# Rocuronium-hameln 10 mg/ml Injection

## 1. NAME OF THE MEDICINAL PRODUCT

Rocuronium-hameln 10 mg/ml Injection

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each ampoule with 5 ml contains 50 mg rocuronium bromide.

For a full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Solution for injection/infusion

Before reconstitution/dilution:

Clear, colourless to pale brownish-yellow solution

pH of the solution: 3.8 to 4.2

Osmolality: 270-310 mOsmol/kg

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

After reconstitution/dilution:

Clear, colourless to pale brownish-yellow solution

## 4. CLINICAL PARTICULARS

### 4.1 INDICATION

Rocuronium-hameln 10 mg/ml injection is indicated as an adjunct to general anaesthesia to facilitate endotracheal intubation, to provide skeletal muscle relaxation and to facilitate mechanical ventilation in adults, children and infants from one month of age. Rocuronium-hameln 10 mg/ml injection is also indicated as an adjunct in the intensive care unit (ICU) to facilitate mechanical ventilation as part of Rapid Sequence Induction.

### 4.2 RECOMMENDED DOSAGE

Like other neuromuscular blocking agents, Rocuronium-hameln 10 mg/ml should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.

As with other neuromuscular blocking agents, the dosage of Rocuronium-hameln 10 mg/ml 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 drugs that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Rocuronium-hameln 10 mg/ml. 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-hameln 10 mg/ml should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuronium-hameln 10 mg/ml during long lasting procedures (longer than 1 hour) under inhalational anaesthesia.

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 rocuronium bromide per kg body weight, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg rocuronium bromide per kg body weight is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg rocuronium bromide per kg body weight is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide. For use of rocuronium bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 'Fertility, pregnancy and lactation'.

*Maintenance dosage:*

The recommended maintenance dose is 0.15 mg rocuronium bromide per kg body weight; in the case of long-term inhalational anaesthesia, this should be reduced to 0.075-0.1 mg rocuronium bromide per kg body weight. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four stimulation are present.

*Continuous infusion:*

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg rocuronium bromide per kg body weight and, when 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 and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

*Dosage in paediatric patients:*

For infants (28 days-23 months), children (2-11 years) and adolescents (12-18 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

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

*Dosage in geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure:*

The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 mg rocuronium bromide per kg body weight. A dose of 0.6 mg per kg body weight should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg rocuronium bromide per kg body weight, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see also Continuous infusion).

*Dosage in overweight and obese patients:*

When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.

Intensive care procedures

*Tracheal intubation*

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

*Maintenance dosing*

The use of an initial loading dose of 0.6 mg rocuronium bromide per kg body weight is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 - 90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3 - 0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6 - 12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.

To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended.

Administration up to 7 days has been investigated.

*Special populations*

Rocuronium-hameln 10 mg/ml is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

**Method of Administration**

Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion (for further information see also section 6.6).

### 4.3 CONTRAINDICATIONS

Rocuronium bromide is contraindicated in patients with hypersensitivity to rocuronium bromide or to the bromide ion or to any of the excipients listed in section 6.1.

### 4.4 WARNING AND PRECAUTIONS

Rocuronium bromide should be administered only by an experienced staff familiar with the use of neuromuscular blocking agents.

Adequate facilities and staff for endotracheal intubation and artificial ventilation have to be available for immediate use.

Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this active substance until adequate spontaneous respiration is restored.

As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual curarization has been reported for Rocuronium. 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 should be considered, especially in those cases where residual curarization is more likely to occur.

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

Anaphylactic reactions (see above) can occur after 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.

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

In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular blockage and/or overdose, it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to the effect in the individual patient. This should be done by or under the supervision of experienced clinicians who are familiar with the effects and with appropriate neuromuscular monitoring techniques.

Because rocuronium bromide is always used with other agents and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering agents, clinicians should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia.

Myopathy has been reported after long-term concurrent use of non-depolarising neuromuscular blockers and corticosteroids. The co-administration period should be reduced to be as short as possible.

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

**The following conditions may influence the pharmaco-kinetics and/or pharmacodynamics of Rocuronium-hameln:**

*Hepatic and/or biliary tract disease and renal failure*

Rocuronium bromide is excreted in urine and bile. Therefore, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of the effect has been observed with doses of 0.6 mg rocuronium bromide per kg body weight.

*Prolonged circulation time*

Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and an oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of the effect. 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-depo-larizing neuromuscular blocking agents. It is recommended that the dose is titrated to the response.

*Conditions which may increase the effects of rocuronium bromide*

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

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

*Paediatric population*

The same warnings and precautions as for adults should be taken into consideration.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'.

### 4.5 DRUG INTERACTIONS

The following medicinal products have been shown to influence the magnitude and/or duration of the effect of non-depolarizing neuromuscular blocking agents:

*Increased effect:*

- Halogenated volatile anaesthetics
- High doses of: thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate and propofol
- Other non-depolarizing neuromuscular blocking agents
- Prior administration of suxamethonium.
- Long term concomitant use of corticosteroids and Rocuronium in the ICU may result in prolonged duration of neuromuscular block or myopathy.

*Other medicinal products:*

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

*Decreased effect:*

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

*Variable effect:*

Administration of other non-depolarizing neuromuscular blocking agents in combination with rocuronium bromide may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.

Suxamethonium given after the administration of rocuronium bromide may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

*Effect of rocuronium on other drugs:*

Combined use with lidocaine could result in a more instant effect of lidocaine. 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).

*Paediatric patients:*

No formal interaction studies have been performed. The above mentioned interactions for adults should also be taken into account for paediatric patients.

### 4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

Caution should be exercised when prescribing rocuronium bromide to pregnant women.

Rocuronium bromide should only be given to pregnant women when strictly necessary and the attending physician decides that the benefits outweigh the risks.

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.

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

Breast-feeding

Rocuronium bromide should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

### 4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

### 4.8 SIDE EFFECTS

The most common undesirable effects are pain/reaction around injection site, changes in vital functions and prolonged neuromuscular block.

| *MedDRA SOC* | *Preferred term*[a] | | |
|---|---|---|---|
| | *Uncommon/ Rare*[b] | *Very Rare* | *Not Known* |
| *Immune system disorders* | | Hypersensitivity; Anaphylactic reaction; Anaphylactoid reaction; Anaphylactic shock; Anaphylactoid shock | |
| *Nervous system disorders* | | Flaccid paralysis | |
| *Eye disorders* | | Mydriasis[b,c]; Fixed pupils[b,c] | |
| *Cardiac disorders* | Tachycardia | | Kounis syndrome |
| *Vascular disorders* | Hypotension | Circulatory collapse and shock; Flushing | |
| *Respiratory thoracic and mediastinal disorders* | | Bronchospasm | Apnoea; Respiratory failure |
| *Skin and subcutaneous tissue disorders* | | Angioneurotic oedema; Urticaria; Rash; Erythematous rash | |
| *Musculoskeletal and connective tissue disorders* | | Muscular weakness[d]; Steroid myopathy[d] | |
| *General disorders and administration site conditions* | Drug ineffective; Drug effect/ therapeutic response decreased; Drug effect/ therapeutic response increased; Injection site pain/ reaction | Face oedema; Malignant hyperthermia | |
| *Injury, poisoning and procedural complications* | Prolonged neuromuscular block; Delayed recovery from anaesthesia | Airway complication of anaesthesia | |

[a] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.

[b] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories.

[c] In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).

[d] after long-term use in the ICU

Anaphylactic reaction

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

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.

Increased histamine level

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically, the possible occurrence of itching and erythematous reaction at the site of injection and/ or generalised histaminoid (anaphylactoid) reactions such as bronchospasm and cardiovascular changes e.g. hypotension and tachycardia should always be taken into consideration when administering these drugs. Rash, exanthema, urticaria, bronchospasm and hypotension have been reported very rarely in patients given rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarizing blocking agents as a class consists of an extension of the agent'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.

**Paediatric patients**

In paediatric patients treated with rocuronium bromide (up to 1 mg/kg), tachycardia was identified as an adverse drug reaction with a frequency of 1.4%.

### 4.9 Overdose

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation.

Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of rocuronium bromide, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase inhibitor can be dangerous.

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

*Pharmacotherapeutic group (ATC code)*

Muscle relaxants, peripherally acting agents.

ATC code: M03AC09

Mechanism of action

Rocuronium-hameln 10 mg/ml (rocuronium bromide) is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent, possessing all of the characteristic pharma-cological actions of this class of drugs (curariform). It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects

The $ED_{90}$ (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$^{-1}$ rocuronium bromide. The $ED_{95}$ in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg.kg$^{-1}$, respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg.kg$^{-1}$ 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$^{-1}$ rocuronium bromide is 14 minutes.

With lower dosages of 0.3-0.45 mg.kg$^{-1}$ rocuronium bromide (1-1½ x $ED_{90}$), onset of action is slower and duration of action is shorter.

Should there be reason for selection of larger doses in individual patients, initial doses up to 2 mg.kg$^{-1}$ rocuronium bromide have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action. With high doses of 2 mg.kg$^{-1}$, clinical duration is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg.kg$^{-1}$ rocuronium bromide (2x $ED_{90}$ 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$^{-1}$ 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$^{-1}$ 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$^{-1}$ 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.

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 mg.kg$^{-1}$ is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. The duration of action of maintenance doses of 0.15 mg.kg$^{-1}$ rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic disease 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 recovery of the train of four ratio to 0.7 depends on the level of block at the end of the 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 approximates 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 scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg.kg-1 Rocuronium 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

Administration of acetylcholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium) at reappearence of $T_2$ or at the first signs of clinical recovery, antagonizes the action of Rocuronium.

### 5.2 PHARMACOKINETIC PROPERTIES

Distribution and elimination

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

The plasma clearance in geriatric patients and in patients with renal dysfunction is reduced. In patients with hepatic diseases, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min.

In infants (3 months to 1 yr), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1-8 yr). In older children (3-8 yr), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

When administered as a continuous infusion to facilitate mechanical ventilation for a time period of 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A high variability between patients was found, related to the nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (±SD) elimination half-life of 21.5 (±3.3) hours, an (apparent) volume of distribution at steady state of 1.5 (±0.8) l/kg and a plasma clearance of 2.1 (±0.8) ml/kg/min were found.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabelled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after 9 days. Approximately 50% is recovered as rocuronium bromide.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Water for injections

Acetic acid, glacial (for pH-adjustment)

Sodium chloride

Sodium acetate trihydrate

### 6.2 Incompatibilities

Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substances: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin.

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

### 6.3 SHELF LIFE

Unopened ampoule: 3 years, provided it is stored under the prescribed conditions (see section 6.4). The date mentioned on the carton and on the label of the ampoule is the expiry date.

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

After dilution:

Chemical and physical in-use stability of a 5.0 mg/ml and 0.1 mg/ml solution (diluted with sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5%) solution for infusion) has been demonstrated for 24 hours when stored at 20-22°C and exposed to room light in glass, PE and PVC.

### 6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C-8°C).

Storage out of the refrigerator:

Rocuronium-hameln may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks, or up to 25°C for 6 months, after which it should be discarded. The product should not be placed back into the refrigerator, once it has been kept outside. The storage period must not exceed the shelf-life.

For storage conditions of the diluted medicinal product, see section 6.3.

### 6.5 DOSAGE FORM AND PACKAGING AVAILABLE

Colourless glass ampoules (type I) with chlorobutyl rubber stopper and aluminium cap.

Content of the ampoules: 5 ml

Package sizes:

Packaging of 10 ampoules containing 5 ml.

Not all pack sizes may be marketed.

### 6.6 Special precautions for disposal and other handling

Any unused solutions should be discarded.

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

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

If rocuronium bromide is administered via the same infusion line with other medicinal products, it is important that the infusion line is adequately flushed (e.g. with sodium chloride 9 mg/ml (0.9%) solution for infusion) between administration of rocuronium bromide and medicinal products for which incompatibility with rocuronium bromide has been demonstrated or for which compatibility with rocuronium bromide has not been established.

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

## 7. MANUFACTURED BY:

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