NEW ZEALAND DATA SHEET

1. PRODUCT NAME

DBL™ Rocuronium Bromide Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of DBL Rocuronium Bromide injection contains 10 mg rocuronium bromide and the following inactive ingredients sodium acetate, sodium chloride and acetic acid and/or sodium hydroxide q.s. to adjust pH to within the range of 3.8 - 4.2.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection

Rocuronium bromide is an off-white to pale-yellow or slightly pink amorphous powder.

Rocuronium bromide is readily soluble in water (> 200 mg/mL) and a 1% w/v solution in water has a pH of 8.9 – 9.5. In aqueous solution rocuronium bromide is more stable at acidic pH.

DBL Rocuronium Bromide Injection is supplied as a sterile, nonpyrogenic, isotonic solution that is clear, colourless to faintly yellow administered by intravenous bolus or infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DBL Rocuronium Bromide Injection is indicated to provide skeletal muscle relaxation during surgery.

DBL Rocuronium Bromide Injection is also indicated as an adjunct to general anaesthesia to facilitate tracheal intubation during routine induction, and during rapid sequence induction when suxamethonium is contraindicated.

DBL Rocuronium Bromide Injection is also indicated as an adjunct in the Intensive Care Unit (ICU) to facilitate intubation and mechanical ventilation.

4.2 Dose and method of administration

Dosage

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store DBL Rocuronium Bromide Injection with the cap and ferrule intact and in a manner that minimises the possibility of selecting the wrong product (**see section 4.4**).

Like other neuromuscular blocking agents rocuronium bromide should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these agents.

The dosage of rocuronium bromide should be individualised in each patient. The method of anaesthesia and the expected duration of surgery, the method of sedation and the expected duration of mechanical ventilation, the possible interaction with other medicines that are administered concomitantly, and the condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for evaluation of the neuromuscular block and recovery.

Inhalation anaesthetics do potentiate the neuromuscular blocking effects of rocuronium bromide. This potentiation, however, becomes clinically relevant in the course of anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with rocuronium bromide should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of rocuronium bromide during long lasting procedures (longer than one hour) under inhalation anaesthesia (**see section 4.5**).

In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for short to long lasting surgical procedures and for use in the intensive care unit.

Surgical Procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0.6 mg rocuronium bromide per kg body weight, after which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0mg rocuronium bromide per kg body weight is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaestesia, after which adequate intubation conditions are also established within 60 seconds in nearly all patients. If a dose of 0.6mg rocuronium bromide per kg body weight is used for rapid sequence induction of anaethesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

In patients undergoing Caesarian section it is recommended to only use a dose of 0.6mg rocuronium bromide per kg body weight, since 1.0mg/kg has not been investigated in this patient group.

Maintenance dose

The recommended maintenance dose is 0.15 mg rocuronium bromide per kg body weight; in the case of long-term inhalational anaesthesia, this should be reduced to 0.075 to 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 two to three responses to train of four stimulation are present.

Continuous infusion

If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6mg rocuronium bromide per kg body weight and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height, or to maintain 1 to 2 responses to

train of four stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6mg/kg/hr and under inhalation anaesthesia the infusion rate ranges from 0.3-0.4mg/kg/hr. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used. A reduction in infusion rate may be required in patients with significant renal and/or hepatic disease.

Paediatric population

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

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

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

Dosing in geriatric patients and patients with hepatobiliary disease and/or renal failure

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

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 bodyweight.

Intensive Care Procedures

Tracheal intubation

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

Maintenance dosing

The use of an initial loading dose of 0.6 mg rocuronium bromide per kg body weight is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of one to two 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 to 90% (one to two twitches to TOF stimulation) in adult patients is 0.3 to 0.6 mg/kg/hour during the first hour of administration, which will

need to be decreased during the following 6 to 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 to 0.5 mg/kg/hour 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 seven days has been investigated. Rocuronium bromide is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Patients with multiple organ failure require lower infusion rates. (**see section 4.4**)

Prolonged use (> 48 hours) of non-depolarising muscle relaxants in the ICU should be avoided. (**see section 4.4**)

Method of Administration

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

Physical compatibilities

Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0.5 mg/mL and 2.0 mg/mL rocuronium bromide has been shown to be compatible with 0.9% NaCl, 5% dextrose, 5% dextrose in saline and sterile water for injections.

Prior to use, prepared infusions and syringes after withdrawal of the product from the vials should be stored at 2 to 8°C and used as soon as practicable after preparation. Any unused solution and product withdrawn into a syringe should be discarded after 24 hours.

If multiple use in one patient is intended, product withdrawn into a syringe should be used within 6 hours of the initial dose, and any remainder discarded.

Physical incompatibilities

Refer Section 6.2 Incompatibilities.

4.3 Contraindications

Known hypersensitivity to rocuronium or the bromide ion or to any of the excipients.

4.4 Special warnings and precautions for use

Risk of death due to medication errors

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

Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this agent until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

In case of intubation difficulties resulting in a clinical need for immediate reversal of a rocuronium induced neuromuscular block, the use of sugammadex should be considered.

As with other neuromuscular blocking agents, residual curarization has been reported for rocuronium bromide. Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular block. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of sugammadex or another reversal agent should be considered, especially in those cases where residual curarization is more likely to occur.

Anaphylactic reactions can occur following administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

In general, following long term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in 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 bromide 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 bromide:

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 0.6mg rocuronium bromide per kg body weight.

Prolonged Circulation Time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age and oedematous state resulting in an increased volume of distribution, may contribute to a

slower onset of action. The duration of action may also be prolonged due to a reduced plasma clearance.

Neuromuscular Disease

Like other neuromuscular blocking agents, rocuronium bromide should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of rocuronium bromide may have profound effects and rocuronium bromide should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of rocuronium bromide is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, rocuronium bromide may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body weight.

Burns

Patients with burns are known to develop resistance to non-depolarising neuromuscular blocking agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of rocuronium bromide

Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypocalcaemia (after massive transfusion), hypermagnesaemia, hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5 Interaction with other medicines and other forms of interaction

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

Increased Effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of rocuronium bromide. The effect only becomes apparent with maintenance dosing (**see section 4.2**). Reversal of the block with anticholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (**see section 4.2**)
- Long term concomitant use of corticosteroids and rocuronium bromide in the ICU may result in prolonged duration of neuromuscular block or myopathy (**see section 4.4 and section 4.8**)

Other Drugs

- Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

- Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lignocaine 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 section 4.4**)

Decreased Effect

- Prior chronic administration of corticosteroids, phenytoin or carbamazepine

- Protease inhibitors (gabexate, ulinastatin)

Variable Effect

- Administration of other non-depolarising neuromuscular blocking agents in combination with DBL Rocuronium Bromide Injection may produce potentiation or attenuation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.

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

Effect of rocuronium bromide on other drugs

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

Paediatric patients

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

4.6 Fertility, pregnancy and lactation

Fertility

No data available.

Pregnancy

Category B2

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

<u>Caesarian section</u>

In patients undergoing Caesarian section, rocuronium bromide can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. Rocuronium bromide administered in doses of 0.6mg/kg, has been shown to be safe in parturients undergoing Caesarian section. Rocuronium bromide does not affect Apgar score, foetal muscle tone nor cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs which does not lead the observation of clinical adverse affects in the newborn.

Note 1: Doses of 1.0mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarian section patients. Therefore, only a dose of 0.6mg/kg is recommended in this patient group.

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

Lactation

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

4.7 Effects on ability to drive and use machinery

Since rocuronium bromide is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is “anaphylactic and anaphylactoid reactions” and associated symptoms. See also the explanation notes below the table.

	Preferred Term[a]		
MedDRA SOC	**Uncommon / Rare[b] (<1/100, >1/10,000)**	**Very Rare (<1/10,000)**	**Not Known**
Immune System Disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock	

		Anaphylactoid shock	
Nervous System Disorders		Flaccid paralysis	
Cardiac Disorders	Tachycardia		Kounis syndrome
Vascular Disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, Thoracic and Mediastinal Disorders		Bronchospasm	
Skin and Subcutaneous Tissue Disorders		Angioneurotic oedema Urticaria Rash Erythematous rash	
Musculoskeletal and Connective Tissue Disorders		Muscular weakness[c] Steroid myopathy[c]	
General Disorders and Administrative Site Conditions	Drug ineffective Drug effect / therapeutic response decreased Drug effect / therapeutic response increased Injection site pain Injection site reaction	Face oedema Malignant hyperthermia	
Injury, Poisoning and Procedural Complications	Prolonged neuromuscular block Delayed recovery from the anaesthesia	Airway complication of anaesthesia	

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

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

c = After long term use in the ICU

Anaphylaxis

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

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

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

Local injection site reactions

During rapid sequence induction of anaesthesia, pain on injection has been reported, especially when the patient has not yet completely lost consciousness and particularly when propofol is used as the induction agent. In clinical studies, pain on injection has been noted in 16% of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0.5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarising 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 apnoea.

Intensive Care Unit myopathy

Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see section 4.4).

Rapid Sequence Induction Clinical Trial Data

The percentage of patients with at least one adverse event, with causality related to the study drug, is tabulated below for the all-patients-treated groups of both pivotal studies. It includes all adverse events reported with an incidence of 1% or greater. A dash represents an incidence of less than 1%.

	Study Group		
Body System	0.6 mg/kg rocuronium bromide (n = 126) %	1.0 mg/kg rocuronium bromide (n = 281) %	1.0 mg/kg suxamethonium (n = 287) %
Skin and Appendages Disorders Rash Urticaria	 3 -	 4 1	 3 -
Nervous & Musculo-Skeletal System Disorders Muscle Weakness Muscle Contractions Involuntary	 - -	 1 -	 - 23
Cardiovascular Disorders Tachycardia	-	1	-
Respiratory System Disorders Bronchospasm	-	2	1
Application Site Disorders Injection Site Pain	7	9	1

Intensive Care Unit Clinical Trial Data

The percentage of patients with at least one adverse event, with causality related to the study drug, are tabulated below for the all-patients-treated groups of both pivotal studies. It includes all adverse events reported with an incidence of 1% or greater.

Body System	All-patients-treated groups (n=95)
Cardiovascular Disorders, General	
ECG abnormal	1
Hypotension	2
Heart Rate and Rhythm Disorders	
Cardiac Arrest	1
Tachycardia	1
Musculo-Skeletal System Disorders	

Myopathy	1
Resistance Mechanism Disorders	
Sepsis	1
Respiratory System Disorders	
Respiratory Insufficiency	1
Vascular (extracardiac) Disorders	
Thrombophlebitis Deep	1

Paediatric patients

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdose

Symptoms

The symptoms of overdosage with a non-depolarising muscle relaxant are those of prolonged paralysis, apnoea, low tidal volume, respiratory depression and/or persistent muscle weakness. In animal studies, severe depression of cardiovascular function ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 times the ED_{90} (135 mg/kg rocuronium bromide) was administered.

Treatment

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) Sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends of the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine and pyridostigmine), with appropriate vagolytic (e.g. atropine) can be used at reappearance of T_2 or at the first signs of clinical recovery and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the effects of rocuronium, ventilation must be continued until spontaneous breathing is restored.

Use of a reversal agent should not begin until definite signs of spontaneous recovery are present. Overdosage of an acetylcholinesterase inhibitor can be dangerous.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Rocuronium bromide is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of medicines (curariform). It acts by competing for nicotinic cholinoceptors at the motor endplate of the striated muscle. This is unlike suxamethonium which causes depolarisation and renders the endplate, after initial contraction, unresponsive to stimuli, thus producing paralysis of the striated muscle. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine and pyridostigmine. The neuromuscular block can also be reversed by sugammadex, a Selective Relaxant Binding Agent. Rocuronium does not produce clinically significant autonomic and cardiovascular effects within the recommended dose range and is not expected to modulate cardiovascular effects of anaesthetics or other drugs used during surgery.

The ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg, respectively).

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

Table 1: Intubating conditions in Adult Patients (18-64 years)

Rocuronium bromide Dose (mg/kg)	Percent of Patients with Excellent or Good Intubating Conditions at:	
	60 seconds	90 seconds
0.30 (n = 14)	86%	86%
0.45 (n = 14)	86%	100%
0.60 (n = 121)	99%	96%

Excellent intubating conditions = jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement.
Good intubating conditions = jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement.

Table 2: Pharmacodynamic Parameter Values for the Total Dose of Rocuronium Bromide in Adults and Geriatric Patients, under Intravenous Anaesthesia (mean values)

Total Dose of Rocuronium Bromide (mg/kg)	Onset Time (minutes)	Clinical Duration* (minutes)

Adults (18 – 64 years)		
0.30 (n = 14)	4.8	11.0
0.45 (n = 14)	3.4	21.4
0.60 (n = 69)	2.1	35.8
0.90 (n = 30)	1.8	55.9
1.20 (n = 15)	1.8	84.6
Geriatrics (65 – 78 years)		
0.30 (n = 5)	3.4	19.7
0.60 (n = 5)	4.5	42.4

* = Clinical duration = duration until spontaneous recovery to 25% of control twitch height

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg rocuronium bromide is 30 to 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 doses of 0.3 to 0.45 mg/kg rocuronium bromide (1 to 1.5 times ED_{90}), 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 anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (two times ED_{90} under intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis for any type of procedure is established within two 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 anaesthesia under propofol or fentanyl/ thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients, respectively, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches one 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.

Special populations

Mean onset time in infants and children at an intubation dose of 0.6 mg/kg is slightly shorter than in adults. The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults.

The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic disease and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes). 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 (ICU), the time to recovery of the train of four (TOF) ratio to 0.7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T_2 to train of four stimulation and recovery of the train of four ratio to 0.7 approximates 1.5 (one to five) hours in patients without multiple organ failure and four (1 to 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 to 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.

The action of rocuronium can be antagonized either by sugammadex or by acetylcholinesterase inhibitors (neostigmine or pyridostigmine). Sugammadex can be given for routine reversal (at 1-2 post-tetanic counts to reappearance of T_2) or immediate reversal (3 minutes after rocuronium bromide administration). Acetylcholinesterase inhibitors can be administered at reappearance of T_2 or at the first signs of clinical recovery.

Clinical trials

The use of rocuronium bromide during rapid sequence induction of anaesthesia was studied in two pivotal studies, including a total of 681 adults and elderly patients, one using 3 to 5 mg/kg thiopentone (plus fentanyl) as the induction agent, and the other using 2.5 mg/kg propofol. The studies included three study groups: 0.6 mg/kg rocuronium, 1.0 mg/kg rocuronium, and 1.0 mg/kg suxamethonium. The patients were intubated within 60 seconds after the end of muscle relaxant administration. In the first part of both studies, intubation conditions after 0.6 mg/kg and 1.0 mg/kg rocuronium bromide were compared. In the second part of both studies, the optimal rocuronium dose was compared with 1.0 mg/kg suxamethonium. The optimal rocuronium dose (i.e. 1.0 mg/kg in both studies) and 1.0 mg/kg suxamethonium were considered to be clinically equivalent if a difference of less than 10% in the number of clinically acceptable intubating conditions was demonstrated. Based on this assumption a 13% rate of clinically unacceptable intubating conditions would have been acceptable. In the first part of both studies, it was demonstrated that the frequency of excellent intubating conditions was higher after a 1.0 mg/kg rocuronium dose than after the 0.6 mg/kg dose (65% versus 28% in the thiopentone study and 66% versus 40% in the propofol study). The percentage of clinically acceptable intubating conditions is comparable for 1.0 mg/kg rocuronium compared to 1.0 mg/kg suxamethonium although rocuronium resulted less frequently in excellent intubating

conditions (65% versus 80% in the thiopentone study and 66% versus 74% in the propofol study, although statistical significance was not reached in the latter study). In the thiopentone study, intubation could not be performed in 2% of the patients in the 0.6 mg/kg rocuronium group and in 1% of the patients in the 1.0 mg/kg rocuronium group 60 seconds after administration of the muscle relaxant. Intubation could be performed in all patients receiving 1.0 mg/kg suxamethonium. In the propofol study, intubation could not be performed in 1% of the patients in the 1.0 mg/kg rocuronium group and in 1% of the patients in the 1.0 mg/kg suxamethonium group but in all patients in the 0.6 mg/kg rocuronium group. These studies do not provide information on the relative time to onset of suxamethonium versus rocuronium bromide as the protocols specified assessment of intubation conditions at 60 seconds.

The use of rocuronium bromide in the Intensive Care Unit to facilitate mechanical ventilation was studied in two pivotal studies, including a total of 95 adult patients; 35 of the 95 patients (37%) had received rocuronium bromide for at least two days, and eleven (12%) for four days. Both patients with and without multiple organ failure were included. In both studies, rocuronium bromide administration started with a large loading bolus of 0.6 mg/kg and upon reappearance of one or two responses to TOF stimulation, a rocuronium bromide infusion was started for as long as required up to a maximum of seven days.

There are no data to support ICU use in infants, children, elderly (> 70 years old), those with burns and pre-existing myopathy.

5.2 Pharmacokinetic properties

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

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 1mL/kg/min. (**see section 4.2**).

Paediatric patients

Pharmacokinetics of rocuronium bromide in paediatric patients with ages ranging from 3 months to 17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance ($l.hr^{-1}.kg^{-1}$). The volume of distribution ($l.kg^{-1}$) and elimination half life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarised below:

PK parameters of rocuronium bromide in typical paediatric patients

PK Parameter		Infants (28 days to 2 months)	Toddlers (3-23 months)	Children (2-11 years)	Adolescents (12-17 years)
Clearance ($l.hr^{-1}.kg^{-1}$)		0.30 (0.08)	0.33 (0.10)	0.35 (0.09)	0.29 (0.14)
Volume of Distribution at Steady State ($l.kg^{-1}$)		0.31 (0.03)	0.23 (0.03)	0.18 (0.02)	0.18 (0.01)
Elimination Half-Life (hr)		0.9 (0.3)	0.8 (0.2)	0.7 (0.2)	0.8 (0.3)

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.

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 faeces after 9 days. Approximately 50% is recovered as the parent compound.

5.3 Preclinical safety data

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

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

6. PHARMACEUTICAL PARTICUALRS

6.1 List of excipients

- Glacial acetic acid
- Sodium acetate
- Sodium chloride

- Sodium hydroxide
- Water for injection

6.2 Incompatibilities

Physical incompatibility has been documented when rocuronium bromide is added to solutions containing the following agents: amoxycillin, amphotericin B, azathioprine, cephazolin, cloxacillin, dexamethasone, diazepam, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, Intralipid, methylprednisolone, prednisolone sodium succinate, thiopentone sodium, trimethoprim and vancomycin hydrochloride.

Rocuronium bromide must not be mixed with other solutions or drugs except those mentioned above **(see section 4.2**).

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

6.3 Shelf life

24 months

6.4 Special precautions for storage

DBL Rocuronium Bromide Injection should be stored at 2°C - 8°C. DBL Rocuronium Bromide Injection is intended to be used for one dose and in one patient only. Unused solutions should be discarded. DBL Rocuronium Bromide Injection should not be returned to 2°C - 8°C storage after it has been kept outside the refrigerator at 8°C - 30°C (i.e. normal use in the anaesthetic room or operating theatre). The date of removal should be noted on the vial and the product discarded if not used in 12 weeks.

6.5 Nature and contents of container

STRENGTH	**PACK**
50 MG/5 ML	10 X 5 ML VIAL

6.6 Special precautions for disposal

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

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Pfizer New Zealand Limited
P O Box 3998
Auckland, New Zealand, 1140
Toll Free Number: 0800 736 363

9. DATE OF FIRST APPROVAL

12 May 2011

10. DATE OF REVISION OF THE TEXT

29 December 2021

Summary table of changes

Section changed	Summary of new information
4.2	Addition of safety warning in relation to risk of medication errors; Addition compatibility information; Update of paediatric data.
4.4	Addition of general warning, warning of geriatric patients relating to risk of residual neuromuscular block, and safety warning in relation to risk of death due to medication errors.
4.5	Addition of reference relating to paediatric patients.
4.8	Addition of side effects 'malignant hyperthermia' and 'Kounis syndrome'; Addition of 'tachycardia" in paediatric patients.
4.9	Addiiton of symptoms.
5.1	Addition of information relating to Mechanism of Action and Clinical trials.
5.2	Addtion of new pharmacokinetics data including update of paediatric data
6.2	Removal of enoxamone

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