organ Class	MedDRA preferred term¹		
	Uncommon/rare ² ($<1/100$ to $\geq 1/10\,000$)	Very rare ² ($<1/10\,000$)	Not known ² (frequency cannot be estimated from the available data)
Immune system disorders		Hypersensitivity Anaphylactic reaction	

		Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Eye disorders			Mydriasis ³ Fixed pupils ³
Cardiac disorders	Tachycardia		Kounis syndrome
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Skin and subcutaneous tissue disorders		Angioedema Urticaria Rash Erythematous rash	
Musculoskeletal and connective tissue disorders		Muscular weakness ⁴ Steroid myopathy ⁴	
General disorders and administration site conditions	Drug ineffective Drug effect/therapeutic response decreased Drug effect/therapeutic response increased Injection site pain Injection site reaction	Face oedema	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia	

¹ Frequencies have been estimated on the basis of post-marketing surveillance reports and data from the general literature.

² Exact frequencies cannot be obtained from post-marketing surveillance data. Hence, the reporting frequency has been divided over 3 rather than 5 categories.

³ In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier.

⁴ After long-term use in intensive care.

Class effects

Anaphylaxis

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 and 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 consideration and the necessary precautions should be taken (see also section 4.4).

Histamine release and histaminoid reactions

As it is known that neuromuscular blocking agents can cause the release of histamine, both locally at the site of injection and systemically, onset of pruritus and erythema at the site of injection and/or systemic histaminoid (anaphylactoid) reactions should always be considered when administering these medicinal products (see also above under 'Anaphylactic reactions'). In clinical studies, only a slight increase in mean histamine plasma levels has been observed following rapid administration of a bolus dose of 0.3 – 0.9 mg.kg⁻¹ rocuronium bromide.

In postmarketing reports, hypersensitivity has been observed for rocuronium as well as for rocuronium-sugammadex complex.

Prolonged neuromuscular blockade

The most frequent adverse reaction to neuromuscular blocking agents as a class consists of a longer than necessary prolongation of the pharmacological action. 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 use of various neuromuscular blocking agents in combination with corticosteroids in intensive care (see also sections 4.4 and 4.5).

Local injection site reactions

Pain on injection has been reported during rapid induction of anaesthesia, 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 observed in 16 % of patients undergoing rapid induction of anaesthesia with propofol and in less than 0.5 % of patients undergoing rapid 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 a maximum of 1 mg / kg) showed that tachycardia occurred as an adverse reaction at 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 HPRC Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

In the event of overdose and prolonged neuromuscular blockade, the patient must continue to receive ventilation and sedation. In this situation, there are two options for the reversal of neuromuscular blockade: (1) In adults, sugammadex can be used for reversal of intense (total) and deep blockade. The dosage of sugammadex administered depends on the intensity of neuromuscular blockade.

(2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex can be used once spontaneous recovery has started and should be administered at the correct dosage. If administration of an acetylcholinesterase inhibitor fails to reverse the neuromuscular effects of rocuronium bromide, ventilation should be continued until spontaneous breathing is restored. Repeated administration of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severely impaired cardiovascular function, ultimately leading to heart failure, became apparent only at a cumulative dose of 750 x ED₉₀ (135 mg.kg⁻¹ rocuronium bromide).

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 (rocuronium bromide) is a non-depolarising neuromuscular blocking agent with a short onset time. It has all of the pharmacological properties characteristic of this class of medicines (curariform). It competitively blocks the cholinergic nicotinic receptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects

The ED₉₀ (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) in intravenous anaesthesia is approximately 0.3 mg.kg⁻¹ rocuronium bromide. The ED₉₅ in neonates and infants is lower than in adults and children (0.25, 0.35 and 0.40 mg.kg⁻¹ respectively).

The clinical duration of action (the duration between the time of administration and onset of recovery of twitch height to 25 % of the control value) at a dosage of 0.6 mg.kg⁻¹ rocuronium bromide is 30 – 40 minutes. The total duration of action (time to spontaneous recovery of twitch height to 90 % of the control value) is 50 minutes. The mean time to spontaneous recovery of twitch response from 25 % to 75 % of the control value after a bolus dose of 0.6 mg.kg⁻¹ rocuronium bromide is 14 minutes. At a lower dose of 0.3 – 0.45 mg.kg⁻¹ rocuronium bromide (1 – 1.5 x ED₉₀), the onset time is later and the duration of action shorter. At a higher dose of 2 mg.kg⁻¹, the duration of action is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg.kg⁻¹ rocuronium bromide (2 x ED₉₀ under intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients, with intubation conditions rated as excellent in 80 % of cases. Within 2 minutes following administration of this dose, general muscle paralysis adequate for any type of procedure is achieved. After administration of 0.45 mg.kg⁻¹ rocuronium bromide, acceptable intubation conditions are achieved after 90 seconds.

Rapid induction

During rapid induction of anaesthesia with propofol or fentanyl/thiopental, acceptable intubation conditions are achieved within 60 seconds in 93 % and 96 % of patients, respectively, following administration of a dose of 1 mg.kg⁻¹ rocuronium bromide. Within these groups, intubation conditions are rated as excellent in 70 % of cases. The clinical duration of action with this dose is roughly 1 hour, after which the neuromuscular block can be safely reversed. Following administration of a dose of 0.6 mg.kg⁻¹ rocuronium bromide, acceptable intubation conditions are achieved within 60 seconds in 81 % and 75 % of patients undergoing rapid induction of anaesthesia with propofol and fentanyl/thiopental, respectively.

Paediatric population

Mean onset time in infants, toddlers and children at an intubation dose of 0.6 mg.kg⁻¹ is slightly shorter than in adults. A comparison across the paediatric age groups showed that the mean onset time in neonates and adolescents (1 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 normally shorter in children than in infants and adults. A comparison across the paediatric age groups showed that mean time to reappearance of T₃ was prolonged in neonates and infants (56.7 and 60.7 minutes, respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 minutes, respectively).

Mean (SD) onset time and clinical duration of action following an initial intubation dose* of 0.6 mg/kg rocuronium bromide during (maintenance) anaesthesia with sevoflurane/nitrous oxide and isoflurane/nitrous oxide (paediatric patients)

	Time to maximum blockade** (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 bromide administered within 5 seconds

** Calculated from the end of administration of the rocuronium bromide intubation dose

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

The duration of action for maintenance doses of 0.15 mg.kg⁻¹ rocuronium bromide may be somewhat prolonged under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic or renal disease (approximately 20 minutes) when compared to patients with normally functioning excretory organs under intravenous anaesthesia (approximately 13 minutes) (see section 4.2). With repeated maintenance doses according to recommendations, no accumulation of effect (progressive prolongation of duration of action) has been observed.

Intensive care

Following long-term continuous infusion in intensive care, the time to recovery of the TOF ratio to 0.7 depends on the depth of neuromuscular blockade at the end of the infusion. After continuous infusion for 20 hours or more, the median (range) time between return of T₂ to TOF stimulation and recovery of the TOF ratio to 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 undergoing cardiovascular surgery, the most common cardiovascular changes during the onset of maximum blockade at doses of 0.6 – 0.9 mg.kg⁻¹ 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

The action of rocuronium bromide can be antagonised either by sugammadex or by acetylcholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium). Sugammadex can be given for routine reversal (at 1 – 2 post-tetanic counts to reappearance of T₂) or for immediate reversal (3 minutes after administration of rocuronium bromide). Acetylcholinesterase inhibitors can be administered at reappearance of T₂ or the first signs of clinical recovery.

5.2 Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide, the plasma concentration time course runs in three exponential phases. In adults, the mean (95 % confidence interval) elimination half-life is 73 (66 – 80) minutes, the (apparent) volume of distribution under steady-state conditions is 203 (193 – 214) mL.kg⁻¹ and plasma clearance is 3.7 (3.5 – 3.9) mL.kg⁻¹.min⁻¹.

Rocuronium bromide is excreted via urine and bile. Excretion via urine is approximately 40 % within 12 – 24 hours. After administration 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 unchanged rocuronium.

Paediatric population

The pharmacokinetics of rocuronium bromide in paediatric patients (n=146) aged 0 to 17 years inclusive were analysed using a population analysis of the pooled pharmacokinetic datasets from two clinical studies, where anaesthesia was induced with sevoflurane and maintained with isoflurane/nitrous oxide. All pharmacokinetic parameters were found to be linearly proportional to body weight, as demonstrated by a similar clearance (L.hr⁻¹.kg⁻¹). The volume of distribution (L.kg⁻¹) and elimination half-life (hour) decrease with age (years). The pharmacokinetic parameters of typical paediatric patients within each age group are summarised below:

Estimated pharmacokinetic (PK) parameters (mean [SD]) of rocuronium bromide in typical paediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/nitrous oxide (maintenance anaesthesia)

PK parameters	Patient age				
	Term neonate infants (0 – 27 days)	Infants (28 days – 2 months)	Toddlers (3 – 23 months)	Children (2 – 11 years)	Adolescents (12 – 17 years)
Cl (L/kg ⁻¹ .hour ⁻¹)	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 ⁻¹)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
t _{1/2 β} (hour)	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 failure

In controlled studies, the plasma clearance in geriatric patients and in patients with renal failure was reduced; in most studies, however, without reaching the level of statistical significance. In patients with liver failure, the mean elimination half-life was prolonged by 30 minutes and the mean plasma clearance was reduced by 1 mL.kg⁻¹.min⁻¹ (see section 4.2).

Intensive care

After continuous infusion over a period of 20 hours or more to facilitate mechanical ventilation, the mean elimination half-life was prolonged and the mean (apparent) volume of distribution under steady-state conditions was increased. Wide interpatient variability has been demonstrated in clinical studies, depending on the nature and extent of (multiple) organ failure and the patient's condition. In patients with multiple organ failure, the mean (\pm SD) elimination half-life is 21.5 (\pm 3.3) hours, the (apparent) volume of distribution under steady-state conditions is 1.5 (\pm 0.8) L.kg⁻¹ and plasma clearance is 2.1 (\pm 0.8) mL.kg⁻¹.min⁻¹.

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 from clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- sodium acetate trihydrate
- sodium chloride
- acetic acid, glacial
- water for injections

6.2 Incompatibilities

Rocuronium bromide is physically incompatible with solutions of the following medicinal products: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Rocuronium bromide is also incompatible with soybean oil.

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

If Rocuronium bromide is administered via the same infusion line used also for other medicinal products, it is important that this infusion line be adequately flushed (e.g. with 0.9 % NaCl) 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.

6.3 Shelf life

Glass ampoule: 30 months

Glass vial: 24 months

Plastic ampoule: 30 months

Rocuronium bromide contains no preservatives and should be used immediately after opening the vial or ampoule.

The diluted product (see section 6.6) is physically and chemically stable for 72 hours at 28°C – 32°C or 72 hours at 2°C – 8°C. From a microbiological point of view, the product should be used immediately after dilution. 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°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

For storage conditions after first opening of the medicinal product, see section 6.3.

Store in a refrigerator (2°C – 8°C).

6.5 Nature and contents of container

Type I glass vials with capacity > 6 mL (containing 5 mL of solution) with bromobutyl rubber stopper and aluminum cap, with plastic flip off top.

Type I glass ampoules with capacity ≥ 5 mL (containing 5 mL of solution).

Polypropylene ampoules of 5 mL.

The medicinal product is supplied in cartons of 10 or 50 vials and cartons of 10 or 50 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Compatibility studies have been performed with the following infusions: Rocuronium bromide at nominal concentrations of 0.5 mg / mL and 2 mg / mL is compatible with 0.9 % NaCl, 5 % glucose, 5 % glucose in 0.9 % NaCl, sterile water for injections, lactated Ringer's solution and Haemaccel. Administration should commence immediately after mixing and should be complete within 24 hours.

For single use only.

Bring the glass vials to room temperature before piercing so as to decrease the potential for fragmentation.

Unused solutions must be discarded.

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

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA1122/022/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17th January 2020

Date of last renewal: 18th December 20224

10 DATE OF REVISION OF THE TEXT

May 2026