Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Rocuronium bromide 10 mg / mL solution for injection in pre-filled syringe

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 10 mg rocuronium bromide.
Each 5 mL pre-filled syringe contains 50 mg rocuronium bromide.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Clear colourless to pale brown-yellowish solution.
pH 3.8 – 4.2
Osmolality: 270 – 330 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocuronium bromide is indicated for use in adult and children from 2 years of age, 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 (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

- *Adults*

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.

- *Paediatric population*

For children (≥ 2 years) above 10 kg of weight, the recommended intubation dose during routine anaesthesia is similar to that in adults.

Rocuronium bromide should not be given to children under 2 years because the subgraduation of the pre-filled syringe does not allow an accurate administration of the product in these populations (see section 6.6). However, other rocuronium formulations are available for use.

The 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.

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 toxaemia of pregnancy. The dosage of rocuronium bromide in these patients should therefore be reduced and titrated to the twitch response obtained.

Caesarean section: 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 (see section 4.6).
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

- *Adults*

The recommended maintenance dosage is 0.15 $mg.kg^{-1}$ rocuronium bromide; in longterm inhalational anaesthesia, this should be reduced to 0.075 – 0.1 $mg.kg^{-1}$ 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.

- *Paediatric population*

For children (≥12 years) above 35 kg of weight, the recommended intubation dose during routine anaesthesia and the maintenance dosage are similar to those in adults.

Maintenance dosage is not suitable for children under 12 years of age because the subgraduation of the pre-filled syringe does not allow an accurate administration of the product in this population. However, other rocuronium formulations are available for maintenance dosage in this population.

- *Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure*

Regardless of the anaesthetic technique used, the recommended maintenance dosage for these patients is 0.075 – 0.1 mg.kg^{-1} rocuronium bromide.

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.

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 (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.

Residual curarization
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 (see section 4.9 and 5.1).

Anaphylaxis
Anaphylactic reactions can occur after administration of neuromuscular blocking agents (see section 4.8). 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.

Use with suxamethonium
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 (see section 4.5).
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.

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 (see section 4.2).

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 (myasthenia gravis), muscular disorders (myopathies) or in presence of motor sequelae (paresis, plegia) at a distance from acute accident (spinal cord trauma, poliomyelitis, prolonged immobilization) 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, with myasthenic (Eaton-Lambert) syndrome, or myopathies low doses of rocuronium bromide may have profound effects. In patients with motor sequelae, there is a decrease in the sensitivity of rocuronium bromide (increased doses). 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.
In the overweight patient or in the obese patient (overweight greater than 30 % or more compared to the ideal weight) the doses should be reduced based on the theoretical 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.

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.

This medicine contains less than 1 mmol sodium (23 mg) per pre-filled syringe, 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)

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).
- Calcium chloride, potassium chloride

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 abovementioned
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 lactation

Fertility
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 Cesarean 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 1, has been shown to be safe in parturients undergoing Cesarean 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 Cesarean 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. 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 below the table.

MedDRA System Organ Class	**MedDRA preferred term[1]**		
	Uncommon/rare[2] (<1/100 to ≥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	
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	
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,	Prolonged	Airway	

poisoning and procedural complications	neuromuscular block Delayed recovery from anaesthesia	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 2 rather than 5 categories.

Class effects

Anaphylactic reactions
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.

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.

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 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. This administration is guided by the data provided by the instrumental monitoring of the curarization with in particular the presence of 4 clear responses to the adductor of the thumb after a stimulation in the train-of-four. 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 ED_{90} (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: M03A C09

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 properties
The ED_{90} (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 ED_{95} 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 ED_{90}), 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 T_3 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 administered within 5 seconds
** Calculated from the end of administration of the rocuronium 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 T_2 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 T_2) or for immediate reversal (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

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 (± SD) elimination half-life is 21.5 (± 3.3) hours, the (apparent) volume of distribution under steady-state conditions is 1.5 (± 0.8) $L.kg^{-1}$ and plasma clearance is 2.1 (± 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 ~~Aguettant~~ 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 (E 262),
Sodium chloride,
Acetic acid, glacial (for pH adjustment) (E 260),
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 intralipid.

6.3 Shelf life

30 months.

After opening, the medicinal product must be used immediately.

This medicinal product may be stored for a short period at temperatures not exceeding 30°C for a period of maximum 12 weeks. In all cases, once initially removed from refrigerated storage, the medicinal product should be discarded after 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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C). Do not freeze.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

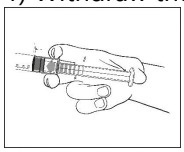
5 mL solution for injection in a pre-filled syringe (polypropylene), with plunger stopper (chlorobutyl), without a needle, with a graduated self- adhesive transparent label (sub - graduations of 0.2 ml from 0 until 5 mL). An end-cap (polypropylene) protects the syringe tip.
The pre-filled syringe is individually packed in a transparent blister.
Available in cardboard boxes of 10 pre-filled syringes.

6.6 Special precautions for disposal and other handling

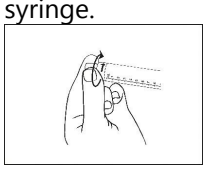
Instructions for use:

Please prepare the syringe carefully as follows
The pre-filled syringe is for single patient only. Discard syringe after use. Do not reuse.
The content of an un-opened and un-damaged blister is sterile, and the blister must not be opened until the syringe is ready to be used.
The product should be inspected visually for particles and discoloration prior to administration. Only a clear colourless to pale brown-yellowish solution free from particles or precipitates should be used.
The product should not be used if the tamper evident seal on the syringe is broken.
Do not use this medicine if you notice visible signs of deterioration.
The external surface of the syringe is sterile until the blister is opened. The blister must not be opened until use.
When handled using an aseptic method, this medicine can be placed on a sterile field once it has been removed from the blister.
The volume to be administer should be calculated regarding the appropriate posology.
The pre-filled syringe is not suitable for accurate administration of the product in children younger than 2 years of age (see section 4.2).

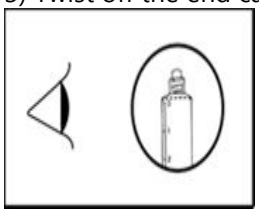
1) Withdraw the sterile pre-filled syringe from the blister.



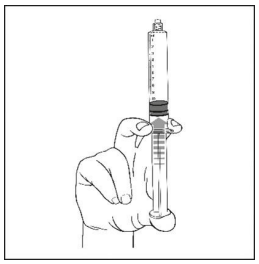
2) Push on the plunger to free the bung. The sterilisationprocess may have caused adhesion of the bung to the body of the syringe.



3) Twist off the end cap tobreak the seal. Do not touch the exposed luer connection in order to avoidcontamination.



4) Check the syringe seal tip has been completely removed. Ifnot, replace the cap and twist again.



5) Expel the air by gently pushing the plunger.

6) Connect the syringe to the vascular access device use a luer/luer lock system. Push the plunger slowly to inject the required volume. Administer the product according to the suitable administration route.

The pre-filled syringe is not suitable for syringe pump drivers. The pre-filled syringe is a ready to administer product, it is not suitable for dilution in an infusion pouch.
Any syringe that has been damaged or has been handled without respecting the conditions of sterility must not be used.
Any unused 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

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd September 2023

10 DATE OF REVISION OF THE TEXT

April 2024