PRODUCT MONOGRAPH

[Pr]Rocuronium Bromide Injection

10 mg/mL, Solution for Injection, 5 mL vial

Sterile and Preservative Free

Non-depolarizing Skeletal Neuromuscular Blocking Agent

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/Strength	All Non-medicinal Ingredients
Intravenous	Solution for Injection / 10 mg/mL	Sodium acetate anhydrous, sodium chloride, water for injection. May contain sodium hydroxide and/or glacial acetic acid to adjust the pH to approximately 4.0.

INDICATIONS AND CLINICAL USE

Rocuronium Bromide Injection (rocuronium bromide) is indicated as an adjunct to general anesthesia to facilitate routine endotracheal intubation or rapid sequence (initiated at 60-90 seconds post-administration) intubation to provide skeletal muscle relaxation during surgery or mechanical ventilation.

Rocuronium bromide is a non-depolarizing neuromuscular blocking agent with a rapid to intermediate onset and an intermediate duration of action depending on dose.

Geriatrics (> 65 years of age):
Lower maintenance doses and infusion rates are recommended as the duration of neuromuscular blockade tends to be longer in the elderly. For details, see **DOSAGE AND ADMINISTRATION, Geriatrics.**

Pediatrics (≤ 18 years of age):
Rocuronium Bromide Injection is indicated for routine adjunct use in all pediatric patients, including term neonates and infants. Caution is advised in selecting the dosage for intubation and maintenance in neonates and infants because of limited controlled safety and efficacy data. Rocuronium Bromide Injection is not recommended for rapid sequence intubation in pediatric patients. For details, see **DOSAGE AND ADMINISTRATION, Pediatrics.**

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

Rocuronium Bromide Injection (rocuronium bromide) should be administered in carefully adjusted dosage by or under the supervision of experienced clinicians who are familiar with its actions and the possible complications of its use. The drug should not be administered unless personnel and facilities for resuscitation and life support (tracheal intubation, artificial ventilation, oxygen therapy), and an antagonist of Rocuronium Bromide Injection are immediately available. It is recommended that an adequate neuromuscular monitoring device be used to measure neuromuscular function during the administration of Rocuronium Bromide Injection in order to monitor drug effect, determine the need for additional doses, and confirm recovery from neuromuscular blockade.

Rocuronium bromide has no known effect on consciousness, pain threshold, thinking, or memory. To avoid distress to the patient, neuromuscular blockade should not be induced before unconsciousness.

General

Neuromuscular Blockade: Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug 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 Intubation technique.

Residual Neuromuscular Blockade: As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for rocuronium bromide. In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular blockade. Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular blockade. Other factors which could cause residual neuromuscular blockade after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. The use of a reversal agent should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

Hypothermia: Hypothermia reduces the requirement for the neuromuscular blocking agent.

Risk of Death due to Medication Errors: Administration of Rocuronium Bromide Injection 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.

Carcinogenesis and Mutagenesis

No human data are available. For data from animal studies, see **TOXICOLOGY**.

Cardiovascular

Electrocardiogram (ECG) Monitoring: The overall analysis of ECG data from two clinical pharmacology studies in pediatric patients indicates that the combined use of rocuronium with general anesthetic agents may prolong the QTc interval. Some of the prolongation may reach clinical significance. Routine ECG monitoring is recommended, especially in pediatric patients. The routine precautions for treating arrhytmia should be taken into consideration.

Delayed Onset of Action: 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.

Pulmonary Vascular Resistance: Rocuronium bromide may be associated with increased pulmonary vascular resistance, so caution is appropriate in patients with pulmonary hypertension or valvular heart disease.

Endocrine and Metabolism

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. See **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**.

Hepatic/Biliary

Because rocuronium is excreted in urine and bile, it should be used with caution in patients with hepatic impairment. In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide. See **DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY**.

Intensive Care Unit (ICU)

Whenever the use of rocuronium bromide, or any neuromuscular blocking agent, is contemplated in the ICU, it is recommended that a peripheral nerve stimulator be used continuously to monitor neuromuscular transmission during administration and recovery. In addition, patients should receive adequate analgesia and sedation. Furthermore, additional doses of rocuronium bromide or any other neuromuscular blocking agent should not be given before there is a definite response to the first twitch. If no response is elicited, infusion administration should be discontinued until a response returns.

Long-Term Use in the ICU:

To reduce the possibility of prolonged neuromuscular blockade and other complications that might occur following long-term use in the ICU, rocuronium bromide, or any other neuromuscular relaxant should be administered in carefully adjusted doses by or under the supervision of experienced clinicians who are familiar with its actions and with appropriate peripheral nerve stimulator muscle monitoring techniques.

In rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation in ICU settings has been associated with prolonged paralysis and/or skeletal muscle weakness that is first noted during attempts to wean patients from the ventilator. In these patients, the actions of the neuromuscular blocking agent may be enhanced by other drugs (e.g., broad spectrum antibiotics, narcotics and/or steroids) or by conditions such as acid-base or electrolyte imbalance, hypoxic episodes of varying duration, or extreme debilitation. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. Recovery may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial muscles and small muscles of the extremities then to the remaining muscles. In rare cases, recovery may involve an extended period of time or even require rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered. The syndrome of critical illness polyneuropathy associated with sepsis and multiorgan failure may be associated with prolonged skeletal muscle paralysis, but can also occur without the use of muscle relaxants. Thus, the role of muscle relaxants in the etiology of prolonged paralysis in the ICU is not known with certainty.

Myopathy: After long term administration of other non-depolarizing neuromuscular blocking agents in the ICU alone or in combination with corticosteroid therapy, myopathy has been reported. 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.

Neurologic

Neuromuscular Disease: In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of non-depolarizing neuromuscular blocking agents may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants. For patients having conditions in which prolonged neuromuscular blockade is a possibility (e.g., neuromuscular disease, carcinomatosis, severe cachexia, or debilitation), a peripheral nerve stimulator and use of a small test dose may be of particular value in assessing and monitoring dosage requirements.

Peri-operative Considerations

Potentiation of Neuromuscular Blockade: Hypokalaemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalcemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia, and debilitation.

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

Rapid Sequence Induction of Anesthesia

Endotracheal intubation during rapid sequence induction has not been adequately studied at time points of less than 60 seconds post-administration of rocuronium bromide.

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

Clinical experience indicates that rocuronium bromide is often unsuitable for facilitating endotracheal intubation during rapid sequence induction in Cesarean section patients. Therefore it is not recommended for rapid sequence induction in obstetric patients. See **Special Populations.**

Renal

Because rocuronium is excreted in urine and bile, it should be used with caution in patients with severe renal impairment (creatinine clearance < 30 mL/min). In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide.

Sensitivity/Resistance

Anaphylaxis: Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. These reactions have, in some cases (including cases with rocuronium bromide) been life threatening. Precautions, like the immediate availability of appropriate emergency treatment, 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.

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.

Malignant Hyperthermia: Since Rocuronium Bromide Injection is always used with other agents and the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the administration of any anesthetic. Cases of delayed-onset malignant hyperthermia have also been reported with the use of rocuronium. Rocuronium bromide has not been studied in susceptible patients (See **TOXICOLOGY**).

Special Populations

Pregnant Women: 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. Rocuronium Bromide Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Obstetrics (Cesarean section): Intubating conditions were poor or inadequate in 5 of 13 women receiving 3-4 mg/kg thiopental when intubation was attempted 60 seconds after administering 0.6 mg/kg (600 mcg/kg) rocuronium bromide. Therefore, Rocuronium Bromide Injection is not recommended for rapid sequence intubation in Cesarean section patients. The possibility of respiratory depression in the neonate should always be considered following a Cesarean section during which a neuromuscular blocking agent has been administered.

Nursing Women: 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 Injection should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

Geriatrics: Lower maintenance doses and infusion rates are recommended for the elderly. Rocuronium Bromide Injection is not recommended for the facilitation of mechanical ventilation in the intensive care in geriatric patients due to a lack of data on safety and efficacy. See **WARNINGS AND PRECAUTIONS**, **General**, **Residual Neuromuscular Blockade**, **Cardiovascular** and **DOSAGE AND ADMINISTRATION, Geriatrics.**

Pediatrics: Caution is advised in selecting intubation and maintenance dosage in neonates and infants because of limited controlled safety and efficacy data. Rocuronium Bromide Injection is not recommended for facilitating intubation during rapid sequence induction in pediatric patients. Rocuronium Bromide Injection is not recommended for facilitating mechanical ventilation in the intensive care unit in pediatric patients because of insufficient safety and efficacy data. See **DOSAGE AND ADMINISTRATION, Pediatrics.**

The overall analysis of ECG data in two clinical pharmacological studies in pediatric patients indicates that the combined use of rocuronium bromide with general anesthetic agents can prolong the QTc interval. The data also suggest that rocuronium bromide may increase heart rate. However, it was not possible to conclusively identify an effect of rocuronium bromide independent of that of anesthesia and other factors. Additionally, when examining plasma levels of rocuronium bromide in correlation to QTc interval prolongation, no relationship was observed. See **WARNINGS AND PRECAUTIONS, Cardiovascular, ECG Monitoring** and **ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions.**

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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 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 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 Blockade
The most frequent adverse reaction to nondepolarizing 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 apnea.

Myopathy
Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see section **WARNING AND PRECAUTIONS, Long-Term Use in the ICU**).

Local Injection Site Reactions
During rapid sequence induction of anesthesia, 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 anesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anesthesia with fentanyl and thiopental.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The patients exposed in North American clinical studies (n=1137) provide the basis for calculation of adverse event rates. The following adverse reactions were reported in patients administered rocuronium bromide and the incidences of these adverse reactions were less than 1%:

Cardiovascular:	arrhythmia, abnormal electrocardiogram, tachycardia
Digestive:	nausea, vomiting
Respiratory:	asthma (bronchospasm, wheezing, or rhonchi), hiccup
Skin and Appendages:	rash, injection site oedema, pruritus

A meta-analysis of 11 clinical studies in pediatric 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%.

Approximately 5% pediatric patients reported QTcB longer than 500 msec in two rocuronium clinical pharmacological studies under general anesthesia and during surgery. Prolonged QTc intervals were observed both before and after rocuronium injection. However, a relationship between the plasma rocuronium concentrations and specific QTc intervals was not identified after rocuronium intubation doses of 0.45, 0.6, or 1.0 mg /kg.

Post-Market Adverse Drug Reactions

The information included in this section is based on post-marketing data and clinical trials (see table below).

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

MedDRA SOC	Preferred term[1]	
	Uncommon (≥1/1000 and <1/100)/ Rare[2] (≥1/10 000 and < 1/1000)	Very rare (<1/10 000)
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
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[3] Steroid myopathy[3]
General disorders and administration site conditions	Drug ineffective Drug effect/ therapeutic response decreased Drug effect/ therapeutic response increased	Face oedema Malignant hyperthermia

	Injection site pain Injection site reaction	
Injury, poisoning and procedural complications	Prolonged neuromuscular blockade Delayed recovery from anesthesia	Airway complication of 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 two rather than five categories.
3 after long-term use in the ICU

DRUG INTERACTIONS

Drug-Drug Interactions

No formal clinical interaction studies have been conducted in adults or in pediatrics with rocuronium bromide and other drugs commonly used for anesthesia. Based on post-market clinical studies and experience, the following drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents:

Antibiotics: Antibiotics from several classes may enhance or prolong the neuromuscular blockade produced by rocuronium regardless of their route of parenteral administration (e.g. intravenous, intraperitoneal). Antibiotics such as aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics have been shown to increase the effect of rocuronium. Residual neuromuscular blockade has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics.

Anticonvulsants: Prior chronic administration of phenytoin or carbamazepine has been shown to decrease the effect of rocuronium. Increased effect of rocuronium has been shown with acute administration of phenytoin.

Corticosteroids: Long-term concomitant use of corticosteroids and rocuronium bromide in the ICU may result in prolonged duration of neuromuscular blockade or myopathy.

Inhalation Anesthetics: Halogenated volatile anesthetics potentiate the neuromuscular blockade of rocuronium bromide during induction and maintenance. Reversal of the blockade with anticholinesterase inhibitors could also be inhibited.

Local anesthetics: Local anesthetics used during combined regional and general anesthesia have been shown to increase the duration of the neuromuscular blockade and decrease requirements of neuromuscular blocking agents.

Other drugs: Increased effect of rocuronium has been shown with: acute administration of ß-blocking agents, calcium channel blocking agents, diuretics, intravenous lidocaine, magnesium salts,

lithium salts, procainamide, or quinidine and its isomer quinine. Residual neuromuscular blockade has been reported after post-operative administration of: quinidine, quinine and magnesium salts.

Other Non-Depolarizing Neuromuscular Blocking Agents: Administration of other non-depolarizing neuromuscular blocking agents in combination with Rocuronium Bromide Injection may produce attenuation or potentiation of the neuromuscular blockade, depending on the order of administration and the neuromuscular blocking agent used.

Protease inhibitors: Protease inhibitors (gabexate, ulinastatin) have been shown to decrease the effect of rocuronium bromide.

Succinylcholine: If rocuronium bromide is given following administration of succinylcholine, it should not be given until recovery from succinylcholine has been observed. The median duration of action of rocuronium bromide 0.6 mg/kg administered after a 1 mg/kg dose of succinylcholine when T1 returned to 75% of control was 36 minutes (range 14 - 57, n = 12) vs. 28 minutes (17 - 51, n = 12) without succinylcholine.

Succinylcholine given after the administration of Rocuronium Bromide Injection may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

It is not recommended to use a small dose of rocuronium bromide before an intubation dose of succinylcholine to reduce muscle fasciculation produced by succinylcholine.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Rocuronium Bromide Injection should be administered only by intravenous route. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents.

To avoid distress to the patient, Rocuronium Bromide Injection should not be administered before unconsciousness has been induced. It should not be mixed in the same syringe or administered simultaneously through the same needle with alkaline solutions (e.g., barbiturate solutions).

As with other neuromuscular blocking agents, doses of Rocuronium Bromide Injection should be individualized in each patient. The method of anesthesia 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. A peripheral nerve stimulator should be used to measure neuromuscular function during administration of Rocuronium Bromide Injection in order to monitor drug effect, to determine the need for additional doses, and to confirm recovery from neuromuscular blockade.

Inhalational anesthetics do potentiate the neuromuscular blocking effects of rocuronium bromide. This potentiation however, becomes clinically relevant in the course of anesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, the choice of an intubating dose of rocuronium bromide should not, therefore, be reduced below 0.45 mg/kg if routine tracheal intubation is to be performed or below 0.60 mg/kg if rapid intubation is to be performed. Yet adjustments with Rocuronium Bromide Injection should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuronium Bromide Injection during long lasting procedures (longer than 1 hour) under inhalational anesthesia (see section Drug Interactions - Drug-Drug Interactions). Otherwise increases in the clinical duration (25-35%) and recovery time (20-70%) of neuromuscular blockade may be apparent in the presence of a halogenated inhalation agents.

Continuous infusion or intermittent bolus dosing to support long term mechanical ventilation has not been studied sufficiently to support dosage recommendations.

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store Rocuronium Bromide Injection with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product (see **WARNINGS AND PRECAUTIONS, General**).

Recommended Dose and Dosage Adjustment

Adults:

The following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures.

Endotracheal intubation

Routine endotracheal intubation: the recommended initial dose regardless of anesthetic regimen is 0.6 mg/kg rocuronium bromide. Neuromuscular blockade sufficient for intubation (80% blockade or greater) is attained in a median (range) time of 1 (0.4-6) minute(s) and most patients have intubation completed within 2 minutes. Maximum blockade is achieved in most patients in less than 3 minutes. This dose may be expected to provide 31 (15-85) minutes of surgical relaxation under opioid/N_2O/O_2 anesthesia. Under halothane, isoflurane, and enflurane anesthesia, some extension of the period of clinical relaxation should be expected (see **DRUG INTERACTIONS**).

Endotracheal Intubation during Rapid Sequence Induction: In appropriately pre-medicated and adequately anesthetized patients, 0.60 - 1.2 mg/kg (600 - 1200 mcg/kg) rocuronium bromide will provide good or excellent intubating conditions in most patients in 60-90 seconds.

Use of lower or higher doses: A lower dose of rocuronium bromide (0.45 mg/kg) may be used. Neuromuscular blockade sufficient for intubation (80% blockade or greater) is attained in a median (range) time of 1.3 (0.8-6.2) minute(s) and most patients have intubation completed within 1.6 (1.0 - 7.0) minutes. Maximum blockade is achieved in most patients in 3.0 (1.3-8.2) minutes. This dose may be expected to provide 22 (12-31) minutes of clinical relaxation under

opioid/N_2O/O_2 anesthesia. Patients receiving this low dose of 0.45 mg/kg who achieve less than 90% blockade (about 16% of these patients) may have a more rapid time to 25% recovery, 12 to 15 minutes.

A large bolus dose of 0.9 or 1.2 mg/kg may be administered under opioid/N_2O/O_2 anesthesia when necessary. These doses will provide > 80% blockade in most patients in 1.1 and 0.7 minutes, respectively, with maximum blockade occurring in most patients in 1.4 and 1.0 minute, respectively. Doses of 0.9 and 1.2 mg/kg may be expected to provide 58 (27-111) and 67 (38-160) minutes of clinical relaxation under opioid/N_2O/O_2 anesthesia, respectively.

A high bolus dose of 1.6 or 2.0 mg/kg may be used when necessary. These doses resulted in good to excellent intubation conditions and excellent intubation conditions within 60 seconds after rocuronium bromide administration, respectively. Doses of 1.6 or 2.0 mg/kg may be expected to provide 76 (55-97) and 110 (80-160) minutes of clinical relaxation under alfentanyl/thiopental anesthesia.

Maintenance dosing

Maintenance doses of 0.1, 0.15, and 0.2 mg/kg (100, 150, and 200 mcg/kg) of rocuronium bromide administered at 25% recovery of control T1, provide a median 12, 17, and 24 minutes of clinically effective neuromuscular blockade during opioid/N_2O/O_2 anesthesia. Smaller or less frequent bolus maintenance doses (0.075-0.1 mg/kg rocuronium bromide) should be considered during anesthesia with a halogenated inhalation agents. Subsequent dosing should be guided based on the clinical duration following initial dose or prior maintenance dose and only when twitch height has recovered to 25% of control twitch height or when 2 to 3 responses to train-of-four stimulation are present. Cumulative effect with repetitive maintenance dosing has been observed but it is of minor clinical significance.

Continuous infusion

After evidence of early spontaneous recovery (<10% of control T1) from initial doses of rocuronium bromide, a continuous infusion can be initiated to maintain a 90% suppression of twitch response or to maintain 1 to 2 responses to train-of-four stimulation. In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular blockade at this level ranges from 0.3-0.6 mg/kg/h and under inhalational anesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular blockade is recommended since infusion rate requirements vary from patient to patient and with the anesthetic method used.

Initiation of the infusion after substantial return of neuromuscular function (more than 10% of control T1), may necessitate additional bolus doses to maintain adequate blockade for surgery.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of rocuronium bromide infusion may be expected to proceed at rates similar to those following comparable total doses administered by repetitive bolus injections.

Infusion solutions of Rocuronium Bromide Injection can be prepared by mixing Rocuronium Bromide Injection with an appropriate infusion solution (see **DOSAGE AND ADMINISTRATION**, **Administration**). Unused portions of infusion solutions should be discarded.

Pediatrics:

Caution is advised in selecting intubation and maintenance dosages in neonates (0 - 1 month) and infants (1 - 3 months) because of limited controlled safety and efficacy data. Rocuronium Bromide Injection is not recommended for rapid sequence intubation in pediatric patients because of insufficient safety and efficacy data.

Routine endotracheal intubation:

The recommended initial intubation dose of Rocuronium Bromide Injection is 0.6 mg/kg, however, a lower dose of 0.45 mg/kg may be used depending on the underlying pathology of the patient, use of other drugs, the surgical procedure planned, anesthetic technique and the age of the patient.

Halothane anesthesia: Initial doses of 0.6 mg/kg (600 mcg/kg) in children (3 months - 12 years) under halothane anesthesia produce 100% neuromuscular blockade and excellent to good intubating conditions within approximately 60 to 90 seconds. This dose will provide approximately 25-30 minutes of clinical relaxation in children aged 1 to 12 years receiving halothane anesthesia. For infants aged 3-12 months, the duration of action of a 0.6 mg/kg dose is longer than in older pediatric patients, averaging 42 minutes under conditions of halothane anesthesia.

Sevoflurane (induction) and Isoflurane/Nitrous Oxide (maintenance): For sevoflurane induction Rocuronium Bromide Injection doses of 0.45 mg/kg and 0.6 mg/kg in general produce excellent to good intubating conditions within 75 seconds in all pediatric ages. The time to maximum block for an intubating dose was approximately 60 seconds on average across all pediatric groups, longest in neonates (0 - 28 days) (70 - 80 seconds), and shortest in infants (1 - 3 months) (40 - 50 seconds). The duration of clinical relaxation following an intubating dose is shortest in children (2 years - 11 years) and approximately 2-fold longer in neonates and infants.

For sevoflurane (induction), the time to maximum block for an intubating dose was shortest in infants (28 days up to 3 months) and longest in neonates (birth to less than 28 days). The duration of clinical relaxation following an intubating dose is shortest in children (greater than 2 years up to 11 years) and longest in infants.

Maintenance Doses

The recommended maintenance dose for pediatric patients of all age groups are similar to those in adults.

Halothane anesthesia: When halothane is used for general anesthesia in pediatric patients aged 4 - 13 years, maintenance doses of 0.075 - 0.125 mg/kg (75 - 125 mcg/kg), administered upon return of T1 to 25% of control, provide surgical relaxation for a median of 7 - 10 minutes.

Sevoflurane (induction) and Isoflurane/Nitrous Oxide (maintenance): When sevoflurane is used for induction and isoflurane/nitrous oxide for maintenance of general anesthesia, maintenance dosing of Rocuronium Bromide Injection can be administered as bolus doses of 0.15 mg/kg at reappearance of T_3 in all pediatric age groups. Maintenance dosing can also be administered at the reappearance of T_2 at a rate of 7-10 mcg/kg/min with the lowest dose requirement for neonates and the highest dose requirement for children.

Continuous Infusion

For continuous infusion in infants (3-23 months), children (2-11 years) and adolescents (12-18 years) the same infusion rates as for adults are recommended. Although for children (2-11 years) higher infusion rates might be necessary.

A continuous infusion of rocuronium bromide initiated at a rate of 0.012 mg/kg/min (12 mcg/kg/min) upon return of T1 to 10% of control has been demonstrated to maintain neuromuscular blockade at 89-99% in children receiving halothane anesthesia.

Geriatrics:

The recommended intubation dose is 0.6 mg/kg rocuronium bromide for the elderly. A dose of 0.6 mg/kg should be considered for Rapid Sequence Induction of anesthesia in the elderly in whom a prolonged duration of action is expected. 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, regardless of the anesthetic technique used.

Geriatric patients exhibited a slightly prolonged median duration of surgical relaxation after an equivalent dose to younger adults. Following doses of 0.6, 0.9, and 1.2 mg/kg, the median (range) duration was 46 (22-73), 62 (49-75), and 94 (64-138) minutes under opioid/N_2O/O_2 anesthesia, respectively. No differences in duration of neuromuscular blockade following maintenance doses of rocuronium bromide were observed between elderly and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. See **WARNINGS AND PRECAUTIONS**, **General**, **Residual Neuromuscular Blockade** and **ACTION AND CLINICAL PHARMACOLOGY**.

Patients with hepatic or renal impairment

The recommended intubation dose for patients with hepatic or renal impairment during routine anesthesia is 0.6 mg/kg rocuronium bromide. A dose of 0.6 mg/kg should be considered for Rapid Sequence Induction of anesthesia in these patients in whom a prolonged duration of action is expected. 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 regardless of the anesthetic technique used (see also Continuous infusion).

When compared with patients with normal hepatic or renal function, no differences in onset time were observed in patients with hepatic or renal impairment at a dose of 0.6 mg/kg rocuronium bromide. The mean duration of surgical relaxation may have a greater variation in patients with renal impairment. It is about 1.5 times longer in patients with hepatic impairment.

Obese patients

When used in 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.

Administration

Rocuronium Bromide Injection is administered intravenously either as a bolus injection or as a continuous infusion.

Do not use Rocuronium Bromide Injection if solution contains particles or is not clear.

Compatibility: Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0.5 mg/mL and 2.0 mg/mL Rocuronium Bromide Injection is compatible in solution with:

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP
Sterile Water for Injection, USP
Lactated Ringer's Solution

Administration should be begun immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

Incompatibility: Rocuronium Bromide Injection (rocuronium bromide), which has an acidic pH (pH: 3.8 - 4.2), should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. If Rocuronium Bromide Injection is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9 % NaCl) between administration of Rocuronium Bromide Injection and drugs for which incompatibility with Rocuronium Bromide Injection has been demonstrated or for which compatibility with Rocuronium Bromide Injection has not been established.

Incompatibility has been documented for rocuronium bromide when added to solutions containing the following drugs: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. Rocuronium bromide is also incompatible with Intralipid.

Antagonism of Neuromuscular Blockade

Antagonists (such as neostigmine, edrophonium and pyridostigmine) should not be administered prior to the demonstration of some spontaneous recovery from neuromuscular blockage (reappearance of T_2 or first signs of functional recovery). The use of an adequate neuromuscular monitoring device to document recovery and antagonism of neuromuscular blockade is recommended. The time required for anticholinesterase mediated recovery is longer for reversals attempted at deeper levels of blockade.

Patients should be evaluated for adequate functional evidence of antagonism, e.g., 5 second head lift, adequate phonation, ventilation and upper airway maintenance. Ventilation must be supported until no longer required.

Antagonism by acetylcholinesterase inhibiting agents may be delayed in the presence of debilitation, carcinomatosis, and concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or depress respiratory function (see **DRUG**

INTERACTIONS). Under such circumstances the management is the same as that of prolonged neuromuscular blockade (see **OVERDOSAGE).**

OVERDOSAGE

For management of a suspected drug overdose, contact your Regional Poison Control Centre immediately.

The possibility of iatrogenic overdosage can be minimized by carefully monitoring the muscle twitch response to peripheral nerve stimulation. In the event of overdosage and prolonged neuromuscular blockade, the patient should continue to receive ventilatory support and sedation. Adequate monitoring of vital organ function is recommended for the period of paralysis and during an extended period post recovery. 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, ventilation must be continued until adequate spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Rocuronium Bromide Injection (rocuronium bromide) is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset and intermediate duration depending on dose. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium.

Pharmacodynamics

Pharmacodynamic Effects: The ED_{95} (dose required to produce 95% suppression of the first [T1] mechanomyographic (MMG) response of the thumb to indirect supramaximal train-of-four stimulation of the ulnar nerve) is approximately 0.3 mg/kg (300 mcg/kg) in adults receiving opioid/N2O/O2 anesthesia. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg, respectively). With high doses of 2 mg/kg, clinical duration is 110 minutes. At equipotent doses, rocuronium has approximately the same clinically effective duration of action as vecuronium. However, the onset of action is approximately 40% shorter for rocuronium than for vecuronium at doses of 2 to 3 times the ED_{95}.

The median pharmacodynamic parameter values for rocuronium bromide over a range of doses are presented in Tables 1 and 2.

TABLE 1. Pharmacodynamic Parameter Values For The Initial Dose Of Rocuronium Bromide Administered During Opioid/N_2O/O_2 Anesthesia (Adults) And Halothane Anesthesia (Children) Median [Range].

Rocuronium bromide Dose administered over 5 s.	Time to ≥ 80% block (min)	Time to Maximum Block (min)	Clinical Duration (min)	Peak Effect (% of control T_1)
Adults 18 to 64yrs				
0.45mg/kg (n=50)	1.3[0.8-6.2]	3.0[1.3-8.2]	22[12-31]	2.5[0-25]
0.6mg/kg (n=142)	1.0[0.4-6.0]	1.8[0.6-13.0]	31[15-85]	0[0-9.7]
0.9mg/kg (n=20)	1.1[0.3-3.8]	1.4[0.8-6.2]	58[27-111]	0[0-7]
1.2mg/kg (n=18)	0.7[0.4-1.7]	1.0[0.6-4.7]	67[38-160]	0[0-4]
Geriatric 65 to 78yrs				
0.6mg/kg (n=31)	2.3[1.0-8.3]	3.7[1.3-11.3]	46[22-73]	0[0-7]
0.9mg/kg (n=5)	2.0[1.0-3.0]	2.5[1.2-5.0]	62[49-75]	0[0-0]
1.2mg/kg (n=7)	1.0[0.8-3.5]	1.3[1.2-4.7]	94[64-138]	0[0-0]
Pediatric				
3mo-1yr				
0.6mg/kg(n=17)	-	0.8[0.3-3]	41[24-68]	0[0-0]
0.8mg/kg(n=9)	-	0.7[0.5-0.8]	40[27-70]	0[0-3]
1-12yrs				
0.6mg/kg(n=27)	0.8[0.4-2]	1.0[0.5-3.3]	26[17-39]	0[0-0]
0.8mg/kg(n=18)	-	0.5[0.3-1.0]	30[17-56]	0[0-0]

n= the number of patients who had Time to Maximum block recorded.
Clinical duration= time until return to 25% of control T_1.
Patients receiving doses of 0.45mg/kg who achieved less than 90% block (16% of these patients) had about 12 to 15 minutes to 25% recovery.

TABLE 2. Intubating Conditions In Patients With Intubation Initiated At 60 To 70 Seconds. Percent, Median [Range]

Rocuronium bromide Dose (mg/kg) administered over 5 sec	Percent of patients with excellent or good intubating conditions	Time to completion of intubation (min)
Adults[1] 18-64 yr		
0.45 (n=43)	86%	1.6 [1.0-7.0]
0.6 (n=51)	96%	1.6 [1.0-3.2]
Pediatric 3 mo-1yr		
0.6 (n=18)	100%	1.0 [1.0-1.5]
Pediatric 1-4 yr		
0.6 (n=12)	100%	1.0 [0.5-2.3]

[1]Excludes patients undergoing Cesarean section
Excellent Intubating Conditions = jaw relaxed, vocal cords apart & immobile, no diaphragmatic movement Good Intubating Conditions = jaw relaxed, vocal cords apart & immobile, some diaphragmatic movement

Intubation Conditions: A dose of 0.60 mg/kg (2 X ED_{95}) rocuronium bromide administered following the induction of thiopental/narcotic anesthesia in adults or halothane anesthesia in children

generally produces good or excellent conditions for tracheal intubation initiated at 60-70 seconds post-administration (see Table 2). After administration of 0.45 mg/kg rocuronium bromide, following intravenous anesthesia (thiopental and fentanyl) in adults, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction of Anesthesia: During rapid sequence induction of anesthesia, following a dose of 1.0 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 93% of the patients with propofol anesthesia and 96% of the patients with fentanyl/thiopental anesthesia. Of these, 70% are rated excellent. The surgical relaxation with this dose approaches 1 hour, at which time the neuromuscular blockade may be reversed when functional recovery is evident. 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.

Maintenance Doses: In adult patients under opioid/N_2O/O_2 anesthesia, the median clinical duration (time from injection of the maintenance dose at a T1 of 25% of control to a return to 25% of the control T1) of maintenance doses of 0.1, 0.15 and 0.2 mg/kg (100, 150 and 200 mcg/kg) of rocuronium bromide is 12 minutes (range 2 - 31 minutes), 17 minutes (range 6 - 50 minutes), and 24 minutes (range 7 - 69 minutes), respectively. Repeated maintenance doses results in insignificant increases in the median time of clinical duration (2 - 4 minutes) between the first and fifth consecutive dose. The median rate of spontaneous recovery of T1 from 25 to 75% (n = 182), following the final maintenance dose of rocuronium bromide, is 13 minutes (4 - 84 minutes).

Inhalation Anesthetics: The duration of the neuromuscular blocking action of rocuronium bromide may be enhanced by approximately 30% in the presence of potent inhalation anesthetics. The median clinical duration of a dose of 0.6 mg/kg was 30, 38, and 42 minutes under opioid/N_2O/O_2, enflurane and isoflurane maintenance anesthesia, respectively. During 1 - 2 h of infusion, the infusion rate of rocuronium bromide required to maintain about 95% blockade was decreased by as much as 40% under enflurane and isoflurane anesthesia (see the **Inhalation Anesthetics** subsection under DRUG INTERACTIONS).

Obstetrics: Rocuronium bromide 0.6 mg/kg (600 mcg/kg) was administered with thiopental, 3-4 mg/kg (n=13) or 4-6 mg/kg (n=42), for rapid sequence induction of anesthesia for Cesarean section. The umbilical venous plasma concentrations were 18% of maternal concentrations at delivery. No neonate had APGAR scores of <7 at 5 minutes post-delivery. Intubating conditions were poor or inadequate in 5 of 13 women receiving 3-4 mg/kg thiopental when intubation was attempted 60 seconds after drug injection. Therefore, Rocuronium Bromide Injection is not recommended for rapid sequence induction in Cesarean section patients.

Pediatrics:
Halothane anesthesia: Children (1-13 years of age) under halothane anesthesia are less sensitive to rocuronium bromide (ED_{50} approximately 0.18 mg/kg [180 mcg/kg], ED_{95} 0.35-0.4 mg/kg [350-400 mcg/kg]) than adults on a mg/kg (mcg/kg) basis. The onset time and duration of blockade are shorter in children (1-13 years) than in adults (see Table 1). The clinical duration of action of 0.6 and 0.8 mg/kg doses of rocuronium bromide are approximately 30-60% longer in infants aged 3 months to 1 year than in children aged 1-13 years (see Table 1). During halothane anesthesia, at

doses of 0.6 mg/kg (600 mcg/kg) of rocuronium bromide, the median onset time is 60 seconds (30 - 200 s.) and the clinical duration is 26 min. (17 - 39 min.). Maintenance doses of 0.1 or 0.125 mg/kg (100 or 125 mcg/kg) rocuronium bromide in children under halothane anesthesia provided a median clinical duration of 7 and 10 minutes, respectively. The median rate of spontaneous recovery of T1 from 25 - 75% was 9.5 minutes (4 - 29 minutes).

Table 3 presents the time to onset and clinical duration for the initial dose of rocuronium bromide injection under opioid/nitrous oxide/oxygen anesthesia in adults and geriatric patients, and under halothane anesthesia in pediatric patients.

TABLE 3. Median (Range) Time to Onset and Clinical Duration Following Initial (Intubating) Dose During Opioid/Nitrous Oxide/Oxygen Anesthesia (Adults) and Halothane Anesthesia (Pediatric Patients)

Rocuronium Bromide Dose (mg/kg) Administered over 5 sec	Time to >80% Block (min)	Time to Maximum Block (min)	Clinical Duration (min)
Adults 18 to 64 yrs			
0.45 (n=50)	1.3 (0.8-6.2)	3.0 (1.3-8.2)	22 (12-31)
0.6 (n=142)	1.0 (0.4-6.0)	1.8 (0.6-13.0)	31 (15-85)
0.9 (n=20)	1.1 (0.3-3.8)	1.4 (0.8-6.2)	58 (27-111)
1.2 (n=18)	0.7 (0.4-1.7)	1.0 (0.6-4.7)	67 (38-160)
Geriatric ≥65 yrs			
0.6 (n=31)	2.3 (1.0-8.3)	3.7 (1.3-11.3)	46 (22-73)
0.9 (n=5)	2.0 (1.0-3.0)	2.5 (1.2-5.0)	62 (49-75)
1.2 (n=7)	1.0 (0.8-3.5)	1.3 (1.2-4.7)	94 (64-138)
Infants 3 mo to 1 yr			
0.6 (n=17)	—	0.8 (0.3-3.0)	41 (24-68)
0.8 (n=9)	—	0.7 (0.5-0.8)	40 (27-70)
Pediatric 1 to 12 yrs			
0.6 (n=27)	0.8 (0.4-2.0)	1.0 (0.5-3.3)	26 (17-39)
0.8 (n=18)	—	0.5 (0.3-1.0)	30 (17-56)

n = the number of patients who had time to maximum block recorded
Clinical duration = time until return to 25% of control T_1. Patients receiving doses of 0.45 mg/kg who achieved less than 90% block (16% of these patients) had about 12 to 15 minutes to 25% recovery.

Sevoflurane (induction) and Isoflurane/Nitrous Oxide (maintenance): Comparison between pediatric 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).

Comparing between pediatric age groups demonstrated that mean time to reappearance of T_3 was prolonged in term 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).

Table 4 presents the time to onset and clinical duration for the initial dose of rocuronium bromide under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia in pediatric patients.

TABLE 4. Median (Range) Time to Onset and Clinical Duration Following Initial (Intubating) Dose During Sevoflurane (induction) and Isoflurane/Nitrous Oxide (maintenance) Anesthesia (Pediatric Patients)

Rocuronium Bromide Dose (mg/kg) Administered over 5 sec	Time to Maximum Block (min)	Time to Reappearance T_3 (min)
Neonates birth to <28 days		
0.45 (n=5)	1.1 (0.6-2.2)	40.3 (32.5-62.6)
0.6 (n=10)	1.0 (0.2-2.1)	49.7 (16.6-119.0)
1 (n=6)	0.6 (0.3-1.8)	114.4 (92.6-136.3)
Infants 28 days to ≤3 mo		
0.45 (n=9)	0.5 (0.4-1.3)	49.1 (13.5-79.9)
0.6 (n=11)	0.4 (0.2-0.8)	59.8 (32.3-87.8)
1 (n=5)	0.3 (0.2-0.7)	103.3 (90.8-155.4)
Toddlers >3 mo to ≤2 yrs		
0.45 (n=17)	0.8 (0.3-1.9)	39.2 (16.9-59.4)
0.6 (n=29)	0.6 (0.2-1.6)	44.2 (18.9-68.8)
1 (n=15)	0.5 (0.2-1.5)	72.0 (36.2-128.2)
Children >2 yrs to ≤11 yrs		
0.45 (n=14)	0.9 (0.4-1.9)	21.5 (17.5-38.0)
0.6 (n=37)	0.8 (0.3-1.7)	36.7 (20.1-65.9)
1 (n=16)	0.7 (0.4-1.2)	53.1 (31.2-89.9)
Adolescents >11 to ≤17 yrs		
0.45 (n=18)	1.0 (0.5-1.7)	37.5 (18.3-65.7)
0.6 (n=31)	0.9 (0.2-2.1)	41.4 (16.3-91.2)
1 (n=14)	0.7 (0.5-1.2)	67.1 (25.6-93.8)

n = the number of patients with the highest number of observations for time to maximum block or reappearance T_3

Geriatric patients: The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anesthesia in geriatric patients (approximately 20 minutes) than in adults under intravenous anesthesia (approximately 13 minutes) (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**). No accumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

Hepatic Impairment: The influence of hepatic impairment on the pharmacodynamics of a 0.60 mg/kg dose of rocuronium bromide was investigated in a study in which 9 patients with alcoholic cirrhosis were compared to 10 patients with normal hepatic function. Relative to the normal group, the patients with hepatic impairment exhibited an increased clinical duration of action (60 versus 42 min). The recovery index (time for recovery from 25-75% T1 suppression) was also prolonged in the cirrhotic patients (53 versus 20 min).

Renal Impairment: Three single centre clinical trials have been performed to compare the pharmacodynamic characteristics of a 0.6 mg/kg dose of rocuronium bromide in patients having normal renal function (n=31) to those for patients (n=30) having renal impairment undergoing kidney transplantation or AV shunt/peritoneal catheter implantation surgery for haemodialysis while receiving steady-state isoflurane anesthesia. The pharmacodynamic characteristics of rocuronium bromide were not altered in a consistent manner in the patients with renal impairment although

clinical duration and recovery times were more variable than in patients with normal renal function.

Hemodynamics: Rocuronium has a weak vagus blocking effect and little effect on sympathetic ganglionic transmission. In most clinical trials, the monitoring of haemodynamic parameters during the period immediately following the administration of rocuronium bromide was confounded by laryngoscopy and intubation; events associated with elevations of heart rate and mean arterial blood pressure may result from multiple factors, including rocuronium bromide administration. In one study in which a six minute period was permitted to elapse between the administration of rocuronium bromide at 0.6, 0.9, and 1.2 mg/kg doses and subsequent intubation, no dose-dependent changes in heart rate or mean arterial pressure were observed. Infrequently clinical signs of histamine release (0.8%) have been reported in clinical trials.

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 blockade at the end of the infusion. After a continuous infusion for 20 hours or more the median 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 blockade following 0.6-0.9 mg/kg rocuronium bromide are a slight increase in heart rate up to 9% and an increase in mean arterial blood pressure up to 16% from the control values.

Antagonism of neuromuscular blockade: Once spontaneous recovery has started (reappearance of T_2 or first signs of clinical recovery), the neuromuscular blockade produced by rocuronium bromide is readily reversed with various anticholinesterase agents, e.g., neostigmine, edrophonium or pyridostigmine.

Pharmacokinetics

The pharmacokinetic characteristics of intravenously administered rocuronium bromide are best described by a three compartment open model. The comparative population estimates for adult and geriatric surgical patients, pediatric patients and patients with renal impairment undergoing cadaver renal transplantation, and patients with hepatic cirrhosis are presented in Tables 5-6.

TABLE 5. Summary of Rocuronium Bromide's Pharmacokinetic Parameters In Adult And Geriatric Patients Receiving A Single 0.6 Mg/Kg Dose During Opioid/N_2O/O_2 Anesthesia.

	C_{max}	$T_{1/2}$ (h)	AUC	Clearance (L/kg/h)	Volume of distribution (L/kg)
Adults (27-58 yr, n=22)	NA	1.4 ± 0.4	NA	0.25 ± 0.08	0.25 ± 0.04
Geriatrics (65-78 yr, n=20)	NA	1.5 ± 0.4	NA	0.21 ± 0.06	0.22 ± 0.03

Data are presented as mean ± SD

Pediatrics: The terminal half-life and other pharmacokinetic parameters of rocuronium in these pediatric patients are presented in Table 6.

TABLE 6. Summary of Rocuronium Bromide's Pharmacokinetic Parameters In Pediatric Patients Receiving A Single 0.8 Mg/Kg Dose During Halothane Anesthesia.

	C_{max}	$T_{1/2}$ (h)	AUC	Clearance (L/kg/h)	Volume of distribution (L/kg)
Pediatrics					
(3-<12 mo, n=6)	NA	1.3 ± 0.5	NA	0.35 ± 0.08	0.30 ± 0.04
(1-<3 yr, n=5)	NA	1.1 ± 0.7	NA	0.32 ± 0.07	0.26 ± 0.06
(3-< 8 yr, n=7)	NA	0.8 ± 0.3	NA	0.44 ± 0.16	0.21 ± 0.03

Data are presented as mean ± SD

Pharmacokinetics of rocuronium bromide in pediatric 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) anesthesia and receiving 0.45, 0.6 or 1.0 mg/kg rocuronium. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance (L/kg/h). The volume of distribution (L/kg) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical pediatrics within each age group are summarized in Table 7 below:

TABLE 7. Pharmacokinetic Parameters of Rocuronium (0.45, 0.6 or 1.0 mg/kg) in Pediatric Patients During Sevoflurane (induction) and Isoflurane/Nitrous Oxide (maintenance) Anesthesia

PK Parameter	Term newborn infants (0-27 days)	Infants (28 days to 2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (11-17 years)
Clearance (L/kg/h)	0.293	0.293	0.293	0.293	0.293
Volume of Distribution at Steady State (L/kg)	0.424	0.295	0.232	0.177	0.174
Elimination Half-Life (h)	1.1	0.9	0.8	0.7	0.7

Renal and Hepatic Impairment:

TABLE 8. Summary Of Rocuronium Bromide's Pharmacokinetic Parameters In Renal Transplant Patients And Hepatic Dysfunction Patients Receiving A Single 0.6 Mg/Kg Dose During Isoflurane Anesthesia.

	C_{max}	$T_{1/2}$ (h)	AUC	Clearance (L/kg/h)	Volume of distribution (L/kg)
Normal renal and hepatic function (23-65 yr, n=10)	NA	2.4 ± 0.8[1]	NA	0.16 ± 0.05[1]	0.26 ± 0.03
Renal transplant patients (21-45 yr, n=10)	NA	2.4 ± 1.1	NA	0.13 ± 0.04	0.34 ± 0.11
Hepatic dysfunction patients (31-67 yr, n=9)	NA	4.3 ± 2.6	NA	0.13 ± 0.06	0.53 ± 0.14

Data are presented as mean ± SD

[1] Differences in the calculated $T_{1/2}\beta$ and C_L between this study and the study in adults vs. geriatrics (≥ 65 yr) are related to the different sample populations and anesthetic techniques

Distribution: The placental transfer of rocuronium bromide was investigated in two studies involving a total of 17 neonates born to women receiving 0.6 mg/kg rocuronium bromide during Cesarean section. The mean umbilical venous to maternal venous plasma ratio ranged from 16-22% in these studies.

Metabolism: Following administration of a single 1.0 mg/kg bolus dose to 10 adult patients, metabolites in the plasma or urine were either absent or below the limit of detection (5 ng/mL).

Excretion: Studies in cats and dogs indicate that rocuronium is eliminated primarily by the liver. In cats cumulative excretion 6 hours after a 6 x ED_{90} dose was 9% in the urine and 54% in the bile. Consistent with the limited role of the kidney in the elimination of rocuronium, renal pedicle ligation did not substantially alter its time course in cats although clearance was significantly reduced. In contrast, hepatic exclusion in the cat significantly increased the duration of action of rocuronium, suggestive of a substantial role for the liver in the elimination of this compound.

Clinical data showed that following administration of a single 1.0 mg/kg bolus dose to 10 adult patients, total urinary excretion was 33% over a 24 h period. Of this, 65% was recovered during the first 2 hours and 94% over the first 6 hours.

If rocuronium bromide is 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.

STORAGE AND STABILITY

Rocuronium Bromide Injection should be stored under refrigeration (2-8°C) until ready to use. To facilitate use in the operating room, the unopened vials may be stored up to 90 days at room temperature (15-30°C). After first removal from the refrigerator, the 90 day shelf life applies. Use punctured vials of Rocuronium Bromide Injection within 30 days.

After dilution with infusion fluids (see **DOSAGE AND ADMINISTRATION, Administration),** 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.

SPECIAL HANDLING INSTRUCTIONS

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

Dosage Form

Rocuronium Bromide Injection is a colorless to slightly yellow/brown solution containing 10 mg/mL rocuronium bromide, which is administered intravenously either as a bolus injection or as a continuous infusion.

Composition

Rocuronium Bromide Injection is a sterile non-pyrogenic solution, without preservative.

Each mL contains:

rocuronium bromide	10.00 mg
sodium acetate, anhydrous	1.20 mg
sodium chloride	approx. 3.1 mg
water for injection	q.s to 1 mL

Rocuronium Bromide Injection may contain sodium hydroxide and/or glacial acetic acid to adjust the pH to approximately 4.0.

Packaging

Rocuronium Bromide Injection (rocuronium bromide) 10 mg/mL Solution for Injection is available in the following forms, in boxes of 10:

WITHOUT PRESERVATIVE:

VIALS

5 mL multiple dose vials containing 50 mg rocuronium bromide (10 mg/mL)

PART II: SCIENTIFIC INFORMATION

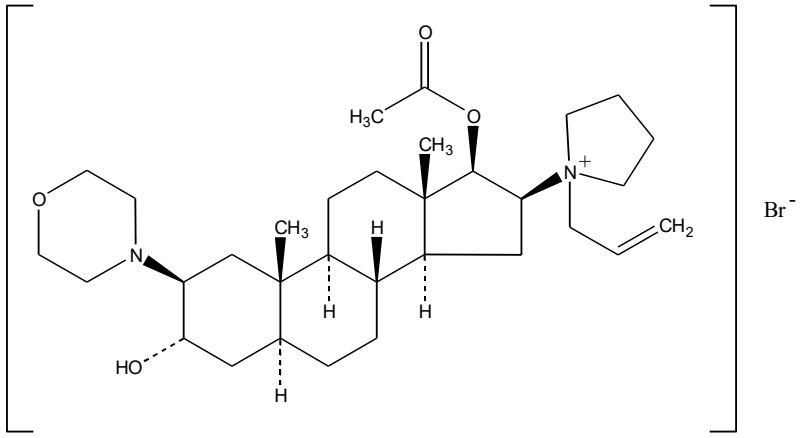
PHARMACEUTICAL INFORMATION

Proper name: rocuronium bromide

Chemical name: l-[17β-(acetyloxy)-3α-hydroxy-2β-(4-morpholinyl)-5α-androstan-16β-yl]-l-(2-propenyl) pyrrolidinium bromide

Molecular formula and molecular mass: $C_{32}H_{53}BrN_2O_4$; 609.70 g/mol

Structural formula:



Physicochemical properties:

- Physical form: rocuronium bromide is an off-white to pale yellow, or slightly pink amorphous powder.
- Solubility: soluble in 15 parts of ethanol, in 20 parts of water, acetone and chloroform. Practically insoluble in ethyl acetate and n-hexane.
- pKa: 7.11 determined in a 1% m/v solution in water
- pH: 8.9 to 9.5 for solution

CLINICAL TRIALS

Adults

The efficacy and safety of rocuronium was evaluated during its clinical development program. Within this program three randomized, double blinded studies conducted in adult ASA 1-2 patients scheduled for elective surgery were considered pivotal. Neuromuscular blockade was evaluated after intravenous administration of 0.6 mg/kg rocuronium vs. 1.0 mg/kg succinylcholine. The following efficacy parameters were evaluated: intubation conditions, onset time and, if measured, time to intubation, spontaneous recovery, clinical duration and safety. One minute after administration of 0.6 mg/kg rocuronium or 1.0 mg/kg succinylcholine adequate intubation conditions were achieved in both patient groups.

Pediatrics

Rocuronium bromide 0.45, 0.6 or 1 mg/kg was evaluated under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia for intubation in 326 pediatric patients in two studies. In one of these studies maintenance bolus and infusion requirements were evaluated in 137 patients. In all age groups, doses of 0.6 mg/kg provided time to maximum block in about 1 minute. Across all age groups, median (range) time to reappearance of T_3 for doses of 0.6 mg/kg was shortest in children (2 - 11 years) [36.7 (20.1-65.9) minutes] and longest in infants (1 - 3 months) [59.8 (32.3-87.8) minutes]. For pediatric patients older than 3 months, the time to recovery was shorter after stopping infusion maintenance when compared with bolus maintenance. See **DOSAGE AND ADMINISTRATION.**

DETAILED PHARMACOLOGY

Like other steroid-based muscle relaxants, rocuronium inhibited neuromuscular transmission both presynaptically, by inhibiting mobilization of acetylcholine to release sites, and postsynaptically, by inhibiting the interaction of acetylcholine with the cholinergic receptors of the post-junctional membrane. The contribution of the pre- and post-synaptic components to the effects of rocuronium varied with the species studied.

Rocuronium has only weak anti-muscarinic activity and does not appear to exert any local anesthetic effects at clinically effective doses. Hormonal activity studies were not supportive of estrogenic, androgenic, anabolic, gonad-inhibiting, glucocorticoid-like, or other hormonal activity. Rocuronium did not produce hemolysis, increased red cell fragility, or plasma protein precipitation when administered intravenously to rats or when studied in vitro in human blood samples.

TOXICOLOGY

Acute Toxicity

The acute toxicity of rocuronium was evaluated in dogs (up to 750 times the ED_{90}) and cats (up to 350 times the ED_{90}) by intravenous routes. In dogs, a transient, slight increase in blood pressure and heart rate was observed at all dose levels. The 135 mg/kg dose was associated with severe depression of cardiovascular function, arrhythmia, and death. The administration of rocuronium to

cats resulted in transient, but severe, decreases in blood pressure and minor decreases in heart rate. No drug-related deaths were reported.

Subacute Toxicity

The effects of repeated administration of rocuronium were studied in two four-week studies, one in anesthetized, ventilated beagle dogs (up to 60 times ED_{90}) and one in cats under halothane anesthesia (up to 36 times ED_{90}). Beagle dogs were treated by intravenous route once a day, twice weekly, with an interval of two to four days between dosing and cats were treated two days a week for four weeks. In dogs, rocuronium was generally well-tolerated with few clinical signs other than those due to its pharmacologic action. Cats showed no untoward or unexpected treatment related pharmacological or toxicological signs or symptoms throughout the study.

A decomposition product of rocuronium, 17-desacetyl-rocuronium (Org 9943), did not produce neuromuscular blockade or significant clinical findings in cats after administration of five 0.72 mg/kg sub-doses at 30 minute intervals.

In a study with anesthetized cats administered heat sterilized rocuronium at dosage levels of 2.5, 5 or 12.5 mg/kg, neuromuscular blockade was produced without signs of toxicity.

Malignant hyperthermia in swine

Rocuronium did not induce malignant hyperthermia in susceptible swine when administered for 2 h at an infusion rate adjusted to maintain 90-95% neuromuscular blockade (72 mcg/kg/min). Following 100% recovery from neuromuscular blockade, only one of the ten animals treated with rocuronium developed malignant hyperthermia when challenged with halothane and succinylcholine as triggering agents for malignant hyperthermia. After a period of one week, seven of the eight pigs from the initial phase developed some signs of malignant hyperthermia (i.e., hypotension, acidosis, tachycardia, decreased respiratory rate) in the absence of increased rectal temperature or muscle rigidity during the rechallenge phase with halothane and succinylcholine.

Mutagenicity

The results of three Ames tests (at concentrations up to 5000 mcg/plate), a reverse mutation assay in *E. coli* (up to 5000 mcg/plate), an in vitro mammalian cell gene mutation assay in Chinese hamster V79 cells (up to 5000 mcg/mL), an *in vitro* chromosomal aberrations test in human lymphocytes (up to 5000 mcg/mL), and an *in vivo* micronucleus test in rat bone marrow (up to 900 mcg/kg/day) demonstrated that rocuronium is not a mutagenic compound.

Reproductive Studies

In a segment II reproductive study, Sprague-Dawley rats treated intravenously with 0.05, 0.1, or 0.3 mg/kg/day of rocuronium on days 6-17 of gestation, demonstrated no maternotoxicity and no significant differences in litter rate or malformation rate at any dosage level. However, as this study was performed at sub-paralyzing doses in non-ventilated animals, the relevance of these studies to the clinical use of the drug cannot be assessed.

Local tolerance

Rocuronium was well-tolerated after intravenous, intra-arterial and perivenous administration in New Zealand White rabbits. The only finding was a slight irritation of surrounding tissues after perivenous administration.

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PART III: CONSUMER INFORMATION

[Pr]Rocuronium Bromide Injection

This leaflet is part III of a three-part "Product Monograph" published when Rocuronium Bromide Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Rocuronium Bromide Injection. Contact you doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Rocuronium Bromide Injection is one of a group of drugs called muscle relaxants for anesthesia. These drugs are used during an operation as part of the general anesthetic. When you have an operation your muscles may have to be completely relaxed. This makes it easier for the surgeon to perform the operation.

What it does:
Rocuronium bromide blocks the nerve impulses to move your muscles. Because the muscles needed for breathing also become relaxed you will need help with your breathing (artificial respiration) during and after your operation until you can breathe on your own. At the end of surgery the effects of rocuronium bromide are allowed to wear off and you can start breathing on your own. Sometimes another drug is given to help speed this up.

When it should not be used:
If you are hypersensitive (allergic) to rocuronium, the bromide ion or any of the other ingredients in Rocuronium Bromide Injection.

What the medicinal ingredient is:
rocuronium bromide

What the nonmedicinal ingredients are:
Sodium acetate anhydrous, sodium chloride, water for injections. May contain sodium hydroxide, and/or glacial acetic acid to adjust the pH to approximately 4.0. No preservative has been added.

What dosage forms it comes in:
Rocuronium Bromide Injection is a colorless to slightly yellow/brown solution containing 10 mg/mL rocuronium bromide, which is administered intravenously either as a bolus injection or as a continuous infusion. It is available in vials containing 50 mg (10 vials per pack).

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

As for all drugs used during an operation, this drug should be administered only in a facility prepared to give resuscitation and life support by adequately trained health care professionals familiar with its actions, characteristics, and hazards.

Your medical history can influence the way that Rocuronium Bromide Injection is given to you. Tell your doctor if you have now or have ever had any of the following:

- an allergy to muscle relaxants
- a decreased kidney function or kidney disease
- a heart disease or heart valve disease
- pulmonary hypertension
- oedema (fluid retention for example at the ankles)
- recent, severe vomiting, diarrhea, and "water pill" use
- a liver or gallbladder disease or decreased liver function
- diseases affecting nerves or muscles.

Tell your doctor if you have any other medical conditions, as they may influence how Rocuronium Bromide Injection works.

Elderly / Children
Rocuronium Bromide Injection can be used in children (from term newborns to adolescents) and elderly.

Pregnancy and Breast-Feeding
Tell your doctor if you are pregnant, or suspect that you are pregnant, or if you are breast-feeding.

Driving and Using Machines
Your doctor will inform you when it is safe to drive and operate potentially dangerous machinery after you have been administered Rocuronium Bromide Injection.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. This will help your doctor to decide the correct dose of Rocuronium Bromide Injection for you.

PROPER USE OF THIS MEDICATION

Usual Dose:
The doctor will determine the dose. You will be given Rocuronium Bromide Injection before and/or during a surgical procedure. The usual dose is 0.6 mg rocuronium bromide per kg body weight and the effect lasts about 30 to 40 minutes. Your doctor may adjust the dose according to your need during the surgery.

Method and route of administration:
Rocuronium Bromide Injection is given by an adequately trained health care professional. It is not meant to be administered by yourself. Rocuronium Bromide Injection is injected in a vein as a solution. It is administered as one single injection or continuous infusion.

Only an adequately trained health care professional may give Rocuronium Bromide Injection.

Overdose:
As medical personnel will be monitoring your condition during the procedure it is unlikely that you will be given too much Rocuronium Bromide Injection. However, if this happens artificial respiration will be continued until you are able to breathe again on your own. It is possible to counteract the effects of (too much)

Rocuronium Bromide Injection and speed-up your recovery by giving you a drug that reverses the effects of Rocuronium Bromide Injection.

If you think you have taken too much ROCURONIUM BROMIDE INJECTION, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Rocuronium Bromide Injection can have side effects, although not everybody gets them.

AFTER SURGERY SERIOUS SIDE EFFECTS AND WHAT TO DO ABOUT THEM

For the following serious side effects, you must seek immediate emergency medical treatment.

- Allergic reactions (rash, swelling of the face, throat, lips, difficulty breathing).
- Feeling cold and/or clammy
- Difficulty breathing/choking/wheezing
- Muscle weakness or paralysis
- Rapid or slow heart beat
- Sudden fever with rapid heartbeat, rapid breathing and stiffness, pain and weakness in your muscles
- Seizure/seizure-like activity

For the following serious side effects, call your doctor or pharmacist.

- Dizziness especially upon standing up quickly
- High or low blood pressure if measured
- Severe itching
- Increase or decrease in blood glucose if measured
- Jaundice/yellowing of the skin/eyeballs

This is not a complete list of side effects. For any unexpected effects after receiving Rocuronium Bromide Injection, contact your doctor or pharmacist.

HOW TO STORE IT

Rocuronium Bromide Injection is handled only by qualified professionals.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about ROCURONIUM BROMIDE INJECTION:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Consumer Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada.html); or by contacting the sponsor, Pfizer Canada ULC at: 1-800-463-6001.

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