NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Rocuronium bromide 50 mg/5 mL solution for injection Medsurge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL rocuronium bromide solution for injection contains 10 mg rocuronium bromide.

For a List of excipients see section 6.1

3 PHARMACEUTICAL FORM

Rocuronium bromide Medsurge is supplied as a clear, colourless to pale yellow solution for intravenous injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocuronium is indicated as an adjunct to general anaesthesia to facilitate endotracheal intubation during routine induction, to provide muscle relaxation and to facilitate mechanical ventilation in adults, and paediatric patients from term newborn infants to adolescents.

In adults, rocuronium is also indicated as an adjunct to general anaesthesia to facilitate endotracheal intubation during rapid sequence induction when suxamethonium is contraindicated.

In adults, rocuronium is also indicated as an adjunct in the intensive care unit (ICU) to facilitate mechanical ventilation.

4.2 Dose and method of administration

Dosage

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 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 medicines 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).

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store Rocuronium bromide

Medsurge solution for injection with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product [see section 4.4]

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 1.0mg 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 also established within 60 seconds in nearly all patients. If a dose of 0.6mg 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.
In patients undergoing Caesarean section it is recommended to only use a dose of 0.6mg rocuronium bromide per kg body weight, since a 1.0mg/kg dose has not been investigated in this patient group.

Maintenance Dosing
The recommended maintenance dose is 0.15mg rocuronium bromide per kg body weight; in the case of long-term inhalational anaesthesia this should be reduced to 0.075-0.1mg 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 2-3 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 0.6mg 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 0.3-0.6mg/kg/hr and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4mg/kg/hr. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosing in Paediatric Patients

For term newborn infants (0-28 days), 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.

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.

Dosing 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 0.6mg rocuronium bromide per kg body weight. A dose of 0.6mg 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 0.075-0.1mg rocuronium bromide per kg body weight, and the recommended infusion rate is 0.3-0.4mg/kg/hr (see also section 4.2 **Continuous infusion** and 4.4).

Dosing 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 0.6mg 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 0.3-0.6mg/kg/hr 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.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5mg/kg/hr depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.

Special Populations
Rocuronium bromide solution for injection 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.

Administration
rocuronium bromide solution for injection 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

Appropriate Administration and Monitoring
Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this agent until adequate spontaneous respiration is

restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique. In case of intubation difficulties resulting in a clinical need for immediate reversal of rocuronium induced neuromuscular block, the use of sugammadex should be considered.

Residual Curarization

As with other neuromuscular blocking agents, residual curarization has been reported for rocuronium bromide. Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular block. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from 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 sugammadex or another reversal agent 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.

Long-Term 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 muscle relaxants. 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.

Risk of Death due to Medication Errors

Administration of rocuronium bromide results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended. Confirm proper selection of intended product and avoid confusion with other injectable solutions that are present in critical care and other clinical settings. If another healthcare provider is administering the product, ensure that the intended dose is clearly labelled and communicated.

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, rocuronium bromide 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 0.6mg rocuronium bromide per kg body weight.

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-depolarizing 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.

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

4.5 Interaction with other medicines and other forms of interaction

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

Effect of other agents 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 4.2).

- Long-term concomitant use of corticosteroids and rocuronium bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other 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 hydrochloride 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

- Prior chronic administration of phenytoin or carbamazepine.
- Protease inhibitors (gabexate, ulinastatin)

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 bromide on other drugs

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

Paediatric patients

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

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Caesarean section

In patients undergoing Caesarean section, rocuronium bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. rocuronium bromide, administered in doses of 0.6mg/kg, has been shown to be safe in parturients undergoing Caesarean section. Rocuronium bromide does not affect Apgar score, foetal 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 1.0mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6mg/kg is recommended in this patient group.

Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium bromide should be reduced and be titrated to twitch response.

Breast-feeding
It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development. rocuronium bromide should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

Fertility
Fertility studies with rocuronium bromide have not been conducted.

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[1]	**Preferred term**[2]		
	Uncommon / rare[3] **(<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, 5] Fixed pupils[3, 5]	
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 Drug effect / therapeutic response decreased Drug effect / therapeutic response increased Injection site pain Injection site reaction	Face oedema Malignant hyperthermia	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia	

[1] medDRA version 8.1

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

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

[4] After long term use in the ICU

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

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 erythematosus reactions 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 agents.

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

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

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://pophealth.my.site.com/carmreportnz/s/

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) 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), with appropriate vagolytic (e.g atropine) can be used at reappearance of T_2 or at the first signs of clinical recovery 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, eventually leading to cardiac collapse did not occur until a cumulative dose of 750 x ED_{90} (135mg per kg body weight) was administered.

For risk assessment and advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action
Rocuronium bromide (rocuronium bromide) is a fast onset, intermediate acting non-depolarizing neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of medicines (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 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 0.3mg/kg rocuronium bromide. The ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40mg/kg, respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6mg/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 0.6mg/kg rocuronium bromide is 14 minutes. With lower dosages of 0.3-0.45mg/kg rocuronium bromide (1-1½ x ED90), onset of action is slower and duration of action is shorter. With high doses of 2mg/kg, clinical duration is 110 minutes.

Intubation during routine anaesthesia
Within 60 seconds following intravenous administration of a dose of 0.6mg/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 0.45mg/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 1.0mg/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 0.6mg/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 patients
Mean onset time in infants and children at an intubation dose of 0.6mg/kg is slightly shorter than in adults. Comparison within paediatric age groups showed that the mean onset time in term newborn infants 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 term newborn infants 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).

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The duration of action of maintenance doses of 0.15mg/kg 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 T2 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 0.6-0.9mg/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 antagonized 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 (3 minutes after rocuronium bromide administration).
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.

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

Paediatric patients
Pharmacokinetics of rocuronium bromide in paediatric patients (n=146) with ages ranging from 0 to 17 years were evaluated using a population analysis of the pooled pharmacokinetic

datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance ($l.hr^{-1}.kg^{-1}$). 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:

PK parameters of rocuronium bromide in typical paediatric patients					
PK Parameter	Term newborn infants (0-27days)	Infants (28 days to 2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (12-17 years)
Clearance ($l.hr^{-1}.kg^{-1}$)	0.31 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of Distribution at Steady State ($l.kg^{-1}$)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
Elimination Half-Life (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure 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 also section 4.2.

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.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of rocuronium bromide when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on the results obtained in clinical studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Rocuronium bromide Medsurge contains the following excipients:
sodium acetate trihydrate
sodium chloride
glacial acetic acid
water for injections
No preservative has been added.

6.2 Incompatibilities

Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following agents: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoxamone, erythromycin, famotidine, frusemide, hydrocortisone sodium succinate, insulin, methohexitol, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Rocuronium bromide is also incompatible with Intralipid.

Rocuronium bromide 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 medicines, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of rocuronium bromide and medicines for which incompatibility with rocuronium bromide has been demonstrated or for which compatibility with rocuronium bromide has not been established.

6.3 Shelf life

Rocuronium bromide has a shelf-life of 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 vial is the expiry date; this is the date up to which rocuronium bromide may be used. Since rocuronium bromide does not contain a preservative, the solution should be used immediately after opening the vial.

After dilution with infusion fluids (see section 6.6), chemical and physical in-use stability has been demonstrated for 72 hours at 30°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 the refrigerator at 2-8°C. The product can be stored outside the refrigerator at a temperature of 8-25°C for a maximum of 12 weeks. After first removal from the refrigerator, the 12 week shelf life applies. The storage period may not exceed the shelf-life.

Please Note: Upon initial transfer of rocuronium bromide from refrigeration (2-8°C) to room temperature (<25°C)

i) Annotate new expiry date of 12 weeks
ii) Discard product after the 12 week expiry date

Important: Even if returned to 2-8°C storage, the 12 week expiry date will remain.

6.5 Nature and contents of container

Rocuronium bromide 50mg/5mL solution for injection Medsurge- packaging of 10 vials each containing 50mg rocuronium bromide.
Drug product is for single use in one patient only.

6.6 Special precautions for disposal and other handling

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

Instructions For Use/Handling
Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0.5mg/mL and 2.0mg/mL, rocuronium bromide solution for injection has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel. Administration should be commenced immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

02 October 2023

10 DATE OF REVISION OF THE TEXT

05 March 2026

SUMMARY TABLE OF CHANGES

Section Changed	Summary of New Information
4.4	Hypertensive crisis in patients with phaeochromocytoma Postmarketing data have identified cases of hypertensive crisis temporally related to administration of rocuronium in patients with diagnosed or latent phaeochromocytoma. Rocuronium should therefore be used with caution in such patients.
4.8	In postmarketing reports, hypersensitivity has been observed for rocuronium as well as for rocuronium-sugammadex complex.