AUSTRALIAN PRODUCT INFORMATION
ESMERON® (Rocuronium bromide)

1 NAME OF THE MEDICINE

Rocuronium bromide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Esmeron 50 mg in 5 mL injection (pH 3.8-4.2) contains 50 mg rocuronium bromide.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Esmeron injection is a clear, colourless to faintly yellow solution.

Esmeron is administered by intravenous bolus or infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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

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

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

4.2 DOSE AND METHOD OF ADMINISTRATION

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

The product is for single patient use and contains no antimicrobial agent.

As with other neuromuscular blocking agents, the dosage of rocuronium bromide should be individualised in each patient. The anaesthetic method used, the 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 evaluation of the neuromuscular block and the recovery.

Inhalation anaesthetics do potentiate the activity of rocuronium. 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 inhalational anaesthesia (see Section 4.5 Interactions with other medicines and other forms of interactions).

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store ESMERON with the cap and ferrule intact and in a manner that minimizes the possibility of selecting the wrong product (see Section 4.4 Special warnings and precaution for use).

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 $mg.kg^{-1}$ rocuronium bromide. This dose can also be used for facilitating intubation during rapid sequence induction of anaesthesia. However, as part of a rapid sequence induction technique, a dose of 1.0 $mg.kg^{-1}$ rocuronium bromide is recommended.

Higher doses: Should there be a reason for selection of larger doses in individual patients, initial doses up to 2 $mg.kg^{-1}$ rocuronium bromide have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of rocuronium decreases the onset time and increases the duration of action (see Section 5.1 Pharmacodynamic properties).

Maintenance Dose: 0.15 $mg.kg^{-1}$ rocuronium bromide; in the case of long-term inhalational anaesthesia, this should be reduced to 0.075-0.1 $mg.kg^{-1}$ 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: A loading dose of 0.6mg/kg is recommended. When neuromuscular block starts to recover the infusion should be started and the rate 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 0.3-0.6 mg/kg/h and under inhalational anaesthesia, the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of the degree of blockade is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric patients: For term newborn infants (0-28 days), infants (28 days-23 months), children (2-11 years) and adolescents (12-18 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.

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

During continuous infusion in paediatric patients, dose and infusion rate must be carefully monitored and adjusted if necessary to allow for age-related differences in pharmacokinetics.

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.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure: The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 $mg.kg^{-1}$ rocuronium bromide. A dose of 0.6 $mg.kg^{-1}$ should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 $mg.kg^{-1}$ rocuronium bromide, and the recommended infusion rate is 0.3-0.4 mg/kg/h (see Section 4.2 Dose and method of administration - continuous infusion and 4.4 Special warnings and precaution for use).

Overweight and obese patients: Doses should be adjusted to conform with lean body mass in patients with a weight more than 30% higher than ideal body weight.

Intensive Care Procedures

Tracheal intubation

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

Maintenance dosing: The use of an initial loading dose of 0.6mg rocuronium bromide per kg body weight is recommended, followed by a continuous infusion as soon as twitch height recovers to 10% or upon reappearance of 1 to 2 twitches to train of four stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80-90% (1 to 2 twitches to TOF stimulation) in adult patients is 0.3 – 0.6 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 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. There are no data to support dose recommendations for the facilitation of mechanical ventilation in paediatric and geriatric patients.

Patients with multiple organ failure require lower infusion rates (see Section 4.4 Special warnings and precaution for use).

Prolonged use (> 48 hours) of non-depolarising muscle relaxants in the ICU should be avoided (see Section 4.4 Special warnings and precaution for use).

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 Esmeron has been shown to be compatible with: 0.9% NaCl, 5% glucose, 5% glucose in saline, sterile water for injections, Compound Sodium Lactate and Haemaccel. Administration should be begun immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

Prior to use, prepared infusions and syringes after withdrawal of the product from the vial, should be stored at 2°C-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.

Those drugs for which incompatibilities have been demonstrated are listed below.

Physical Incompatibilities:

Physical incompatibility has been documented when Esmeron is added to solutions containing amoxicillin, amphotericin B, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, erythromycin, enoximone, famotidine, furosemide, hydrocortisone sodium succinate, insulin, Intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopentone sodium, trimethoprim and vancomycin hydrochloride.

Esmeron must not be mixed with other solutions or drugs except those mentioned above (see Physical Compatibilities).

If Esmeron 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 Esmeron and drugs for which incompatibility with Esmeron has been demonstrated or for which compatibility with Esmeron has not been established.

4.3 CONTRAINDICATIONS

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

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Particularly in the case of former anaphylactic reactions, rocuronium bromide should be administered only under the supervision of an experienced clinician.

Appropriate Administration and Monitoring

Since rocuronium causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug. Ventilation should be continued 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.

Doses of rocuronium bromide greater than 0.9mg/kg may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation.

Patients with multiple organ failure require lower infusion rates (see Section 4.2 Dose and method of administration).

Residual Curarization

As with other neuromuscular blocking agents, residual curarization has been reported for Esmeron. Geriatric patients (65 years or older) may be at increased risk for residual neuromuscular block. 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 already used as part of usual clinical practice, the use of sugammadex or another reversal agent should be considered, especially in those cases where residual curarization is more likely to occur.

Anaphylaxis

Anaphylactic reactions can occur following administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Allergic cross-reactivity between muscle relaxants has been reported.

Long-Term Use in an Intensive Care Unit

In general, following long-term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of 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 the period of use of the neuromuscular blocking agent should be limited as much as possible in patients receiving both neuromuscular blocking agents and corticosteroids.

Prolonged use (> 48 hours) of non-depolarising muscle relaxants in the ICU should be avoided (see Section 4.2 Dose and method of administration).

Use with Suxamethonium

If suxamethonium is used for intubation, the administration of Esmeron should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Risk of Death due to Medication Errors

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

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuronium. A peripheral nerve stimulator may be of use in monitoring the neuromuscular response in patients presenting with such complications.

Infants (one month to twelve months of age): Mean onset time in infants and children at an intubation dose of 0.6 $mg.kg^{-1}$ 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.

In one study the clinical duration of action was 43 minutes in infants compared with 26 minutes in children aged 3 to 8 years. In a second study two of twenty subjects exhibited a prolonged duration of response and another two subjects appeared to be resistant to reversal of effects with neostigmine.

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 $mg.kg^{-1}$ rocuronium bromide. It is recommended the infusion rate is titrated to effect.

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 of rocuronium. 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 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 is increased and the duration prolonged.

Obesity: Like other neuromuscular blocking agents, rocuronium may exhibit a prolonged duration of action 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 Esmeron: Hypokalemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypocalcemia (after massive transfusion), hypermagnesemia, hypoproteinemia, dehydration, acidosis, hypercapnia and cachexia may all increase the effects of rocuronium. Severe electrolyte disturbances, altered blood pH and dehydration should therefore be corrected prior to surgery whenever possible.

Use in hepatic impairment
See Section 4.2 Dose and method of administration, 4.4 Special warnings and precaution for use - Hepatic and/or biliary tract disease and renal failure and 5.2 Pharmacokinetic properties.

Use in renal impairment
See Section 4.2 Dose and method of administration, 4.4 Special warnings and precaution for use - Hepatic and/or biliary tract disease and renal failure and 5.2 Pharmacokinetic properties.

Use in the elderly
See Section 4.2 Dose and method of administration, 4.4 Special warnings and precaution for use and 5.2 Pharmacokinetic properties.

Paediatric use
See Section 4.2 Dose and method of administration.

Effects on laboratory test
Not applicable

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Coadministration of the following compounds has been shown to influence the magnitude and/or the duration of action of non-depolarising neuromuscular blocking agents.

Effect of other drugs on Esmeron

Increased effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of Esmeron. The effect only becomes apparent with maintenance dosing (see Section 4.2 Dose and method of administration). With the presence of these volatile agents reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see Section 4.2 Dose and method of administration).
- Long-term concomitant use of corticosteroids and Esmeron in the ICU may result in prolonged duration of neuromuscular block or myopathy (see Section 4.4 Special warnings and precaution for use and 4.8 Adverse effects (Undesirable 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 anaesthetics (lidocaine I.V., bupivacaine hydrochloride epidural) and acute administration of phenytoin or β-blocking agents.

Recurarization has been reported after post-operative administration of:
aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see Section 4.4 Special warnings and precaution for use).

Decreased effect:

- prior chronic administration of corticosteroids, phenytoin or carbamazepine.

Variable effect:

- Administration of other non-depolarising neuromuscular blocking agents in combination with Esmeron 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 a non-depolarising neuromuscular blocking agent may produce potentiation or attenuation of the neuromuscular blocking effect of the non-depolarising neuromuscular blocking agent.

Effect of Esmeron on other drugs
Esmeron combined with lidocaine may result in a quicker onset of action of lidocaine.

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility
Fertility studies with rocuronium bromide have not been conducted.

Use in Pregnancy (Category B2).
Rocuronium bromide was not embryotoxic and/or teratogenic when administered to rats during pregnancy (day-6 to day-17) at IV neuromuscular blocking doses of 0.3mg/kg. There are no adequate and well-controlled studies in pregnant women. Esmeron should be used in pregnancy only if the potential benefits justify the potential risk to the foetus.

In patients receiving magnesium sulfate for toxaemia the dose of rocuronium bromide should be reduced and carefully titrated to twitch response.

Use in Lactation
Insignificant levels of rocuronium were found in the milk of lactating rats, however there are no data on the use of rocuronium bromide in lactating women. Rocuronium bromide should only be given to lactating women when the attending physician decides that the benefits outweigh the risks.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is “anaphylactic and anaphylactoid reactions” and associated symptoms. See also the explanations below **Table 1**.

Table 1

MedDRA SOC[1]	**Preferred term[2]**		
	Uncommon / rare[3] (<1/100, >1/10 000)	**Very rare (<1/10 000)**	**Not Known**
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Eye disorders		Mydriasis[3, 5] Fixed pupils[3, 5]	
Cardiac disorders	Tachycardia		Kounis syndrome
Vascular Disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Skin and subcutaneous tissue disorders		Angioneurotic oedema Urticaria Rash Erythematous rash	

Musculoskeletal and connective tissue disorders		Muscular weakness[4] Steroid myopathy[4]	
General disorders and administration site conditins	Drug ineffective Drug effect / therapeutic response decreased Drug effect / therapeutic response increased Injection site pain Injection site reaction	Face oedema Malignant hyperthermia	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia	

[1] medDRA version 8.1
[2] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
[3] Post marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories.
[4] After long term use in the ICU
[5] In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).

Anaphylaxis
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Esmeron, 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.

Since neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically, the possible occurrence of itching or erythematous reactions at the site of injection and/or generalised 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 of 0.3-0.9 mg .kg^{-1} 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 5% of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Prolonged neuromuscular block
The most frequent adverse reaction to nondepolarising 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.

ICU myopathy

Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU in combination with corticosteroids (see Section 4.4 Special warnings and precaution for use).

Rapid Sequence Induction Clinical Trial Data:

The percentage of patients with at least one adverse event, with causality related to the study drug, is summarised below in **Table 2** 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%.

Table 2

	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 & appendages disorders			
Rash	3	4	3
Urticaria	-	1	-
Nervous- & musculo-skeletal system disorders			
Muscle weakness	-	1	-
Muscle contractions involuntary	-	-	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 percentages of patients with at least one adverse event, with causality related to the study drug, are summarised below in **Table 3** for the all-patients-treated groups of both pivotal studies. It includes all adverse events reported with an incidence of 1% or greater.

Table 3

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 suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at https://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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 x ED_{90} (135mg.kg^{-1} rocuronium bromide) was administered.

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. In this situation there are two options for the reversal of neuromuscular block: (1) Sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block. (2) An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine), with appropriate vagolytic (e.g atropine) can be used at reappearance of T_2 or at the first signs of clinical recovery and should be administered in adequate doses. If 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 information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Rocuronium is a fast onset (relative to vecuronium), intermediate acting non-depolarising neuromuscular blocking agent. It acts by competing with the natural transmitter acetylcholine and blocking the cholinoceptors located at the motor end-plate of the striated muscle. This is unlike suxamethonium which causes depolarisation and renders the end-plate, after initial contraction, unresponsive to stimuli, thus producing paralysis of the striated muscle. The action of rocuronium is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium 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.

Pharmacodynamic effects

The ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0.3mg.kg^{-1} rocuronium bromide. The ED95 in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg.kg^{-1}, respectively).

The mean pharmacodynamic parameter values for rocuronium over a range of doses are presented in **Table 4** and **Table 5**.

Table 4: Intubating Conditions in Adult Patients (18-64 years)

	Percent of Patients with Excellent or Good Intubating Conditions at	
Rocuronium bromide Dose (mg/kg).	**60 sec.**	**90 sec.**
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 & immobile, no diaphragmatic movement.

Good intubating conditions = jaw relaxed, vocal cords apart & immobile, some diaphragmatic movement.

Table 5: Pharmacodynamic Parameter Values for the Total Dose of Rocuronium Bromide in Adults and Geriatric Patients, under Intravenous Anaesthesia, and in Children under Halothane Anaesthesia (mean values).

Total Dose of Rocuronium Bromide (mg/kg)	**Onset Time (min)**	**Clinical Duration* (min)**
Adults 18 to 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 to 78 years		
0.30 (n=5)	3.4	19.7
0.60 (n=5)	4.5	42.4
Paediatrics 3 months to 1 year		
0.80 (n=9)	0.6	43.4

1 to 14 years 0.30 (n=108) 0.80 (n=16)	 - 0.5	 15.7 32.3

*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 $mg.kg^{-1}$ 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$mg.kg^{-1}$ rocuronium bromide is 14 minutes.

With lower doses of 0.3 to 0.45$mg.kg^{-1}$ rocuronium bromide (1 - 1.5 x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2$mg.kg^{-1}$, clinical duration is 110 minutes.

Intubation during routine anaesthesia

Within 60 seconds following intravenous administration of a dose of 0.6 $mg.kg^{-1}$ rocuronium bromide (2 x 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 2 minutes. After administration of 0.45 $mg.kg^{-1}$ rocuronium bromide, acceptable 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 $mg.kg^{-1}$ rocuronium bromide. The rate of excellent intubations after a 1.0 $mg.kg^{-1}$ rocuronium dose was achieved in 66% and 65% of the patients, respectively. 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 $mg.kg^{-1}$ 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 and fentanyl/thiopental, respectively.

Paediatric patients

Mean onset time in infants and children at an intubation dose of 0.6 $mg.kg^{-1}$ is slightly shorter than in adults. Comparison within paediatric age groups showed that the mean onset time in term newborn infants and adolescents (1.0 min) is slightly longer than in infants, toddlers and children (0.4, 0.6 and 0.8 min., respectively). The duration of relaxation and the time to recovery tend to be shorter in children compared to infants and adults. Comparing within paediatric age groups demonstrated that mean time to reappearance of T_3 was prolonged in term newborn infants and infants (56.7 and 60.7 min., respectively) when compared to toddlers, children and adolescents (45.4, 37.6 and 42.9 min., respectively).

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

The duration of action of maintenance doses of 0.15$mg.kg^{-1}$ rocuronium bromide might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic disease and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes) (See Section 4.2 Dose and method of 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 T_2 to train of four stimulation and recovery of the train

of four ratio to 0.7 approximates 1.5 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

Cardiovascular surgery

In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6 - 0.9 $mg.kg^{-1}$ 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 antagonised either by sugammadex or by acetylcholinesterase inhibitors (neostigmine, pyridostigmine or edrophonium). Sugammadex can be given for routine reversal (at 1-2 post-tetanic counts to reappearance of T_2) or immediate reversal (3 minutes after rocuronium bromide administration). Acetylcholinesterase inhibitors can be administered in appropriate dosage, 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 adult and geriatric patients, one using 3-5 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 vs 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 2 days, and 11 (12%) for 4 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.

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.

Paediatric patients

Pharmacokinetics of rocuronium bromide in paediatric patients (n=146) with ages ranging from 0 to 17 years were evaluated using a population analysis of the pooled pharmacokinetic datasets from two clinical trials under sevoflurane (induction) and isoflurane/nitrous oxide (maintenance) anaesthesia. All pharmacokinetic parameters were found to be linearly proportional to body weight illustrated by a similar clearance ($l.hr^{-1}.kg^{-1}$). The volume of distribution ($l.kg^{-1}$) and elimination half life (h) decrease with age (years). The pharmacokinetic parameters of typical paediatrics within each age group are summarized in **Table 6**:

Table 6: PK parameters of rocuronium bromide in typical paediatric patients

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

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

In controlled studies in geriatric patients and in patients with renal dysfunction, the plasma clearance was reduced. In most studies, however, this reduction was not statistically significant. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1.0 mL/kg/min. (See also Section 4.2 Dose and method of 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 1500 (± 800) mL/kg and a plasma clearance of 2.1 (± 0.8) mL/kg/min were found.

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

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
Rocuronium bromide showed no genotoxic potential in standard assays of gene mutation and chromosomal damage.

Carcinogenicity
Carcinogenicity with rocuronium bromide have not been conducted

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

sodium acetate trihydrate
sodium chloride
glacial acetic acid
water for injections

6.2 INCOMPATIBILITIES

Refer to Section 4.2 DOSE AND METHOD OF ADMINISTRATION

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG).

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2ºC-8ºC until the expiry date indicated on the label. Esmeron is intended to be used for one dose and in one patient only. Unused solutions should be discarded. The product can be stored outside the refrigerator at a temperature of 8-30°C (normal use in the anaesthetic room or operating theatre) for a maximum of 12 weeks. After first removal from the refrigerator (2ºC-8ºC storage), the 12 week shelf life applies. 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

Packs of 10 or 12 clear Type 1 glass vials in an outer cardboard box – AUST R 57063

The rubber stopper in the vial does not contain latex.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

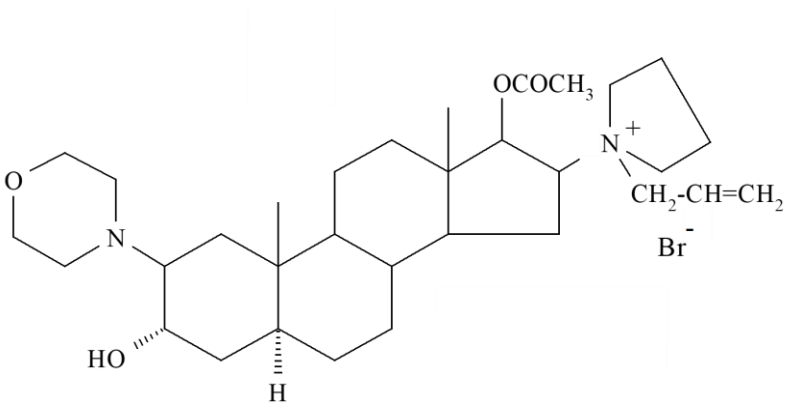
Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

1-(17β-Acetoxy-3α-hydroxy-2 β-morpholino-5α-androstan-16β-yl)-1-allylpyrrolidinium bromide; $C_{32}H_{53}BrN_2O_4$

Rocuronium bromide is a quaternary aminosteroid and an analogue of vecuronium bromide. It is an off-white to pale yellow or slightly pink amorphous powder which is readily soluble in water (>200mg/mL). 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.

Chemical structure



CAS number
119302-91-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4-Prescription Only Medicine

8 SPONSOR

Merck Sharp & Dohme (Australia) Pty Limited
Level 1, Building A,
26 Talavera Road
Macquarie Park, NSW 2113
Australia
www.msd-australia.com.au

9 DATE OF FIRST APPROVAL

8 June 2007

10 DATE OF REVISION

24 May 2024

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Removal of name and address of Sponsor in New Zealand
Multiple	Editorial changes including removal of dual labelled ingredient names, update of copyright statement, and correction of spelling

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