ROCURONIUM BROMIDE

REPOSE

10 mg/mL Solution for Injection (I.V.)
Muscle Relaxant

℞

FORMULATION:
Each ml of solution contains:
Rocuronium (as bromide)…….10mg

INDICATIONS:
Rocuronium (Repose) is indicated in adult and pediatric patients (from term neonates to adolescents [0 to <18 years]) as an adjunct to general anesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery. In adults Rocuronium (Repose) is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

DOSAGE AND ADMINISTRATION:
Posology
Like other neuromuscular blocking agents, Rocuronium (Repose) should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.
As with other neuromuscular blocking agents, the dosage of Rocuronium (Repose) 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.
The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.
Inhalational anesthetics do potentiate the neuromuscular blocking effects of Rocuronium (Repose). 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, adjustments with Rocuronium (Repose) should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuronium (Repose) during long lasting procedures (longer than 1 hour) under inhalational anesthesia (see Interaction with Other Medicinal Products and Other Forms of Interaction).
In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.
Surgical Procedures
Tracheal intubation
The standard intubating dose during routine anesthesia is 0.6 mg/kg rocuronium bromide, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.
For use of rocuronium bromide during rapid sequence induction of anesthesia in patients undergoing Caesarean section reference is made to Pregnancy and Lactation.
Higher doses
Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide decreases the onset time and increases the duration of action (see Pharmacodynamic Properties).
Maintenance dosing
The recommended maintenance dose is 0.15 mg/kg rocuronium bromide; in the case of long-term inhalational anesthesia this should be reduced to 0.075-0.1 mg/kg rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four stimulation are present.
Continuous infusion
If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational anesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anesthetic method used.
Pediatric population
For neonates (0-27 days), infants (28 days-2 months), toddlers (3-23 months), children (2-11 years) and adolescents (12-17 years) the recommended intubation dose during routine anesthesia and maintenance dose are similar to those in adults. However, the duration of action of the single intubating dose will be longer in neonates and infants than in children (see Pharmacodynamic Properties)
For continuous infusion in pediatrics, the infusion rates, with the exception of children (2-11 years), are the same as for adults. For children aged 2-11 years higher infusion rates might be necessary.
Thus, for children (2-11 years) the same initial infusion rates as for adults are recommended and then this should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 or 2 responses to train of four stimulation during the procedure.
The experience with rocuronium bromide in rapid sequence induction in pediatric patients is limited. Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in pediatric patients.
Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine 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 patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see Continuous Infusion). (See also Special Warnings and Precautions for Use)
Overweight and obese patients
When used in overweight or obese patients (defined as patients with a body weight of 30% or more above ideal body weight) doses should be reduced taking into account ideal body weight.
Intensive Care Procedures
Tracheal intubation
For tracheal intubation, the same doses should be used as described above under surgical procedures.
Maintenance dosing
The use of an initial loading dose of 0.6 mg/kg rocuronium bromide is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3-0.6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6-12 hours, according to the individual response. Thereafter, individual dose requirements remain relatively constant.
A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal individual patient control, monitoring of neuromuscular transmission is strongly recommended. Administration up to 7 days has been investigated.
Special populations
Rocuronium (Repose) is not recommended for the facilitation of mechanical ventilation in the intensive care in pediatric and geriatric patients due to a lack of data on safety and efficacy.
Method of administration
Rocuronium (Repose) is administered intravenously either as a bolus injection or as a continuous infusion (see Special Precautions for Disposal and Other Handling).

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

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Since Rocuronium (Repose) 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 induction technique.
As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for Rocuronium (Repose). In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block.
Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual neuromuscular blockade after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent (such as sugammadex or acetylcholinesterase inhibitors) should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.
High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering Rocuronium (Repose), hypersensitivity to other neuromuscular blocking agents should be excluded. Rocuronium (Repose) should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.
Rocuronium may increase the heart rate.
In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques.
Myopathy after long term administration of other non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.
If suxamethonium is used for intubation, the administration of Rocuronium (Repose) should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.
The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Rocuronium (Repose):
Hepatic and/or biliary tract disease and renal failure
Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide.
Prolonged circulation time
Conditions associated with prolonged circulation time such as cardiovascular disease, old age and edematous state resulting in an increased volume of distribution, may contribute to a slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.
Neuromuscular disease
Like other neuromuscular blocking agents, Rocuronium (Repose) should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of Rocuronium (Repose) may have profound effects and Rocuronium (Repose) should be titrated to the response.
Hypothermia
In surgery under hypothermic conditions, the neuromuscular blocking effect of Rocuronium (Repose) is increased and the duration prolonged.
Obesity
Like other neuromuscular blocking agents, Rocuronium (Repose) may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients when the administered doses are calculated on actual body weight.
Burns
Patients with burns are known to develop resistance to non-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to response.
Conditions which may increase the effects of Rocuronium (Repose)
Hypokalemia (e.g. after severe vomiting, diarrhea and diuretic therapy), hypermagnesemia, hypocalemia (after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnia, cachexia.
Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION
The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents.
Effect of other drugs on Rocuronium (Repose)
Increased effect:
• Halogenated volatile anesthetics potentiate the neuromuscular block of Rocuronium (Repose). The effect only becomes apparent with maintenance dosing (see Dosage and Administration). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
• After intubation with suxamethonium (see Special Warnings and Precautions for Use).
• Long-term concomitant use of corticosteroids and Rocuronium (Repose) in the ICU may result in prolonged duration of neuromuscular block or myopathy (see Special Warnings and Precautions for Use and Adverse Effects).
Other drugs:
• antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.
• diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents.
Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see Special Warnings and Precautions).
Decreased effect:
• Prior chronic administration of phenytoin or carbamazepine.
• Calcium chloride, potassium chloride.
• Protease inhibitors (gabexate, ulinastatin).
Variable effect:
• Administration of other non-depolarizing neuromuscular blocking agents in combination with Rocuronium (Repose) may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
• Suxamethonium given after the administration of Rocuronium (Repose) may produce potentiation or attenuation of the neuromuscular blocking effect of Rocuronium (Repose).
Effect of Rocuronium (Repose) on other drugs
Rocuronium (Repose) combined with lidocaine may result in a quicker onset of action of lidocaine.
Pediatric population
No formal interaction studies have been performed. The above mentioned interactions for adults and their special warnings and precautions for use (see Special Warnings and Precautions for Use) should be taken into account for pediatric patients.

PREGNANCY AND LACTATION
Pregnancy
For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fetal development, parturition or postnatal development. Caution should be exercised when prescribing Rocuronium (Repose) to pregnant women.
Caesarean Section
In patients undergoing Caesarean section, Rocuronium (Repose) can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anesthetic agent is administered or following suxamethonium facilitated intubation. However, Rocuronium (Repose), administered in doses of 0.6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in parturients undergoing Caesarean section. Rocuronium (Repose) does not affect Apgar score, fetal muscle tone or cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead to the observation of clinical adverse effects in the newborn.
Note 1: doses of 1.0 mg/kg have been investigated during rapid sequence induction of anesthesia, but not in Caesarean section patients. Therefore, only a dose of 0.6 mg/kg is recommended in this patient group.
Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of Rocuronium (Repose) should be reduced and be titrated to twitch response.
Breast-feeding
It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk.
Insignificant levels of rocuronium bromide were found in the milk of lactating rats. There are no human data on the use of Rocuronium (Repose) during lactation. Rocuronium (Repose) should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
Since Rocuronium (Repose) is used as an adjunct to general anesthesia, the usual precautionary measures after a general anesthesia should be taken for ambulatory patients.

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

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MedDRA SOC	Preferred term	
	Uncommon/rare (<1/100, >1/10 000)	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 edema
		Urticaria
		Rash
		Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness
		Steroid myopathy
General disorders and administration site conditions	Drug ineffective	Face edema
	Drug effect/ therapeutic response decreased	Malignant hyperthermia
	Drug effect/ therapeutic response increased	
	Injection site pain	
	Injection site reaction	
Injury, poisoning and procedural complications	Prolonged neuromuscular block	Airway complication of anesthesia
	Delayed recovery from anesthesia	

MedDRA version 8.1

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Rocuronium (Repose), have been reported.

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

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

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

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarizing 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 Special Warnings and Precautions for Use).

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.

Pediatric population

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%.

OVERDOSE

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. There are two options for the reversal of neuromuscular block: (1) In adults, sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Rocuronium (Repose), ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

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

Mechanism of Action

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

Pharmacodynamic effects

The ED90 (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively).

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

Intubation during routine anesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED90 under intravenous anesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established within 2 minutes. After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction

During rapid sequence induction of anesthesia under propofol or fentanyl/thiopental anesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Pediatric population

Mean onset time in infants, toddlers and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. Comparison within pediatric age groups showed that the mean onset time in neonates and adolescents (1.0 min.) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min., respectively). The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. Comparing within pediatric age groups demonstrated that mean time to reappearance of T3 was prolonged in neonates and infants (56.7 and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 min., respectively).

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

	Time to maximum block ** (min)	Time to reappearance of T3 ** (min)
Neonates (0-27 days) n=10	0.98 (0.62)	56.69 (37.04) n=9
Infants (28 days-2 months) n=11	0.44 (0.19) n=10	60.71 (16.52)
Toddler (3 months-23 months) n=28	0.59 (0.27)	45.46 (12.94) n=27
Children (2-11 years) n=34	0.84 (0.29)	37.58 (11.82)
Adolescents (12-17 years) n=31	0.98 (0.38)	42.90 (15.83) n=30

* Dose of rocuronium administered within 5 seconds.
** Calculated from the end of administration of the rocuronium intubating dose

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

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

Intensive Care Unit

Following continuous infusion in the Intensive Care Unit, the time to recovery of the train of four ratio to 0.7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T2 to train of four stimulation and recovery of the train of four ratio to 0.7 approximates 1.5 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

Cardiovascular surgery

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

Reversal of muscle relaxation

Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T2 or at the first signs of clinical recovery, antagonizes the action of Rocuronium (Repose).

Pharmacokinetic properties

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

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabeled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in feces after 9 days. Approximately 50% is recovered as the parent compound. No metabolites are detected in plasma.

Pediatric population

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. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance (l.hr-1.kg-1). The volume of distribution (l.kg-1) and elimination half-life (h) decrease with age (years). The pharmacokinetic parameters of typical pediatrics within each age group are summarized below:

Estimated PK parameters (Mean [SD]) of rocuronium bromide in typical pediatric patients during sevoflurane and nitrous oxide (induction) and isoflurane/nitrous oxide (maintenance anesthesia)

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

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

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

Intensive Care unit

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

INCOMPATIBILITIES

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

Rocuronium (Repose) must not be mixed with other medicinal products.

If Rocuronium (Repose) 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 (Repose) and drugs for which incompatibility with Rocuronium (Repose) has been demonstrated or for which compatibility with Rocuronium (Repose) has not been established.

CAUTION:

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

ADR STATEMENT:

For suspected adverse drug reaction, report to FDA: www.fda.gov.ph

STORAGE CONDITIONS

Store at temperatures between 2°-8°C in the dark.

AVAILABILITY

5mL clear, colorless, glass vial USP Type I stoppered with dark grey bromobutyl rubber stoppers with aluminum flip-off seal (yellow).

Shelf-life : 24 months

Date of first authorization:

Date of revision statement: April 22, 2020

Reg. No.:

Manufactured by:

GLAND PHARMA LIMITED
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