

CONTRAINDICATIONS
These highlights do not include all the information needed to use **ROCURONIUM BROMIDE Injection** safely and effectively. See full prescribing information for **ROCURONIUM BROMIDE Injection**.
ROCURONIUM BROMIDE Injection, for intravenous use
Initial U.S. Approval: 1994

RECENT MAJOR CHANGES
Dosage and Administration, (2.1, 2.7) 07/2026
INDICATIONS AND USAGE
Rocuronium Bromide Injection is a nondepolarizing neuromuscular blocking agent indicated as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation. (1)

DOSEAGE FORMS AND STRENGTHS
Rocuronium Bromide Injection is for intravenous use only. Rocuronium Bromide Injection should only be administered by experienced clinicians or trained individuals supervised by an experienced clinician familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents. (2,1)
Individuals should be given each of the following doses for each patient. (2,1)
• Peripheral nerve stimulator recommended for determination of drug response and need for additional doses, and to evaluate recovery. (2,1)
• Store Rocuronium Bromide Injection with tamper evidence cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product. (2,1)
• Tracheal intubation: Recommended initial dose is 0.6 mg/kg. (2,2)
• Rapid sequence intubation: 0.6 mg/kg to 1.2 mg/kg. (2,3)
• Maintenance dosing: Guided by response to prior dose, not administered until recovery is evident. (2,4)
• Continuous infusion: Initial rate of 10 mcg/kg/min to 12 mcg/kg/min. Start only after early evidence of spontaneous recovery from an intubating dose. (2,5)

ADVERSE REACTIONS
• 50 mg/5 mL (10 mg/mL), single-dose vial and single-dose prefilled syringe. (3)
• 100 mg/10 mL (10 mg/mL), single-dose vial. (3)

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FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Rocuronium Bromide Injection is indicated as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.
2. DOSAGE AND ADMINISTRATION
2.1 Important Dosing and Administration Information
Rocuronium Bromide Injection is for intravenous use only.
Rocuronium Bromide Injection should only be administered by experienced clinicians or trained individuals supervised by an experienced clinician familiar with the use, actions, characteristics, and complications of neuromuscular blocking agents. Doses of Rocuronium Bromide Injection should be individualized and a peripheral nerve stimulator should be used to monitor drug effect, need for additional doses, adequacy of spontaneous recovery or antagonism, and to decrease the complications of overdosage if additional doses are administered.
The dosage information which follows is derived from studies based upon units of drug per unit of body weight. It is intended to serve as an initial guide to clinicians familiar with other neuromuscular blocking agents to acquire experience with Rocuronium Bromide Injection.
In patients in whom potentiation of, or resistance to, neuromuscular block is anticipated, a dose adjustment should be considered [see *Dosage and Administration* (2.6), *Warnings and Precautions* (5.1, 5.13), *Drug Interactions* (7.2, 7.3), 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, *Use in Specific Populations* (5.6)].

Risk of Medication Errors
Accidental administration of neuromuscular blocking agents may be fatal. Store Rocuronium Bromide Injection Single-Dose Vials with the tamper evidence cap and ferrule intact, and store Rocuronium Bromide Injection Single-Dose Prefilled Syringe with the tamper evidence cap intact. Store Rocuronium Bromide Injection in a manner that minimizes the possibility of selecting the wrong product [see *Warnings and Precautions* (5.3)].

2.2 Dose for Tracheal Intubation
The recommended initial dose of Rocuronium Bromide Injection, regardless of anesthetic technique, is 0.6 mg/kg. Neuromuscular block sufficient for intubation (80% block or greater) is attained in a median (range) time of 1 (0.4-6) minutes 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 clinical relaxation under opioid/nitrous oxide/oxygen anesthesia. Under halothane, isoflurane, and enflurane anesthesia, some extension of the period of clinical relaxation should be expected [see *Drug Interactions* (7.3)].
A lower dose of Rocuronium Bromide Injection (0.45 mg/kg) may be used. Neuromuscular block sufficient for intubation (80% block or greater) is attained in a median (range) time of 1.3 (0.8-6.2) minutes(s), and most patients have intubation completed within 2 minutes. Maximum blockade is achieved in most patients in less than 4 minutes. This dose may be expected to provide 22 (12-31) minutes of clinical relaxation under opioid/nitrous oxide/oxygen anesthesia. Patients receiving this low dose of 0.45 mg/kg who achieve less than 90% block (about 16% of these patients) may have a large bolus dose of 0.9 mg/kg or 1.2 mg/kg can be administered under opioid/nitrous oxide/oxygen anesthesia without adverse effects on the cardiovascular system [see *Clinical Pharmacology* (12.2)].

2.3 Rapid Sequence Intubation
In appropriately premedicated and adequately anesthetized patients, Rocuronium Bromide Injection 0.6 mg/kg to 1.2 mg/kg will provide excellent and good intubating conditions in most patients in less than 2 minutes [see *Clinical Studies* (14.1)].

2.4 Maintenance Dosing
Maintenance dosing of 0.1 mg/kg/30, 0.15 mg/kg, and 0.2 mg/kg Rocuronium Bromide Injection, administered at 25% recovery of control T₁ (defined as 3 twitches of train-of-four), provide a median (range) of 12 (2-31), 17 (6-50), and 24 (7-69) minutes of clinical duration under opioid/nitrous oxide/oxygen anesthesia [see *Clinical Pharmacology* (12.2)]. In all cases, dosing should be guided based on the clinical duration following initial dose or prior maintenance dosing and not administration until recovery of neuromuscular function is evident. A clinically insignificant accumulation of effect with repetitive maintenance dosing has been observed [see *Clinical Pharmacology* (12.2)].

2.5 Use by Continuous Infusion
Infusion at an initial rate of 10 mcg/kg/min to 12 mcg/kg/min of Rocuronium Bromide Injection should be initiated only after early evidence of spontaneous recovery from an intubating dose. Due to not redistribution [see *Clinical Pharmacology* (12.3)] and the associated rapid spontaneous recovery, initiation of the infusion after substantial return of neuromuscular function (more than 10% of control T₁) may necessitate additional bolus doses to maintain adequate block for surgery.

Upon reaching the desired level of neuromuscular block, the infusion of Rocuronium Bromide Injection must be individualized for each patient. The rate of administration should be adjusted according to the patient's switch response as monitored with the use of a peripheral nerve stimulator. In clinical trials, infusion rates have ranged from 4 mcg/kg/min to 16 mcg/kg/min.
Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion by 30% to 50%, at 45 to 60 minutes after the intubating dose.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Rocuronium Bromide Injection infusion may be expected to proceed at rates comparable to that following comparable total doses administered by repetitive bolus injections [see *Clinical Pharmacology* (12.2)].

Dilution
Infusion solutions of Rocuronium Bromide Injection can be prepared to concentrations of 0.5 mg/mL to 5 mg/mL by mixing Rocuronium Bromide Injection with an appropriate infusion solution such as 5% glucose in water or lactated Ringers solution [see *Dosage and Administration* (2.7)]. Use the infusion solutions within 24 hours of mixing. Discard any portions of infusion solutions.

Hypersensitivity (e.g., anaphylaxis) to rocuronium bromide or other neuromuscular blocking agents. (4)
WARNINGS AND PRECAUTIONS
• **Appropriate Administration and Monitoring:** Use only if facilities for intubation, mechanical ventilation, oxygen therapy, and an antagonist are immediately available. (5,1)
• **Anaphylaxis:** Severe anaphylaxis has been reported. Consider cross-reactivity among neuromuscular blocking agents. (5,2)
• **Risk of Death due to Medication Errors:** Accidental administration can cause death. (5,3)
• **Need for Adequate Anesthesia:** Must be accompanied by adequate anesthesia or sedation. (5,4)
• **Residual Paralysis:** Consider using a reversal agent in cases where residual paralysis is more likely to occur. (5,5)
ADVERSE REACTIONS
Most common adverse reactions (2%) are transient hypotension and hypertension. (6,6)
To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
• **Succinylcholine:** Use before succinylcholine has not been studied. (7,11)
• **Nondepolarizing muscle relaxants:** Interactions have been observed. (7,7)
• **Enhanced Rocuronium Bromide Injection activity possible:** Inhalation anesthetics (7,3), certain antibiotics (7,1), quinine (7,10), magnesium (7,6), lithium (7,4), and other neuromuscular blocking agents (7,5), procainamide (7,8)
• **Reduced Rocuronium Bromide Injection activity possible:** Anticonvulsants. (7,2)
USE IN SPECIFIC POPULATIONS
• **Pregnancy:** Not recommended for rapid sequence induction in patients undergoing Cesarean section. (8,1, 14,1)
• **Pediatric Use:** Onset time and duration will vary with dose, age, and anesthetic technique. Not recommended for rapid sequence intubation in pediatric patients. (8,4)
See 17 for PATIENT COUNSELING INFORMATION.

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2.6 Dosage in Specific Populations
Pediatric Patients
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 age of the patient.
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. When halothane is used, a 0.6 mg/kg dose of Rocuronium Bromide Injection resulted in excellent to good intubating conditions within 60 seconds.
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.
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 T₁ in all pediatric age groups. Maintenance dosing can also be administered at the reappearance of T₁ at a rate of 7 mcg/kg/min to 10 mcg/kg/min, with the lowest dose requirement for neonates (birth to less than 28 days) and the highest dose requirement for children (greater than 2 years up to 11 years).

When halothane is used for general anesthesia, patients ranging from 3 months old through adolescence can be administered Rocuronium Bromide Injection maintenance doses of 0.075 mg/kg to 0.125 mg/kg upon return of T₁ to 0.25% to provide clinical relaxation. No differences in duration of neuromuscular blockade following maintenance doses of Rocuronium Bromide Injection were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out [see *Warnings and Precautions* (5.5), *Clinical Pharmacology* (12.2), *Clinical Studies* (14.2)].

Additional information for administration to pediatric patients of all age groups is presented elsewhere in the label [see *Clinical Pharmacology* (12.2)].
The infusion of Rocuronium Bromide Injection must be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as monitored with the use of a peripheral nerve stimulator. Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Rocuronium Bromide Injection infusion may be expected to proceed at rates comparable to that following similar total exposure to single bolus doses [see *Clinical Pharmacology* (12.2)].
Rocuronium Bromide Injection is not recommended for rapid sequence intubation in pediatric patients.

Geriatric Patients
Geriatric patients (65 years or older) exhibited a slightly prolonged median (range) clinical duration of 46 (22-73), 62 (49-75), and 94 (64-138) minutes under opioid/nitrous oxide/oxygen anesthesia following doses of 0.6 mg/kg, 0.9 mg/kg, and 1.2 mg/kg, respectively. No differences in duration of neuromuscular blockade following maintenance doses of Rocuronium Bromide Injection were observed between these subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out [see *Warnings and Precautions* (5.5), *Clinical Pharmacology* (12.2), *Clinical Studies* (14.2)].
Patients with Renal or Hepatic Impairment
No differences from patients with normal hepatic and kidney function were observed for onset time at a dose of 0.6 mg/kg Rocuronium Bromide Injection. When compared to patients with normal renal and hepatic function, the mean clinical duration of action was prolonged in patients undergoing renal transplant and a peripheral nerve stimulator 1.5 times longer in patients with hepatic disease. Patients with renal failure may have a greater variation in duration of effect [see *Use in Specific Populations* (8.6, 8.7), *Clinical Pharmacology* (12.3)].
Obese Patients
In obese patients, the initial dose of Rocuronium Bromide Injection 0.6 mg/kg should be based upon the patient's actual body weight [see *Clinical Studies* (14.1)].
An analysis across all US controlled clinical studies indicates that the pharmacodynamics of Rocuronium Bromide Injection are not different between obese and nonobese patients when dosed based upon their actual body weight.

Patients with Reduced Plasma Cholinesterase Activity
Rocuronium metabolism does not depend on plasma cholinesterase so dosing adjustments are not needed in patients with reduced plasma cholinesterase activity.

Patients with Prolonged Circulation Time
Because higher doses of Rocuronium Bromide Injection produce a longer duration of action, the initial dosage should usually not be increased in these patients to reduce onset time; instead, in these situations, when feasible, more time should be allowed for the drug to achieve onset of effect [see *Warnings and Precautions* (5.8)].

Patients with Drugs or Conditions Causing Potentiation of Neuromuscular Block
The neuromuscular blocking action of Rocuronium Bromide Injection is potentiated by isoflurane and enflurane anesthesia. Potentiation is minimal when administration of the recommended dose of Rocuronium Bromide Injection occurs prior to the administration of these anesthetics. The median clinical duration of a dose of 0.57 mg/kg to 0.85 mg/kg was 34, 38, and 42 minutes under opioid/nitrous oxide/oxygen, enflurane and isoflurane maintenance anesthesia, respectively. During 1 to 2 hours of infusion, the infusion rate of Rocuronium Bromide Injection required to maintain about 80% block was decreased by as much as 40% under enflurane and isoflurane anesthesia [see *Drug Interactions* (7.3)].

Drug Compatibilities for Rocuronium Bromide Injection
Diluent Compatibility
Rocuronium Bromide Injection is compatible in solution with:
0.9% NaCl solution sterile water for injection
5% glucose in water lactated Ringers
5% glucose in saline

Rocuronium Bromide Injection is compatible in the above solutions at concentrations up to 5 mg/mL for 24 hours at room temperature in plastic bags, glass bottles, and plastic syringe pumps.

Drug Admixture Incompatibility
Rocuronium Bromide Injection is physically incompatible when mixed with the following drugs:
amphotericin hydrocortisone sodium succinate
insulin
azathioprine
cefazolin
lorazepam
cloxacillin
methohexital
diazepam
thiopental
erythromycin
fentanyl
furosemide
trimethoprim
tocamycin

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 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.

Infusion solutions should be used within 24 hours of mixing. Unused portions of infusion solutions should be discarded.
Rocuronium Bromide Injection should not be mixed with alkaline solutions [see *Warnings and Precautions* (5.11)].
Visual Inspection
Parental drug products should be inspected visually for particulate matter and clarity prior to administration whenever solution and container permit. Do not use solution if particulate matter is present.

3. DOSAGE FORMS AND STRENGTHS
Rocuronium Bromide Injection is a clear, colorless to yellow/orange solution, free from visible particulate matter available as:
• 50 mg/5 mL (10 mg/mL), single-dose vials
• 100 mg/10 mL (10 mg/mL), single-dose vials
• 50 mg/5 mL (10 mg/mL), single-dose prefilled syringes

CONTRAINDICATIONS
Rocuronium Bromide Injection is contraindicated in patients known to have hypersensitivity (e.g., anaphylaxis) to rocuronium bromide or other neuromuscular blocking agents [see *Warnings and Precautions* (5.2)].

WARNINGS AND PRECAUTIONS
Appropriate Administration and Monitoring
Rocuronium Bromide Injection should be administered in carefully adjusted dosages by or under the supervision of experienced clinicians who are familiar with the drug's actions and the possible complications of its use. Rocuronium Bromide Injection should not be administered unless facilities for intubation, mechanical ventilation, oxygen therapy, and an antagonist are immediately available. Other factors which could cause residual paralysis after discontinuation of Rocuronium Bromide Injection should be considered. Patients receiving this low dose of 0.45 mg/kg who achieve less than 90% block (about 16% of these patients) may have a large bolus dose of 0.9 mg/kg or 1.2 mg/kg can be administered under opioid/nitrous oxide/oxygen anesthesia without adverse effects on the cardiovascular system [see *Clinical Pharmacology* (12.2)].
Anaphylaxis
Severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium Bromide Injection, have been reported. These reactions have, in some cases (including cases with Rocuronium Bromide Injection), been life threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should also be taken in those patients who have had previous anaphylactic reactions to other neuromuscular blocking agents, since cross-reactivity between neuromuscular blocking agents, both depolarizing and nondepolarizing, has been reported.

5.2 Anaphylaxis
Severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium Bromide Injection, have been reported. These reactions have, in some cases (including cases with Rocuronium Bromide Injection), been life threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should also be taken in those patients who have had previous anaphylactic reactions to other neuromuscular blocking agents, since cross-reactivity between neuromuscular blocking agents, both depolarizing and nondepolarizing, has been reported.

5.3 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 Rocuronium Bromide Injection, ensure that the intended dose is clearly labeled and communicated.

5.4 Need for Adequate Anesthesia
Rocuronium Bromide Injection has no known effect on consciousness, pain threshold, or cerebation. Therefore, its use should be accompanied by adequate anesthesia or sedation.

5.5 Residual Paralysis
To prevent complications resulting from residual paralysis from Rocuronium Bromide Injection, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Geriatric patients (65 years or older) may be at increased risk of residual paralysis. Other factors which could cause residual paralysis after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice the use of a reversal agent should be considered, especially in those cases where residual paralysis is more likely to occur.

5.6 Long-Term Use in an Intensive Care Unit
Rocuronium Bromide Injection has not been studied for long-term use in the intensive care unit (ICU). As with other nondepolarizing neuromuscular blocking drugs, apparent tolerance to Rocuronium Bromide Injection may develop during chronic administration in the ICU. While the mechanism for development of this resistance is not known, receptor up-regulation may be a contributing factor. It is strongly recommended that neuromuscular transmission be monitored continuously during Rocuronium Bromide Injection administration and recovery with the help of a nerve

stimulator. Additional doses of Rocuronium Bromide Injection or any other neuromuscular blocking agent should not be given until there is a definite response (one twitch of the train-of-four) to nerve stimulation. Prolonged paralysis of the skeletal muscle weakness may be used depending on the patient's condition. Patients should be monitored for who have chronically received neuromuscular blocking drugs in the ICU.

Myopathy after long-term administration of other nondepolarizing neuromuscular blocking agents in the ICU alone or in combination with corticosteroid therapy has been reported. Therefore, for patients receiving both neuromuscular blocking agents (including Rocuronium Bromide Injection) and corticosteroids, the setting of use of neuromuscular blocking agent should be limited much as possible and only used in the setting where in the opinion of the prescribing physician, the specific advantages of the drug outweigh the risk.

5.7 Malignant Hyperthermia
Rocuronium Bromide Injection has not been studied in malignant hyperthermia (MH)-susceptible patients. In an animal study in MH-susceptible swine, the administration of Rocuronium Bromide Injection did not appear to trigger malignant hyperthermia.

Because Rocuronium Bromide Injection is always used with other agents, and the occurrence of MH during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis, and treatment of MH prior to the start of any anesthetic [see *Adverse Reactions* (6.2)].

5.8 Prolonged Circulation Time
Conditions associated with an increased circulation delayed time, e.g., cardiovascular disease or advanced age, in patients treated with Rocuronium Bromide Injection may be associated with a delay in onset time [see *Dosage and Administration* (2.6)].

5.9 QT Interval Prolongation
The overall analysis of ECG data in pediatric patients indicates that the concomitant use of Rocuronium Bromide Injection with general anesthetic agents can prolong the QTc interval [see *Clinical Studies* (14.3)].

5.10 Conditions/Drugs Causing Potentiation of, or Resistance to, Neuromuscular Block
Potentiation
Nondepolarizing neuromuscular blocking agents have been found to exhibit profound neuromuscular blocking effects in cachectic or debilitated patients, patients with neuromuscular diseases, and patients with carcinomatosis.

Certain inhalation anesthetics, particularly enflurane and isoflurane, antibiotics, magnesium salts, lithium, local anesthetics, procainamide, and quinine have been shown to increase the duration of neuromuscular block and decrease infusion requirements of neuromuscular blocking agents [see *Drug Interactions* (7.3)].

In these or other patients in whom potentiation of neuromuscular block or difficulty with reversal may be anticipated, a decrease from the recommended initial dose of Rocuronium Bromide Injection should be considered [see *Dosage and Administration* (2.6)].

Resistance
Resistance to nondepolarizing agents, consistent with up-regulation of skeletal muscle acetylcholine receptors, is associated with burns, disuse atrophy, denervation, and direct muscle trauma. Receptor up-regulation may also contribute to the resistance to nondepolarizing muscle relaxants which sometimes develops in patients with cerebral palsy, patients chronically receiving anticonvulsant agents such as carbamazepine or phenytoin, or with chronic exposure to nondepolarizing agents. When Rocuronium Bromide Injection is administered to these patients, shorter durations of neuromuscular block may occur, and infusion rates may be higher due to the development of resistance to nondepolarizing muscle relaxants.

Potentiation or Resistance
Severe acid-base and/or electrolyte abnormalities may potentiate or cause resistance to the neuromuscular blocking action of Rocuronium Bromide Injection. No data are available in such patients and no dosing recommendations can be made.

Rocuronium Bromide Injection-induced neuromuscular blockade was modified by alkalosis and acidosis in experimental pigs. Both respiratory and metabolic acidosis prolonged the recovery time. The potency of Rocuronium Bromide Injection was significantly enhanced in metabolic acidosis and alkalosis but was reduced in respiratory alkalosis. In addition, experience with other drugs has suggested that acute (e.g., diarrhea) or chronic (e.g., adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur.

5.11 Incompatibility with Alkaline Solutions
Rocuronium Bromide Injection, which has an acid pH, 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.

5.12 Increase in Pulmonary Vascular Resistance
Rocuronium Bromide Injection may be associated with increased pulmonary vascular resistance, so caution is appropriate in patients with pulmonary hypertension or valvular heart disease [see *Clinical Studies* (14.1)].

5.13 Use in Patients with Myasthenia
In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of nondepolarizing neuro-muscular blocking agents, including Rocuronium Bromide Injection, 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.

5.14 Extravasation
Extravasation occurs after Rocuronium Bromide Injection administration, it may be associated with signs or symptoms of local irritation. The Rocuronium Bromide Injection or infusion should be terminated immediately and restarted in another vein.

6. ADVERSE REACTIONS
In clinical trials, the most common adverse reactions (2%) are transient hypotension and hypertension. The following adverse reactions are described, or described in greater detail, in other sections:
• Anaphylaxis [see *Warnings and Precautions* (5.2)]
• Residual paralysis [see *Warnings and Precautions* (5.5)]
• Increased pulmonary vascular resistance [see *Warnings and Precautions* (5.12)]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of other drugs and may not reflect the rates observed in practice.
Clinical studies of another rocuronium bromide injection product in the U.S. (n=1137) and Europe (n=1994) totaled 2531 patients. The following adverse reactions were reported in patients administered another rocuronium bromide injection [all events judged by investigators during the clinical trials to have a possible causal relationship]:
Adverse reactions in greater than 1% of patients: None

Adverse reactions in less than 1% of patients (probably related or relationship unknown):
Cardiovascular: arrhythmia, abnormal electrocardiogram, tachycardia
Digestive: nausea, vomiting
Respiratory: asthma (bronchospasm, wheezing, or rhonch), hiccup
Skin and Appendages: rash, injection site edema, pruritus

In the European studies of another rocuronium bromide injection product, the most commonly reported reactions were transient hypotension (2%), hypertension (1%), tachycardia (1%), and tachypnea (1%). In the clinical trials, 0.1% of patients had adverse reactions in greater than 1% of patients. Changes in heart rate and blood pressure were defined differently from in the US studies in which changes in cardiovascular parameters were not considered as adverse events unless judged by the investigator as unexpected, clinically significant, or thought to be histamine related.

In a clinical study of another rocuronium bromide injection product in patients with clinically significant cardiovascular disease undergoing coronary artery bypass graft, hypertension and tachycardia were observed in some patients; however, these occurrences were less frequent in patients receiving beta or calcium channel-blocking drugs. In some patients, the use of another rocuronium bromide injection product was associated with transient increases (30% or greater) in pulmonary vascular resistance. In another clinical study of patients undergoing cardiac surgery, transient increases (30% or greater) in pulmonary vascular resistance were observed in about 24% of patients who received another rocuronium bromide injection product at 0.6 mg/kg or 0.9 mg/kg.

In pediatric patient studies worldwide of another rocuronium bromide injection product (n=704), tachycardia occurred in 3.3% of patients (n=37), and it was judged by the investigator as related in 10 cases (1.4%).

6.2 Postmarketing Experience
The following adverse reactions have been identified during post-appraisal use of rocuronium bromide injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune system disorders: In clinical practice, there have been reports of severe allergic reactions (anaphylactic reactions and shock) with rocuronium bromide injection, including some that have been life-threatening and fatal [see *Warnings and Precautions* (5.2)].

General disorders and administration site conditions: There have been reports of malignant hyperthermia with the use of rocuronium bromide injection [see *Warnings and Precautions* (5.7)].

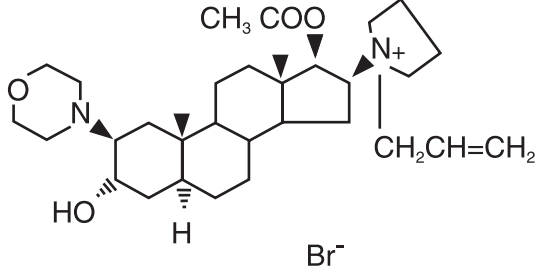
7. DRUG INTERACTIONS
Antibiotics
Drugs may enhance the neuromuscular blocking action of nondepolarizing agents such as Rocuronium Bromide Injection include certain antibiotics (e.g., aminoglycosides; vancomycin; tetracyclines; bacitracin; polymyxins; colistin; and sodium colistimethate). If these antibiotics are used in conjunction with Rocuronium Bromide Injection, prolongation of neuromuscular block may occur.

7.2 Anticonvulsants
In 2 of 4 patients who received chronic anticonvulsant therapy, apparent resistance to the effects of another rocuronium bromide injection product was observed in the form of diminished magnitude of neuromuscular block or shortened clinical duration. As with other nondepolarizing neuromuscular blocking drugs, if Rocuronium Bromide Injection is administered to patients chronically receiving anticonvulsant agents such as carbamazepine or phenytoin, shorter durations of neuromuscular block may occur and infusion rates may be higher due to the development of resistance to nondepolarizing muscle relaxants. While the mechanism for development of this resistance is not known, receptor up-regulation may be a contributing factor [see *Warnings and Precautions* (5.10)].

7.3 Inhalation Anesthetics
Use of inhalation anesthetics (enflurane > isoflurane > halothane) has been shown to enhance the activity of other neuromuscular blocking agents. Isoflurane and enflurane may also prolong the duration of action of initial and maintenance doses of Rocuronium Bromide Injection. The maintenance doses of Rocuronium Bromide Injection may be increased by 40% compared to opioid/nitrous oxide/oxygen anesthesia. No definite interaction between rocuronium bromide injection and halothane has been demonstrated. In one study, use of enflurane in 10 patients who received another rocuronium bromide injection product resulted in a mean increase in the duration of action of the initial intubating dose, and a 37% increase in the duration of subsequent maintenance doses, when compared in the same study to 10 patients under opioid/nitrous oxide/oxygen anesthesia. The clinical duration of initial doses of another rocuronium bromide injection product (0.57 mg/kg to 0.85 mg/kg) under enflurane or isoflurane anesthesia, as used clinically, was increased by 11% and 23%, respectively. The duration of maintenance doses was affected to a greater extent, increasing by 30% to 50% under either enflurane or isoflurane anesthesia.

Potentiality by these agents was also observed with respect to the infusion rates of rocuronium bromide injection required to maintain approximately 95% neuromuscular block. Under isoflurane and enflurane anesthesia, the infusion rates of Rocuronium Bromide Injection were decreased by 15% and 25%, respectively, compared to the infusion rates of Rocuronium Bromide Injection required to maintain approximately 95% neuromuscular block. Under isoflurane and enflurane anesthesia, the median spontaneous recovery time (from 25% to 75% of control T₁

11 DESCRIPTION
Rocuronium bromide is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose and intermediate duration. Rocuronium bromide is chemically designated as 1-[17β-(acetyloxy)-3α-hydroxy-2β-(4-morpholinyl)-5α-androstan-16β-yl]-1-(2-propenyl) pyridolinium bromide.
The structural formula is:



Rocuronium bromide USP is an almost white to pale yellow, hygroscopic powder. Rocuronium bromide is soluble in water and dichloromethane, slightly soluble in ethanol and methanol. The chemical formula is $C_{34}H_{48}BrN_3O_5$ with a molecular weight of 609.70. The partition coefficient of rocuronium bromide in n-octanol/water is 0.5 at 20°C.
Rocuronium Bromide Injection single-dose vials is supplied as a sterile, nonpyrogenic, isotonic solution that is clear, colorless to yellow/orange for intravenous use only. Each mL contains 10 mg rocuronium bromide (equivalent to 8.69 mg of rocuronium) and inactive ingredients 17.1 mL hydrochloric acid, 8 mg sodium chloride. The solution pH is adjusted to 2.8 to 3.2 with hydrochloric acid and/or sodium hydroxide.
Rocuronium Bromide Injection single-dose prefilled syringe is supplied as a sterile, nonpyrogenic, isotonic solution that is clear, colorless to yellow/orange for intravenous use only. Each mL contains 10 mg rocuronium bromide (equivalent to 8.69 mg of rocuronium) and inactive ingredients 17.1 mL hydrochloric acid, 8 mg sodium chloride. The solution pH is adjusted to 2.8 to 3.3 with hydrochloric acid and/or sodium hydroxide.

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
Rocuronium Bromide Injection is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium.
12.2 Pharmacodynamics
The Rocuronium Bromide Injection dose required to produce 95% suppression (ED_{95}) of the first $T_{1/2}$ mechanomyographic (MMG) response of the adductor pollicis muscle (thumb) to indirect supramaximal train-of-four stimulation of the ulnar nerve) during opioid/nitrous oxide/oxygen anesthesia is approximately 0.3 mg/kg. Patient variability around the ED_{95} dose suggests that 50% of patients will exhibit T_1 depression of 91% to 97%.
Table 4 presents intubating conditions in patients with intubation initiated at 60 to 70 seconds.

Table 4: Percent of Excellent or Good Intubating Conditions and Median (Range) Time to Completion of Intubation in Patients with Intubation Initiated at 60 to 70 Seconds

rocuronium bromide Injection Dose (mg/kg) Administered Over 5 sec	Percent of Patients with Excellent or Good Intubating Conditions	Time to Completion of Intubation (min)
Adults* 18 to 64 yrs 0.45 (n=43) 0.6 (n=51)	86% 96%	1.6 (1.0-7.0) 1.6 (1.0-3.2)
Infants* 3 mo to 1 yr 0.6 (n=18)	100%	1.0 (1.0-1.5)
Pediatric* 1 to 12 yrs 0.6 (n=12)	100%	1.0 (0.5-2.3)

* Excludes patients undergoing Cesarean section.
† Pediatric patients were under halothane anesthesia.
‡ Excellent intubating conditions= jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement.
Good intubating conditions=same as excellent but with some diaphragmatic movement.

Table 5 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 5: Median (Range) Time to Onset and Clinical Duration Following Initial (Intubating) Dose During Opioid/Nitrous Oxide/Oxygen Anesthesia (Adults) and Halothane Anesthesia (Pediatric Patients)

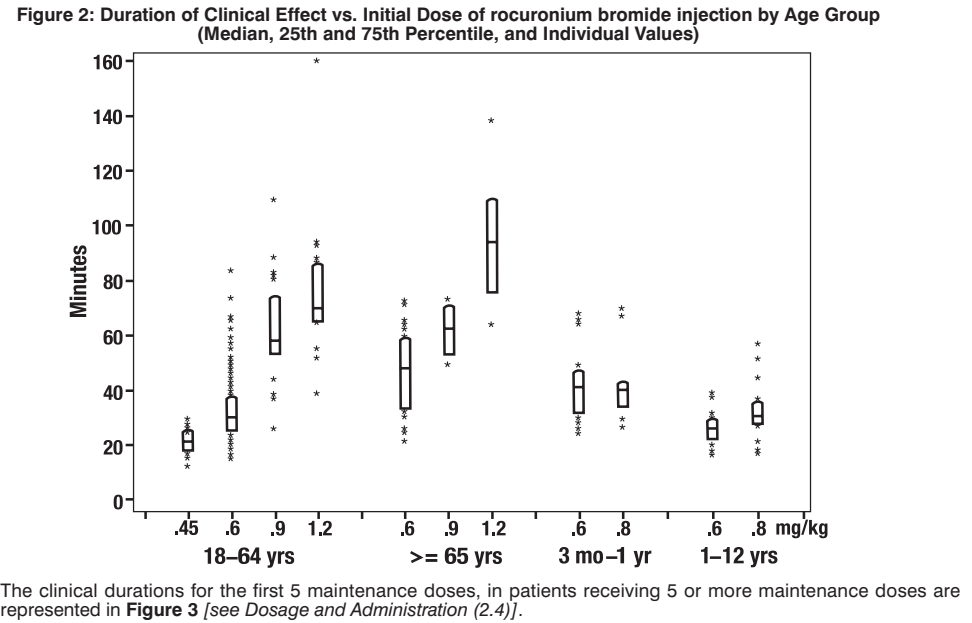
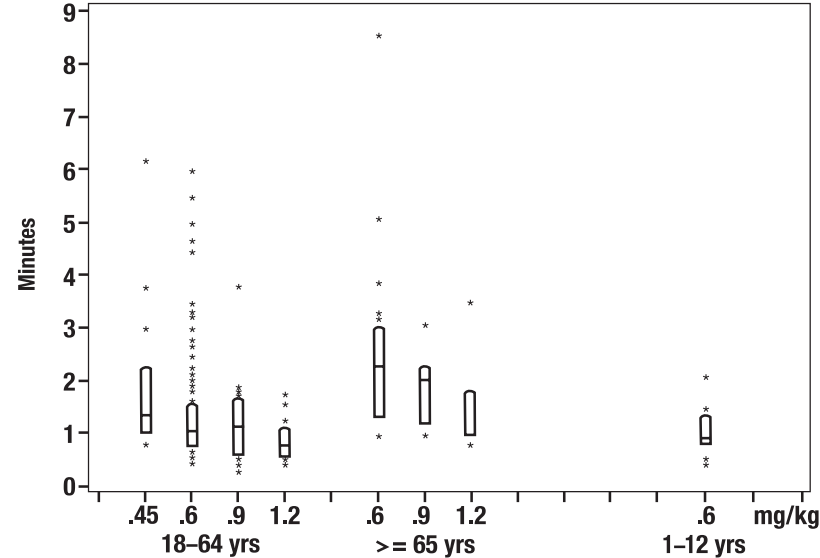
rocuronium bromide Injection Dose (mg/kg) Administered Over 5 sec	Time to >80% Block (min)	Time to Maximum Block (min)	Clinical Duration (min)
Adults 18 to 64 yrs 0.45 (n=50) 0.6 (n=142) 0.9 (n=20) 1.2 (n=18)	1.3 (0.8-6.2) 1.0 (0.4-0.7) 1.1 (0.3-3.8) 1.0 (0.4-1.7)	3.0 (1.3-8.2) 1.9 (0.6-13.0) 1.4 (0.6-6.2) 1.0 (0.6-4.7)	22 (12-31) 31 (15-85) 58 (27-111) 67 (38-160)
Geriatric ≥65 yrs 0.6 (n=31) 0.9 (n=5) 1.2 (n=7)	2.3 (1.0-8.3) 2.0 (1.0-3.0) 1.0 (0.8-3.5)	3.7 (1.3-11.3) 2.5 (1.2-5.0) 1.3 (1.2-4.7)	46 (22-73) 62 (49-75) 94 (64-138)
Infants 3 mo to 1 yr 0.6 (n=17) 0.8 (n=9)	—	0.8 (0.3-3.0) 0.7 (0.5-0.8)	41 (24-68) 40 (27-73)
Pediatric 1 to 12 yrs 0.6 (n=27) 0.8 (n=18)	0.8 (0.4-2.0)	1.0 (0.5-3.3) 0.5 (0.3-1.0)	26 (17-39) 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.
Table 6 presents the time to onset and clinical duration for the initial dose of Rocuronium Bromide Injection (rocuronium bromide) Injection under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia in pediatric patients.

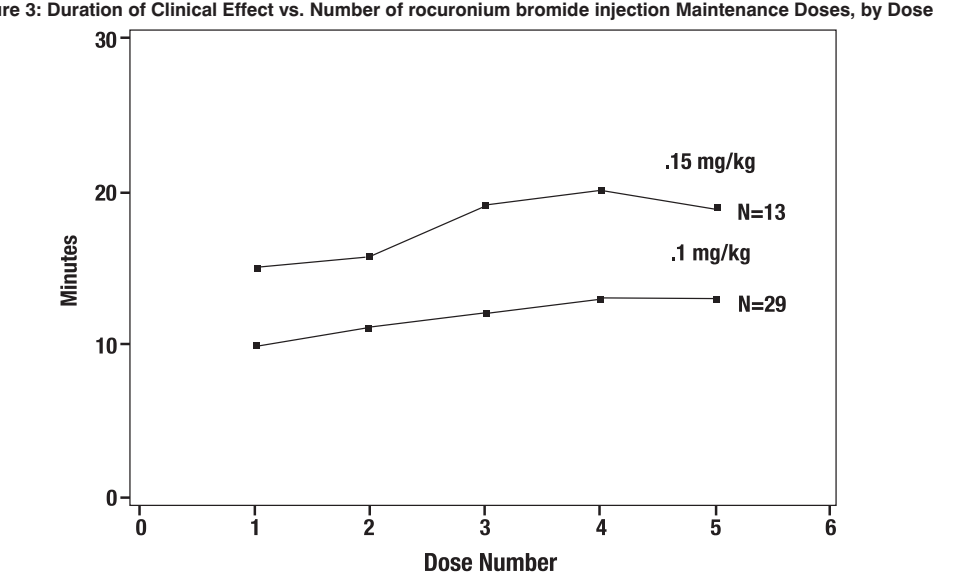
Table 6: Median (Range) Time to Onset and Clinical Duration Following Initial (Intubating) Dose During Sevoflurane (Induction) and Isoflurane/Nitrous Oxide (Maintenance) Anesthesia (Pediatric Patients)

rocuronium bromide Injection Dose (mg/kg) Administered Over 5 sec	Time to Maximum Block (min)	Time to Reappearance T_1 (min)
Neonates birth to <28 days 0.45 (n=5) 0.6 (n=10) 1 (n=6)	1.1 (0.6-2.2) 1.0 (0.2-2.1) 0.6 (0.3-1.8)	40.3 (32.5-62.6) 49.7 (16.1-119.0) 114.4 (92.6-156.3)
Infants 28 days to ≤3 mo 0.45 (n=9) 0.6 (n=11) 1 (n=5)	0.6 (0.4-1.3) 0.4 (0.2-0.8) 0.3 (0.2-0.7)	49.1 (13.5-79.9) 59.3 (32.3-87.8) 103.3 (90.8-155.4)
Toddlers >3 mo to ≤2 yrs 0.45 (n=17) 0.6 (n=29) 1 (n=15)	0.8 (0.3-1.9) 0.6 (0.2-1.6) 0.5 (0.2-1.5)	39.2 (16.9-59.4) 44.2 (18.9-68.8) 72.0 (36.2-128.2)
Children >2 yrs to ≤11 yrs 0.45 (n=14) 0.6 (n=37) 1 (n=16)	0.9 (0.4-1.9) 0.6 (0.3-1.7) 0.7 (0.4-1.2)	21.5 (17.5-38.0) 36.7 (20.1-65.9) 53.1 (31.2-89.2)
Adolescents >11 to ≤17 yrs 0.45 (n=18) 0.6 (n=31) 1 (n=14)	1.0 (0.5-1.7) 0.9 (0.3-1.1) 0.7 (0.5-1.2)	37.5 (18.3-65.7) 41.4 (16.3-81.2) 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_1 .
The time to 80% or greater block and clinical duration as a function of dose are presented in Figures 1 and 2.
Figure 1: Time to 80% or Greater Block vs. Initial Dose of rocuronium bromide injection by Age Group (Median, 25th and 75th Percentile, and Individual Values)



The clinical durations for the first 5 maintenance doses, in patients receiving 5 or more maintenance doses are represented in Figure 3 [see Dosage and Administration (2.4)].



Once spontaneous recovery has reached 25% of control T_1 , the neuromuscular block produced by rocuronium bromide injection is readily reversed with anticholinesterase agents, e.g., edrophonium or neostigmine.
The median spontaneous recovery from 25% to 75% T_1 was 13 minutes in adult patients. When neuromuscular block was reversed in 36 adults at a T_1 of 22% to 27%, recovery to a T_1 of 69 (50-132%) and T_1/T_0 of 69 (36-92%) was achieved within 5 minutes. Only 5 of 320 adults reversed received an additional dose of reversal agent. The median (range) dose of neostigmine was 0.04 (0.01-0.09) mg/kg and the median (range) dose of edrophonium was 0.5 (0.3-1.0) mg/kg.
In geriatric patients (n=51) reversed with neostigmine, the median T_1/T_0 increased from 40% to 88% in 5 minutes.
In clinical trials with halothane, pediatric patients (n=27) who received 0.5 mg/kg edrophonium had increases in the median T_1/T_0 from 37% at reversal to 83% after 2 minutes. Pediatric patients (n=58) who received 1 mg/kg edrophonium had increases in the median T_1/T_0 from 72% at reversal to 100% after 2 minutes. Infants (n=10) who were reversed with 0.03 mg/kg neostigmine recovered from 25% to 75% T_1 within 4 minutes.
There were no reports of less than satisfactory clinical recovery of neuromuscular function.
The neuromuscular blocking action of Rocuronium Bromide Injection may be enhanced in the presence of potent inhalation anesthetics [see Drug Interactions (7.3)].
Hemodynamics
There were no dose-related effects on the incidence of changes from baseline (30% or greater) in mean arterial blood pressure (MAP) or heart rate associated with rocuronium bromide injection administration over the dose range of 0.12 mg/kg to 1.2 mg/kg (4 x ED_{50}) within 5 minutes after rocuronium bromide injection administration and prior to intubation. Increases or decreases in MAP were observed in 2% to 5% of geriatric and other adult patients, and in about 1% of pediatric patients. Heart rate changes (30% or greater) occurred in 0% to 2% of geriatric and other adult patients. Tachycardia (30% or greater) occurred in 12 of 127 pediatric patients. Most of the pediatric patients developing tachycardia were from a single study where the patients were anesthetized with halothane and who did not receive atropine for induction [see Clinical Studies (14.3)]. In US studies, laryngoscopy and tracheal intubation following rocuronium bromide injection administration were accompanied by transient tachycardia (30% or greater increases) in about one-third of adult patients under opioid/nitrous oxide/oxygen anesthesia. Animal studies have indicated that the ratio of vagal:neuromuscular block following Rocuronium Bromide Injection administration is less than vecuronium but greater than pancuronium. The tachycardia observed in some patients may result from this vagal blocking activity.
Histamine Release
In studies of histamine release, clinically significant concentrations of plasma histamine occurred in 1 of 88 patients. Clinical signs of histamine release (flushing, rash, or bronchospasm) associated with the administration of Rocuronium Bromide Injection were assessed in clinical trials and reported in 9 of 1137 (0.8%) patients.

12.3 Pharmacokinetics
Adult and Geriatric Patients
In an effort to maximize the information gathered in the *in vivo* pharmacokinetic studies, the data from the studies was used to develop population estimates of the parameters for the subpopulations represented (e.g., geriatric, pediatric, renal, and hepatic impairment). These population-based estimates and a measure of the estimate variability are contained in the following section.
Following intravenous administration of rocuronium bromide injection, plasma levels of rocuronium follow a three-compartment open model. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Rocuronium is approximately 30% bound to human plasma proteins. In geriatric and other adult surgical patients undergoing either opioid/nitrous oxide/oxygen or inhalational anesthesia, the observed pharmacokinetic profile was essentially unchanged [see Dosage and Administration (2.6)].

Table 7: Mean (SD) Pharmacokinetic Parameters in Adults (n=22; ages 27 to 58 yrs) and Geriatric (n=20; 65 yrs or greater) During Opioid/Nitrous Oxide/Oxygen Anesthesia

PK Parameters	Adults (Ages 27-58 yrs)	Geriatrics (≥65 yrs)
Clearance (L/kg/hr)	0.25 (0.08)	0.21 (0.06)
Volume of Distribution at Steady State (L/kg)	0.25 (0.04)	0.22 (0.03)
$t_{1/2 \beta}$ Elimination (hr)	1.4 (0.4)	1.5 (0.4)

In general, studies with normal adult subjects did not reveal any differences in the pharmacokinetics of rocuronium due to gender.
Studies of distribution, metabolism, and excretion in cats and dogs indicate that rocuronium is eliminated primarily by the liver. The rocuronium analog 17-desacetyl-rocuronium, a metabolite, has been rarely observed in the plasma or urine of humans administered single doses of 0.5 mg/kg to 1 mg/kg with or without a subsequent infusion (for up to 12 hr) of rocuronium. In the cat, 17-desacetyl-rocuronium has approximately one-twentieth the neuromuscular blocking potency of rocuronium. The effects of renal failure and hepatic disease on the pharmacokinetics and pharmacodynamics of rocuronium in humans are consistent with these findings.
In general, patients undergoing cadaver kidney transplant have a small reduction in clearance which is offset pharmacokinetically by a corresponding increase in volume, such that the net effect is an unchanged plasma half-life. Patients with demonstrated liver cirrhosis have a marked increase in their volume of distribution resulting in a plasma half-life approximately twice that of patients with normal hepatic function. Table 8 shows the pharmacokinetic parameters in subjects with either impaired renal or hepatic function.

Table 8: Mean (SD) Pharmacokinetic Parameters in Adults with Normal Renal and Hepatic Function (n=10; ages 23 to 65), Renal Transplant Patients (n=10; ages 21 to 45), and Hepatic Dysfunction Patients (n=9; ages 31 to 67) During Isoflurane Anesthesia

PK Parameters	Normal Renal and Hepatic Function	Renal Transplant Patients	Hepatic Dysfunction Patients
Clearance (L/kg/hr)	0.16 (0.05)*	0.13 (0.04)	0.13 (0.06)
Volume of Distribution at Steady State (L/kg)	0.26 (0.03)	0.34 (0.11)	0.53 (0.14)
$t_{1/2 \beta}$ Elimination (hr)	2.4 (0.8)*	2.4 (1.1)	4.3 (2.6)

* Differences in the calculated $t_{1/2 \beta}$ and CI between this study and the study in young adults vs. geriatrics (≥65 years) is related to the different sample populations and anesthetic techniques.

The net result of these findings is that subjects with renal failure have clinical durations that are similar to but somewhat more variable than the duration that one would expect in subjects with normal renal function. Hepatically impaired patients, due to the reduced clearance of rocuronium, may have clinical durations approaching 1.5 times that of subjects with normal hepatic function. In both populations the clinician should individualize the dose to the needs of the patient [see Dosage and Administration (2.6)].
Tissue redistribution accounts for most (about 80%) of the initial amount of rocuronium administered. As tissue compartments fill with continued dosing (4-8 hours), less drug is redistributed away from the site of action and, for an infusion-only dose, the rate to maintain neuromuscular blockade falls to about 20% of the initial infusion rate. The use of a loading dose and a smaller infusion rate reduces the need for adjustment of dose.

Pediatric Patients
Under halothane anesthesia, the clinical duration of effects of rocuronium bromide injection did not vary with age in patients 4 months to 8 years of age. The terminal half-life and other pharmacokinetic parameters of rocuronium in these pediatric patients are presented in Table 9.
Table 9: Mean (SD) Pharmacokinetic Parameters of Rocuronium in Pediatric Patients (ages 3 to less than 12 mos, n=6; 1 to less than 3 yrs, n=5; 3 to less than 8 yrs, n=7) During Halothane Anesthesia

PK Parameters	3 to <12 mos	1 to <3 yrs	3 to <8 yrs
Clearance (L/kg/hr)	0.35 (0.08)	0.32 (0.07)	0.44 (0.16)
Volume of Distribution at Steady State (L/kg)	0.30 (0.04)	0.26 (0.06)	0.21 (0.03)
$t_{1/2 \beta}$ Elimination (hr)	1.3 (0.5)	1.1 (0.7)	0.8 (0.3)

Pharmacokinetics of rocuronium bromide injection were evaluated using a population analysis of the pooled pharmacokinetic datasets from 2 trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight. In patients under the age of 18 years, clearance (L/kg) and volume of distribution (V_{ss}) increase with bodyweight (kg) and age (years). As a result, the terminal half-life of rocuronium bromide injection decreases with increasing age from 1.1 hour to 0.7-0.8 hour. Table 10 presents the pharmacokinetic parameters in the different age groups in the studies with sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia.

Table 10: Mean (SD) Pharmacokinetic Parameters of Rocuronium in Pediatric Patients During Sevoflurane (Induction) and Isoflurane/Nitrous Oxide (Maintenance) Anesthesia

PK Parameters	Birth to <28 days	28 days to ≤3 mos	3 mos to ≤2 yrs	2 to ≤11 yrs	11 to ≤17 yrs
CL (L/kg/hr)	0.31 (0.07)	0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of Distribution (L/kg)	0.42 (0.06)	0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
$t_{1/2 \beta}$ (hr)	1.1 (0.2)	0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Studies in animals have not been performed with rocuronium bromide to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, analysis of chromosomal aberrations in mammalian cells, and micronucleus test) conducted with rocuronium bromide did not suggest mutagenic potential.
14 CLINICAL STUDIES
The effectiveness of Rocuronium Bromide Injection has been established based on adequate and well-controlled studies of another formulation of rocuronium bromide injection in adult patients. Below is a display of the efficacy results of the adequate and well-controlled studies of the other formulation of rocuronium bromide injection.
In US clinical studies, a total of 1137 patients received another rocuronium bromide injection, product, including 176 pediatric, 140 geriatric, 55 obstetric, and 766 other adults. Most patients (90%) were ASA physical status I or II, about 9% were ASA III, and 10 patients undergoing coronary artery bypass grafting or valvular surgery were ASA IV. In European clinical studies, a total of 1394 patients received rocuronium bromide injection, including 52 pediatric, 128 geriatric (65 years or greater), and 1214 other adults.

14.1 Adult Patients
Intubation using doses of rocuronium bromide injection 0.6 mg/kg to 0.85 mg/kg was evaluated in 203 adults in 11 clinical studies. Excellent to good intubating conditions were generally achieved within 2 minutes and maximum block occurred within 3 minutes in most patients. Doses within this range provide clinical relaxation for a median (range) time of 33 (14-85) minutes under opioid/nitrous oxide/oxygen anesthesia. Larger doses (0.9 mg/kg and 1.2 mg/kg) were evaluated in 2 studies with 19 and 16 patients under opioid/nitrous oxide/oxygen anesthesia and provided 58 (27-111) and 67 (38-160) minutes of clinical relaxation, respectively.
Cardiovascular Disease
In 1 clinical study, 10 patients with clinically significant cardiovascular disease undergoing coronary artery bypass graft received an initial dose of 0.6 mg/kg rocuronium bromide injection. Neuromuscular block was maintained during surgery with bolus maintenance doses of 0.3 mg/kg. Following induction, continuous 8 mcg/kg/min infusion of rocuronium bromide injection produced relaxation sufficient to support mechanical ventilation for 6 to 12 hours in the surgical intensive care unit (SICU) while the patients were recovering from surgery.

Rapid Sequence Intubation
Intubation was assessed in patients in 6 clinical studies where anesthesia was induced with either thiopental (3-6 mg/kg) or propofol (1.5 mg/kg to 2.5 mg/kg) in combination with either fentanyl (2 mcg/kg to 5 mcg/kg) or alfentanil (1 mg). Most of the patients also received a premedication such as midazolam or temazepam. Most patients had intubation attempted within 60 to 90 seconds of administration of rocuronium bromide injection 0.6 mg/kg or succinylcholine 1 mg/kg to 1.5 mg/kg. Excellent or good intubating conditions were achieved in 119/120 (99% [95% confidence interval: 95% to 99.9%]) patients receiving Rocuronium Bromide Injection and in 108/110 (98% [94% to 99.8%]) patients receiving succinylcholine. The duration of action of Rocuronium Bromide Injection 0.6 mg/kg is longer than succinylcholine and at this dose is approximately equivalent to the duration of other intermediate-acting neuromuscular blocking drugs.
Obese Patients
Rocuronium bromide injection was dosed according to actual body weight (ABW) in most clinical studies. The administration of rocuronium bromide injection in the 47 of 330 (14%) patients who were at least 30% or more above their ideal body weight (IBW) was not associated with clinically significant differences in the onset, duration, recovery, or reversal of rocuronium bromide injection-induced neuromuscular blockade.

In 1 clinical study in obese patients, rocuronium bromide injection 0.6 mg/kg was dosed according to ABW (n=12) or IBW (n=11). Obese patients dosed according to IBW had a longer time to maximum block, a shorter median (range) clinical duration of 25 (14-29) minutes, and did not achieve intubating conditions comparable to those dosed based on ABW. These results support the recommendation that obese patients be dosed based on actual body weight [see Dosage and Administration (2.6)].

Obstetric Patients
Rocuronium bromide injection 0.6 mg/kg was administered with thiopental, 3 mg/kg to 4 mg/kg (n=13) or 4 mg/kg to 6 mg/kg (n=42), for rapid sequence induction of anesthesia for Cesarean section. No neonate had APGAR scores greater than 7 at 5 minutes. The umbilical venous plasma concentrations were 18% of maternal concentrations at delivery. Intubating conditions were poor or inadequate in 5 of 13 women receiving 3 mg/kg to 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.

14.2 Geriatric Patients
Rocuronium bromide injection was evaluated in 55 geriatric patients (ages 65-80 years) in 6 clinical studies. Doses of 0.6 mg/kg provided excellent to good intubating conditions in a median (range) time of 2.3 (1-8) minutes. Recovery times from 25% to 75% after these doses were not prolonged in geriatric patients compared to other adult patients [see Dosage and Administration (2.6) and Use in Specific Populations (8.5)].

14.3 Pediatric Patients
Rocuronium bromide injection 0.45 mg/kg, 0.6 mg/kg, or 1 mg/kg was evaluated under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anesthesia for intubation in 326 patients in 2 studies. In 1 of these studies maintenance bolus and infusion equivalents 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_1 for doses of 0.6 mg/kg was shortest in the children [36.7 (20.1-65.9) minutes] and longest in infants [59.8 (32.3-87.9) 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 (2.6) and Use in Specific Populations (8.4)].

Rocuronium bromide injection 0.6 mg/kg or 0.8 mg/kg was evaluated for intubation in 75 pediatric patients (n=28; age 3-12 months; n=47; age 1-12 years) in 3 studies using halothane (1-5%) and nitrous oxide (60%-70%) in oxygen. Doses of 0.6 mg/kg provided a median (range) time to maximum block of 1 (0.5-3.3) minute(s). This dose provided a median (range) time of clinical relaxation of 41 (24-68) minutes in 3-month to 1-year-old infants and 26 (17-39) minutes in 1- to 12-year-old pediatric patients [see Dosage and Administration (2.6) and Use in Specific Populations (8.4)].

16 HOW SUPPLIED/STORAGE AND HANDLING
Rocuronium Bromide Injection is a clear, colorless to yellow/orange solution, free from visible particulate matter and available in single-dose vials and single-dose prefilled syringes in the following packaging configurations:

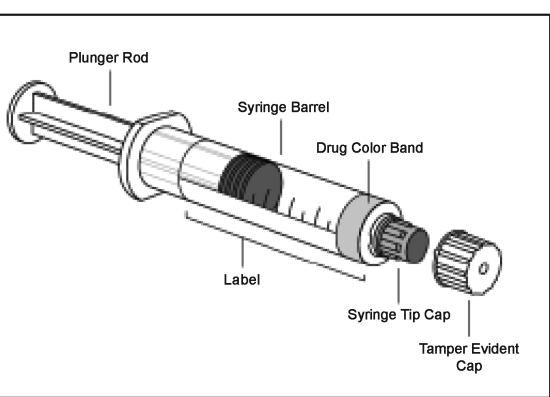
Product Code	Unit of Sale	Strength	Each
442105	NDC 65219-442-05 Unit of 10	50 mg per 5 mL (10 mg per mL)	NDC 65219-442-02 Single-Dose Vial
	NDC 65219-444-10 Unit of 10	100 mg per 10 mL (10 mg per mL)	NDC 65219-444-04 Single-Dose Vial
RF762250	NDC 76045-221-50 Unit of 10	50 mg per 5 mL (10 mg per mL)	NDC 76045-221-05 Single-Dose Prefilled Syringe This product is RFID-enabled.
	NDC 76045-220-50 Unit of 10	50 mg per 5 mL (10 mg per mL)	NDC 76045-220-05 Single-Dose Prefilled Syringe

The container closure is not made with natural rubber latex.
Rocuronium Bromide Injection should be stored at 20°C to 25°C (68°F to 77°F); Excursion permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. DO NOT FREEZE.
Safety and Handling
There is no specific work exposure limit for Rocuronium Bromide Injection. In case of eye contact, flush with water for at least 10 minutes.
Single-Dose Vial and Single-Dose Prefilled Syringe. Discard Unused Portion.

17 PATIENT COUNSELING INFORMATION
Obtain information about your patient's medical history, current medications, any history of hypersensitivity to rocuronium bromide or other neuromuscular blocking agents. If applicable, inform your patient that certain medical conditions and medications might influence how Rocuronium Bromide Injection works [see Warnings and Precautions (5.1), Drug Interactions (7)].
In addition, inform your patient that severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium Bromide Injection, have been reported. Because allergic cross-reactivity has been reported in this class, request information from your patients about previous anaphylactic reactions to other neuromuscular blocking agents [see Warnings and Precautions (5.2)].

INSTRUCTIONS FOR USE

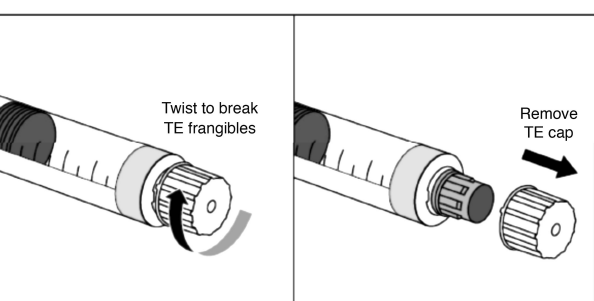
Figure 1: Prefilled Syringe



NOTES:

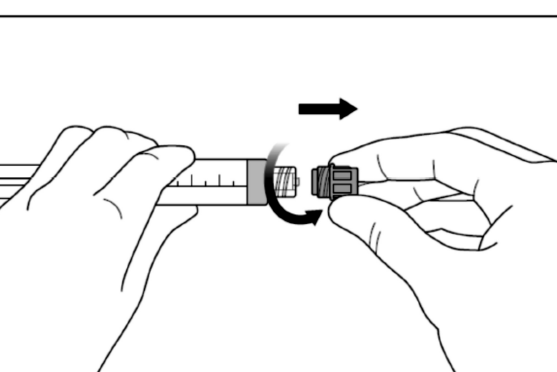
- Do not introduce any other fluid into the syringe at any time.
 - Do not dilute for intravenous push.
 - Do not re-sterilize the syringe.
 - Do not use this product on a sterile field.
 - This product is for single dose only.
1. Visually inspect the syringe. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the prefilled syringe has been damaged.
 2. Twist the tamper evident (TE) cap to remove. The syringe tip cap should remain attached. (Figure 2)

Figure 2



3. Push plunger rod slightly to break the stopper loose while syringe tip cap is still on.
4. Remove and discard the syringe tip cap (Figure 3).

Figure 3



5. Expel air bubble(s). Adjust the dose (if applicable).
 6. Administer the dose. Discard the used syringe into an appropriate receptacle.
- For more information concerning this drug, please call Fresenius Kabi USA, LLC at 1-800-551-7176.
To report SUSPECTED ADVERSE REACTIONS, contact Fresenius Kabi USA, LLC at 1-800-551-7176 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

US Patents 10661030, 11964142, and 12171992 (prefilled syringe)

Manufactured by:

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