# 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 solution of Rocuronium bromide contains 10 mg rocuronium bromide.

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

Excipient with known effect
Sodium 1.6 - 3.7 mg per mL

For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection/infusion
Clear, colourless up to pale brown-yellowish solution
pH: 3.5-4.5
Osmolality: 270 - 330 mOsmol/kg

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic indications

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

### 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 medicinal products.

As with other neuromuscular blocking agents, the dosage of Rocuronium bromide should be individualized in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicinal products that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Rocuronium bromide. This potentiation however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Rocuronium bromide should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuronium bromide during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see section 4.5).

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

**Surgical Procedures**

*Tracheal intubation*

The standard intubating dose during routine anaesthesia is 0.6 mg/kg rocuronium bromide, 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. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

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

*Higher doses*

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

*Maintenance 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 given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four 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 control twitch height or to maintain 1 to 2 responses to train of four stimulation.
In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational 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.

*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 paediatrics, the infusion rates, with the exception of children (2-11 years), are the same as for adults. For children aged 2-11 years, higher infusion rates might be necessary. Thus, for children (2-11 years) the same initial infusion rates as for adults are recommended and then this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure.

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

*Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure*
The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 mg/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 used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see Continuous infusion). (See 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 taking into account ideal body weight.

**Intensive Care Procedures**

*Tracheal intubation*

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

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

Method of administration

This medicinal product is for single use only. Any unused solution should be discarded.

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

**4.3 Contraindications**

Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients.

**4.4 Special warnings and precautions for use**

Rocuronium bromide should be administered only by anaesthetists familiar with the use of neuromuscular blocking agents and when facilities for controlled ventilation, insufflation with oxygen and tracheal intubation are available for immediate use.

**Appropriate Administration and Monitoring**
Since Rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicinal product until adequate spontaneous respiration is restored.
As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. In the case of intubation difficulties resulting in a clinical need for immediate reversal of rocuronium induced neuromuscular block, the use of a reversal agent should be considered.

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

**Anaphylaxis**
Anaphylactic reactions can occur following the 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.

**Use in an Intensive Care Unit**
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-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

**Use with Suxamethonium**
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.

Because rocuronium bromide is always used with other drugs and because of the risk of malignant hyperthermia during anaesthesia, even in the absence of known triggering factors, physicians should be aware of the early symptoms, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of anaesthesia. Animal studies have shown that rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with rocuronium bromide have been observed through post-marketing surveillance however, the 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
Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of 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, old age and oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.

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

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

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

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

Conditions which may increase the effects of Rocuronium bromide
Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia, cachexia.
Severe electrolyte disturbances altered blood pH or dehydration should therefore be corrected when possible.

This medicine contains less than 1 mmol sodium (23 mg) per 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 magnitude and/or duration of action of non-depolarising neuromuscular blocking agents.

**Effect of other drugs on Rocuronium bromide**

Increased effect:

- Halogenated volatile anaesthetics: potentiate the neuromuscular block of rocuronium bromide. The effect only becomes apparent with maintenance dosing (see section 4.2). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.4).
- Long-term concomitant use of corticosteroids and Rocuronium bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).

Other drugs:

- Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
- 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 β-blocking agents.

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

Decreased effect:

- Neostigmine, edrophonium, pyridostigmine
- Prior chronic administration of phenytoin or carbamazepine
- Calcium chloride and potassium chloride
- Protease inhibitors (gabexate, ulinastatin)

Variable effect:

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

**Effect of Rocuronium bromide on other drugs**

Rocuronium bromide combined with lidocaine may result in a quicker onset of action of lidocaine.

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

**4.6 Fertility, pregnancy and lactation**

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

Caesarean section
In patients undergoing Caesarean section, rocuronium bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. Rocuronium bromide, administered in doses of 0.6 mg/kg has been shown to be safe in patients undergoing Caesarean section. Rocuronium bromide does not affect Apgar score, foetal muscle tone or

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 have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg/kg is recommended in this patient group.

*Note 2:* reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for 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.

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

Fertility
There is no data available regarding the effect in the fertility for this product.

**4.7 Effects on ability to drive and use machines**

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

| MedDRA SOC | Preferred term[1] | | |
|---|---|---|---|
| | Uncommon/rare[2] (<1/100 >1/10 000) | Very rare (<1/10 000) | Not known |
| Immune system disorders | | Hypersensitivity | |
| | | Anaphylactic reaction | |
| | | Anaphylactoid reaction | |
| | | Anaphylactic shock | |
| | | Anaphylactoid shock | |
| Nervous system disorders | | Flaccid paralysis | |
| Eye disorders | | | Mydriasis[3]<br>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 | | Angioneurotic oedema | |
| | | Urticaria | |
| | | Rash | |
| | | Erythematous rash | |
| Musculoskeletal and connective tissue disorders | | Muscular weakness[4] | |
| | | Steroid myopathy[4] | |
| General disorders and administration site conditions | Drug ineffective | Face oedema | |

| | | | |
|---|---|---|---|
| | Drug effect/ therapeutic response decreased | | |
| | Drug effect/ therapeutic response increased | | |
| | Injection site pain | | |
| | Injection site reaction | | |
| Injury, poisoning and procedural complications | Prolonged neuromuscular block | Airway complication of anaesthesia | |
| | Delayed recovery from anaesthesia | | |
| MedDRA version 8.1 | | | |

[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 three rather than five categories.
[3]In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).
[4]After long-term use in the ICU.

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium bromide, have been reported. Anaphylactic/anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse - shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

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

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

Prolonged neuromuscular block

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

Myopathy

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

Local injection site reactions

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

Paediatric population

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

Reporting of suspected adverse reactions

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

**4.9 Overdose**

In the event of 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. The dose of sugammadex to be administered depends on the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of rocuronium bromide, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED90 (135 mg/kg rocuronium bromide) was administered.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, other quaternary ammonium compounds ATC code: M03AC09

Mechanism of action

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

Pharmacodynamic effects
The ED90 (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED95 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) with 0.6 mg/kg rocuronium bromide is 30–40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6 mg/kg rocuronium bromide is 14 minutes.
With lower dosages of 0.3-0.45 mg/kg rocuronium bromide (1 -1½ x ED90), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

Intubation during routine anaesthesia
Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED90 under 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, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. 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 population
Mean onset time in infants, toddlers and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. Comparison within paediatric age groups showed that the mean onset time in neonates and adolescents (1.0 min) is slightly

longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min., respectively). The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. Comparing within paediatric age groups demonstrated that mean time to reappearance of $T_3$ was prolonged in neonates and infants (56.7 and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 min., respectively).

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

| | Time to maximum block** (min) | Time to reappearance of $T_3$** (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) |
| Toddler (3 months–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 intubating dose

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

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

Intensive Care Unit
Following continuous infusion in the Intensive Care Unit, the time to recover of the train of four ratio to 0.7 is not significantly correlated to the total duration of rocuronium infusion. After a continuous infusion for 20 hours or more the median (range) time between return of $T_2$ to train of four stimulation and recovery of the train of four ratio to 0.7 varied between 0,8 and 12,5 hours in patients without multiple organ failure and 1.2 – 25.5 hours in patients with multiple organ failure.

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

Reversal of muscle relaxation
The action of rocuronium 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 immediate reversal. Acetylcholinesterase inhibitors can be administered at reappearance of $T_2$ or at 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 normal adults, the mean (95%CI) elimination half-life is 73 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193-214) mL/kg and plasma clearance is 3.7 (3.5-3.9) mL/kg/min.

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

Paediatric population

Pharmacokinetics of rocuronium bromide in paediatric patients (n=146) with ages ranging from 0 to 17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance

(1 $hr^{-1}kg^{-1}$). The volume of distribution (l $kg^{-1}$) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarized below:

**Estimated 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 range | | | | |
|---|---|---|---|---|---|
| | Term Newborn infants (0-27 days) | Infants (28 days to 2 months) | Toddlers (3-23 months) | Children (2-11 years) | Adolescents (12-17 years) |
| CL L/kg/hr | 0.31 (0.07) | 0.30 (0.08) | 0.33 (0.10) | 0.35 (0.09) | 0.29 (0.14) |
| Volume of distribution (L/kg) | 0.42 (0.06) | 0.31 (0.03) | 0.23 (0.03) | 0.18 (0.02) | 0.18 (0.01) |
| $t_{½}$ β (hr) | 1.1 (0.2) | 0.9 (0.3) | 0.8 (0.2) | 0.7 (0.2) | 0.8 (0.3) |

Intensive Care unit
When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased.
A large between patient variability is found in controlled clinical studies, related to 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, a (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. (see section 4.2).

Rocuronium bromide is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours.
After injection of a radiolabeled 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 the parent compound. No metabolites are detected in plasma.

**5.3 Preclinical safety data**

In subacute toxicity studies rocuronium bromide was intravenously administered to cats and dogs up to a dose of 37 x ED90 and 60 x ED90 respectively two times per week for a period of 4 weeks. Unforeseen mortalities occurred in three out of seven dogs at the dose of 60 x ED90 (10,8 mg per kg body weight). The cause of death could not be established, but was considered to be related to interactions between rocuronium treatment and experimental procedures and/or instrumentation and anaesthesia.
No chronic toxicity studies of rocuronium bromide have been conducted.

*In vivo* and *in vitro* mutagenicity studies have revealed no mutagenic potential of rocuronium bromide.

No carcinogenicity studies of rocuronium bromide have been conducted.

Studies using sub-pharmacological intravenous doses of rocuronium bromide in rats during organogenesis have produced no evidence of embryolethal effects, teratological alterations or foetal growth inhibition. Rocuronium bromide crosses the placental barrier in rats to a limited extent, and is recovered in milk in small amounts.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium acetate trihydrate
Sodium chloride
Acetic acid 99% (for pH adjustment)
Acetic acid 30% (for pH adjustment)
Water for injections
Sodium hydroxide (for pH adjustment)

**6.2 Incompatibilities**

Physical incompatibility has been documented for Rocuronium bromide when added to solutions containing the following active substances: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone,

erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin.

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

If Rocuronium bromide is administered via the same infusion line that is also used for other medicinal products, it is important that this infusion line is 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**

3 years
Shelf-life after first opening.
The solution should be used immediately after opening the ampoule/vial. Discard any unused content.

In-use shelf-life of diluted medicinal product
After dilution with infusion fluids (see section 6.6), chemical and physical in-use stability has been demonstrated for 24 hours at 25°C. From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

**6.4 Special precautions for storage**

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the ampoule/vial in the outer carton in order to protect from light.

Rocuronium bromide may also be stored outside the refrigerator at a temperature of up to 25°C for a maximum of 12 weeks.

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

**6.5 Nature and contents of container**

For vials: Clear, colourless glass (type I), closed with bromobutyl rubber stopper and polypropylene flip-off cap.
For ampoules: Clear, colourless glass (type I).

Ampoules/Vials of 5 and 10 ml
Pack sizes:
10 x 5 ml
12 x 5 ml
(6 x 10) x 5 ml

10 x 10 ml
(2 x 10) x 10 ml

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Compatibility studies with the following infusion fluids have been performed: in nominal concentration of 5 mg/ml Rocuronium bromide has been shown to be compatible with: sodium chloride 9 mg/ml (0.9%) solution, glucose 50 mg/ml (5%) solution, glucose 33 mg/ml (3.3 %) in sodium chloride 3 mg/ml (0.3%) solution, water for injections and Lactated Ringers. Administration should begin immediately after mixing, and should be completed within 24 hours.

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

Do not use Rocuronium bromide if you notice that the solution is not clear and not free from particles.

## 7 MARKETING AUTHORISATION HOLDER

Ibigen Srl
via Fossignano 2
04011 Aprilia (LT)
Italy

## 8 MARKETING AUTHORISATION NUMBER

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## 10 DATE OF REVISION OF THE TEXT

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