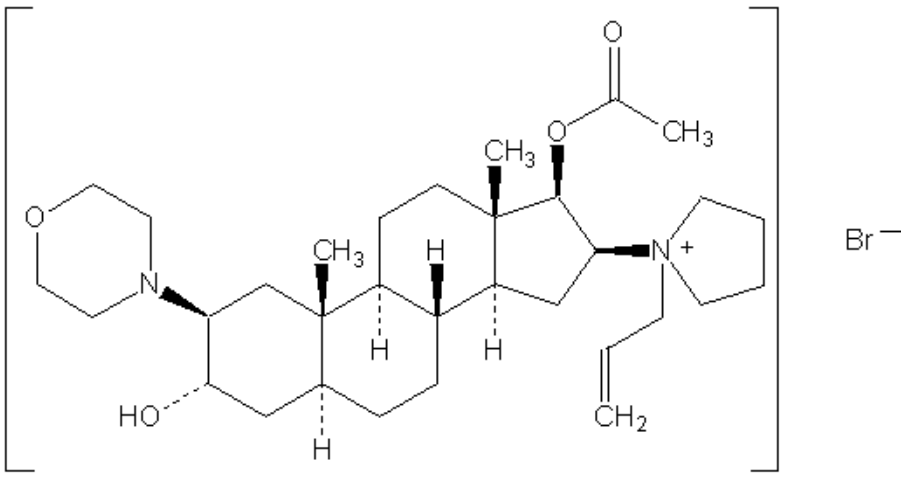
PRODUCT INFORMATION
ROCURONIUM SANDOZ 50MG/5ML and 100MG/10ML
SOLUTION FOR INJECTION

NAME OF THE MEDICINE

Generic name: Rocuronium bromide
Chemical name: 1-(17β-acetoxy-3α-hydroxy-2β-morpholino-5α-androstan-16β-yl)-1-allylpyrrolidinium bromide

Chemical structure:



CAS: 119302-91-9
Empirical formula: $C_{32}H_{53}BrN_2O_4$ MW: 609.696

DESCRIPTION

Rocuronium bromide 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 to 9.5. In aqueous solution rocuronium bromide is more stable at acidic pH. Rocuronium bromide is administered by intravenous bolus or infusion.

As well as the active ingredient Rocuronium Sandoz contains the following inactive ingredients: sodium acetate trihydrate, sodium chloride, sodium hydroxide, acetic acid - glacial, water for injections.

PHARMACOLOGY

Pharmacodynamics

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 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. The action of rocuronium is

antagonised by acetylcholinesterase inhibitors, e.g. 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 medicines 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 balanced anaesthesia is approximately rocuronium bromide 0.3mg/kg. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40mg/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 to 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 elderly patients under intravenous anaesthesia and in children under halothane 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
Elderly (65-78 years)		
0.30 (n=5)	3.4	19.7
0.60 (n=5)	4.5	42.4
Infants (3 months-1 year)		
0.80 (n=9)	0.6	43.4
Children (1-14 years)		
0.30 (n=108)	--	15.7
0.80 (n=16)	0.5	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 rocuronium bromide 0.6mg/kg 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 rocuronium bromide 0.6mg/kg is 14 minutes.

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

Intubation during routine anaesthesia
Within 60 seconds following intravenous administration of a dose of rocuronium bromide 0.6mg/kg (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 rocuronium bromide 0.45mg/kg, 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 rocuronium bromide 1.0mg/kg. The rate of excellent intubations after a rocuronium 1.0mg/kg dose was achieved in 66 and 65% of the patients, respectively. The clinical duration with this dose approaches one hour, at which time the neuromuscular block can be safely reversed. Following a dose of rocuronium bromide 0.6mg/kg, 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.

Special populations
Mean onset time in infants and children at an intubation dose of 0.6mg/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 rocuronium bromide 0.15mg/kg might be somewhat longer under enflurane and isoflurane anaesthesia and in patients with hepatic 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 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 to 5) 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 rocuronium bromide 0.6 to 0.9mg/kg 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.

Pharmacokinetics
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% confidence interval) elimination half-life is 73 (66 to 80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193 to 214) mL/kg and plasma clearance is 3.7 (3.5 to 3.9) mL/kg/minute.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12 to 24 hours. After injection of a radiolabelled dose of rocuronium bromide, excretion of the radiolabel is on average 47% in urine and 43% in faeces after nine days. Approximately 50% is recovered as the parent compound.

In infants (3 months to 1 year), the apparent volume of distribution at steady-state conditions is increased compared to adults and children (1 to 8 years). In older children (3 to 8 years), a trend is seen toward higher clearance and shorter elimination half-life compared to adults, younger children and infants. The mean (± standard deviation (SD)) elimination half-life in older children (3 to 8 years), adults, younger children (1 to 3 years) and infants (3 to 12 months) is respectively 48 (± 18), 73 (± 32), 65 (± 39) and 79 (± 30) minutes.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
In controlled studies in elderly 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 1.0mL/kg/minute (see also 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, an (apparent) volume of distribution

at steady state of 1,500 (± 800) mL/kg and a plasma clearance of 2.1 (± 0.8) mL/kg/minute were found.

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 ICU is mainly based on the results obtained in clinical studies.

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 thiopental 3 to 5mg/kg (plus fentanyl) as the induction agent, and the other using 2.5mg/kg propofol. The studies included three study groups: rocuronium 0.6mg/kg, rocuronium 1.0mg/kg, and suxamethonium 1.0mg/kg. The patients were intubated within 60 seconds after the end of muscle relaxant administration. In the first part of both studies, intubation conditions after rocuronium bromide 0.6mg/kg and 1.0mg/kg were compared. In the second part of both studies, the optimal rocuronium dose was compared with suxamethonium 1.0mg/kg. The optimal rocuronium dose (i.e. 1.0mg/kg in both studies) and suxamethonium 1.0mg/kg 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 rocuronium 1.0mg/kg dose than after the 0.6mg/kg dose (65 versus 28% in the thiopental study and 66 versus 40% in the propofol study). The percentage of clinically acceptable intubating conditions is comparable for rocuronium 1.0 mg/kg compared to suxamethonium 1.0mg/kg although rocuronium resulted less frequently in excellent intubating conditions (65 versus 80% in the thiopental study and 66 versus 74% in the propofol study, although statistical significance was not reached in the latter study). In the thiopental study, intubation could not be performed in 2% of the patients in the rocuronium 0.6mg/kg group and in 1% of the patients in the rocuronium 1.0mg/kg group 60 seconds after administration of the muscle relaxant. Intubation could be performed in all patients receiving suxamethonium 1.0mg/kg. In the propofol study, intubation could not be performed in 1% of the patients in the rocuronium 1.0mg/kg group and in 1% of the patients in the suxamethonium 1.0mg/kg group but in all patients in the rocuronium 0.6mg/kg 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 (ICU) 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 0.6mg/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.

INDICATIONS

Adjunct to general anaesthesia to facilitate endotracheal intubation during routine induction, to provide muscle relaxation and to facilitate mechanical ventilation in adults, children and infants over 1 month of age.

Adjunct to general anaesthesia to facilitate endotracheal intubation during rapid sequence induction when suxamethonium is contraindicated, however, this has not been studied in infants and children.

Rocuronium is also indicated as an adjunct in the intensive care unit (ICU) to facilitate mechanical ventilation.

CONTRAINDICATIONS

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

PRECAUTIONS

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

Since rocuronium causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine. 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.

As with other neuromuscular blocking agents, residual curarisation 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 curarisation, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Factors which could cause residual curarisation after extubation in the postoperative phase (e.g. medicine interactions or patient condition) should also be considered. If not already used as part of usual clinical practice, the use of a reversal agent should be considered, especially in those cases where residual curarisation is more likely to occur.

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.

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-depolarising 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.

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

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.

Prolonged use (> 48 hours) of non-depolarising muscle relaxants in the ICU should be avoided (see also DOSAGE AND ADMINISTRATION).

Patients with multiple organ failure require lower infusion rates (see also DOSAGE AND ADMINISTRATION).

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 (1 to 12 months of age)
Mean onset time in infants and children at an intubation dose of 0.6mg/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.

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 2 of 20 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

rocuronium bromide 0.6 mg/kg. It is recommended the infusion rate is titrated to effect.

Prolonged circulation time
Conditions associated with prolonged circulation time, e.g. 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 bodyweight.

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
Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypocalcaemia (after massive transfusion), hypermagnesaemia, hypoproteinaemia, 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.

Effects on fertility
Studies with rocuronium bromide have not been conducted.

Use in pregnancy

Australian Pregnancy Category B2 Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.

Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
Rocuronium bromide was not embryotoxic and/or teratogenic when administered to rats during pregnancy (day 6 to day 17) at intravenous neuromuscular blocking doses of 0.3 mg/kg. There are no adequate and well controlled studies in pregnant women. Rocuronium should be used in pregnancy only if the potential benefits justify the potential risk to the fetus.

In patients receiving magnesium sulfate for toxaemia the dose of rocuronium bromide should be reduced and carefully titrated to the 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 breastfeeding women when the attending doctor decides that the benefits outweigh the risks.

Paediatric use

No formal interaction studies have been performed.

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

Carcinogenesis and mutagenesis
Studies with rocuronium bromide have not been conducted.

Effect on ability to drive or operate machinery
Since rocuronium is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthetic should be taken for ambulatory patients.

INTERACTIONS WITH OTHER MEDICINES
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 medicines on Rocuronium Sandoz
Increased effect
Halogenated volatile anaesthetics potentiate the neuromuscular block of Rocuronium Sandoz: The effect only becomes apparent with maintenance dosing (see DOSAGE AND ADMINISTRATION). With the presence of these volatile agents reversal of the block with anticholinesterase inhibitors could also be inhibited.

After intubation with suxamethonium (see DOSAGE AND ADMINISTRATION).

Long-term concomitant use of corticosteroids and Rocuronium Sandoz in the ICU may result in prolonged duration of neuromuscular block or myopathy (see PRECAUTIONS and ADVERSE EFFECTS).

Other medicines: Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylaminopenicillin antibiotics.

Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lignocaine intravenous (IV), bupivacaine epidural) and acute administration of phenytoin or beta-blocking agents.

Recurarisation has been reported after postoperative administration of aminoglycoside, lincosamide, polypeptide and acylaminopenicillin antibiotics, quinidine, quinine and magnesium salts (see PRECAUTIONS).

Decreased effect
Prior chronic administration of corticosteroids, phenytoin or carbamazepine.

Variable effect
Administration of other non-depolarising neuromuscular blocking agents in combination with Rocuronium Sandoz 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 Rocuronium Sandoz on other medicines
Rocuronium Sandoz combined with lignocaine may result in a quicker onset of action of lignocaine.

ADVERSE EFFECTS

The most commonly occurring adverse effects include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse effects during postmarketing surveillance is anaphylactic and anaphylactoid reactions and associated symptoms. See also the explanations below Table 3.

Table 3

Adverse effects		
MedDRA SOC	**Preferred Term[a]**	
	Uncommon / rare[b] (<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 oedema Urticaria Rash Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness[c] Steroid myopathy[c]
General disorders and administration site conditions	Medicine ineffective Medicine effect / therapeutic response decreased Medicine effect / therapeutic response increased Injection site pain Injection site reaction	Face oedema
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia

[a] Frequencies are estimated from postmarketing surveillance reports and data from general literature
[b] Postmarketing 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.

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 anaphylactic reactions, above) should always be considered when administering these medicines.

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

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 non-depolarising blocking agents as a class consists of an extension of the medicine'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 PRECAUTIONS).

Rapid sequence induction clinical trial data
The percentages of patients with at least one adverse event, with causality related to the study medicine, are listed in Table 4 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 4

Adverse events reported in rapid sequence induction clinical trials with incidence ≥ 1%			
	Study Group		
Body System	**Rocuronium bromide 0.6mg/kg (n=126) %**	**Rocuronium bromide 1.0mg/kg (n=281) %**	**Suxamethonium 1.0mg/kg (n=287) %**
Skin & appendages disorders			
Rash	3	4	3
Urticaria	--	1	--
Nervous & musculoskeletal 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

-- = incidence < 1%

Intensive care unit clinical trial data
The percentages of patients with at least one adverse event, with causality related to the study medicine, are shown in Table 5 for the all-patients-treated groups of both pivotal studies. It includes all adverse events reported with an incidence of 1% or greater.

Table 5

Adverse events reported in intensive care unit clinical trials with incidence ≥ 1%

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
Musculoskeletal system disorders	
Myopathy	1
Resistance mechanism disorders	
Sepsis	1
Respiratory system disorders	
Respiratory insufficiency	1
Vascular (extracardiac) disorders	
Thrombophlebitis, deep	1

DOSAGE AND ADMINISTRATION

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

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 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 the recovery.

Inhalational 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 PRECAUTIONS, Interactions with other medicines).

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. Elderly patients (65 to 80 years) manifest similar sensitivity to rocuronium as younger adults.

Surgical procedures

Tracheal intubation

The standard intubating dose during routine anaesthesia is rocuronium bromide 0.6mg/kg. 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 rocuronium bromide 1.0mg/kg is recommended.

Higher doses
Should there be a reason for selection of larger doses in individual patients, initial doses up to rocuronium bromide 2mg/kg 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 PHARMACOLOGY, Pharmacodynamics).

Maintenance dose
Rocuronium bromide 0.15mg/kg; in the case of long-term inhalational anaesthesia, this should be reduced to rocuronium bromide 0.075 to 0.1mg/kg. 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
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 one to two 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 to 0.6mg/kg/hour and under inhalational anaesthesia, the infusion rate ranges from 0.3 to 0.4mg/kg/hour. Continuous monitoring of the degree of blockade 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 patients
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 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 one or two 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. There are no data to support recommendations for the use of rocuronium bromide in neonates (0 to 1 month).

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 intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure is rocuronium bromide 0.6mg/kg. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is rocuronium bromide 0.075 to 0.1mg/kg and the recommended infusion rate is 0.3 to 0.4mg/kg/hour (see also Continuous infusion).

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 bodyweight.

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 rocuronium bromide 0.6mg/kg bodyweight 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 0.6mg/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 studies, with mean hourly infusion rates ranging from 0.2 to 0.5mg/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. 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 also PRECAUTIONS).

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

Physical compatibilities
Compatibility studies with commonly used infusion fluids have been performed.
In nominal concentrations of 0.5 and 2.0mg/mL Rocuronium Sandoz has been shown to be compatible with the following infusion fluids:
- sodium chloride (NaCl) 0.9%
- glucose 5%

- glucose 5% in saline
- compound sodium lactate
- sterile water for injections
- 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 vials should be stored at 2-8°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 six hours of the initial dose and any remainder discarded.

Those medicines for which incompatibilities have been demonstrated are listed below

Physical incompatibilities
Physical incompatibility has been documented when rocuronium bromide is added to solutions containing amoxycillin, amphotericin, azathioprine, cephazolin, cloxacillin, dexamethasone, diazepam, erythromycin, enoximone, famotidine, frusemide, hydrocortisone sodium succinate, insulin, Intralipid, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental sodium, trimethoprim and vancomycin hydrochloride.

Rocuronium Sandoz must not be mixed with other solutions or medicines except those mentioned above (see Physical compatibilities).

If Rocuronium Sandoz 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 NaCl 0.9%) between administration of Rocuronium Sandoz and medicines for which incompatibility with Rocuronium Sandoz has been demonstrated or for which compatibility with Rocuronium Sandoz has not been established.

OVERDOSAGE

Contact the Poisons Information Centre on 13 11 26 on advice on the management of 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} (rocuronium bromide 135mg/kg) was administered.

Treatment
In case of overdose treatment should be supportive and symptomatic.

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.

PRESENTATION AND STORAGE CONDITIONS

Rocuronium Sandoz 50mg/5mL solution for injection is a clear, colourless to yellow/orange solution. It is available in packs of 10 and 12 vials.
Rocuronium Sandoz 100mg/10mL solution for injection is a clear, colourless to yellow/orange solution. It is available in packs of 10 vials.

The rubber stopper used with Rocuronium Sandoz is latex-free.

Store at 2-8°C. Use by the expiry date indicated on the label. Intended to be used for one dose and in one patient only. Unused solutions should be discarded. An unopened vial of product should not be returned to 2-8°C storage after it has been kept outside the refrigerator at 8 to 30°C, i.e. in normal use in the anaesthetic room or operating theatre. The date of removal of the unopened vial should be noted on the vial and the product discarded if not opened and used as a single dose within 12 weeks.

Not all presentations may be marketed in Australia

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
ABN 60 075 449 553
54 Waterloo Road
Macquarie Park, NSW 2113
Australia
Tel: 1800 634 500

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 31/03/2010
Date of most recent amendment: 10/08/2016