ROCURONIUM 50 IV BIOTECH

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROCURONIUM 50 IV BIOTECH, 10 mg/mL, Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL contains 10 mg rocuronium bromide. Each 5 mL vial contains 50 mg rocuronium bromide.
For the full list of excipients, see section 6.1.
Sugar free.

3. PHARMACEUTICAL FORM

Injection.
A clear, colourless to yellow or orange solution.
pH: 3,5 to 4,5.
Osmolarity: 270 to 330 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROCURONIUM 50 IV BIOTECH is indicated as an adjunct:
- to general anaesthesia to facilitate tracheal intubation during routine and rapid sequence induction and to provide skeletal muscle relaxation during surgery.
- in the Intensive Care Unit (ICU) to facilitate intubation and mechanical ventilation for up to 3 days in adults aged 18 to 65 years.

4.2 Posology and method of administration

Posology

ROCURONIUM 50 IV BIOTECH should only be administered by, or under supervision of, experienced medical practitioners who are familiar with the action and use of neuromuscular blocking medicines.

The dosage of ROCURONIUM 50 IV BIOTECH should be individualised in each patient.

The following should be taken into account when determining the dose:
- 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 medication that is administered concomitantly,
- the condition of the patient.

The use of an appropriate neuromuscular monitoring technique is recommended for the evaluation of neuromuscular block and recovery.

Inhalation anaesthetics potentiate the neuromuscular blocking effects of ROCURONIUM 50 IV BIOTECH. Potentiation, however, becomes clinically relevant in the course of anaesthesia, when the volatile medicines have reached the tissue concentrations required for this interaction.
Consequently, adjustments with ROCURONIUM 50 IV BIOTECH should be made by:
- administering smaller maintenance doses at less frequent intervals or
- by using lower infusion rates of ROCURONIUM 50 IV BIOTECH during long lasting procedures (longer than 1 hour) under inhalation anaesthesia (see section 4.5).

Risk of medicine errors:
Accidental administration of neuromuscular blocking medicines may result in serious adverse events, including fatal outcomes. Store ROCURONIUM 50 IV BIOTECH with the cap and ferrule intact and in a manner that minimises the possibility of selecting the wrong product (see section 4.4).

In adult patients the following dosage recommendations 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 anaesthesia is 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg ROCURONIUM 50 IV BIOTECH per kg body mass is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia. At this dose adequate intubation conditions are established within 60 seconds in nearly all patients.

A twitch suppression of 90 % or a train-of-four of 1 or less must be obtained prior to intubation. Disappearance of the TOF will correspond to optimal intubation conditions.

Higher doses
Should there be a reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg ROCURONIUM 50 IV BIOTECH have been administered during surgery. The use of these high doses of ROCURONIUM 50 IV BIOTECH decreases the onset time and increases the duration of action (see section 5.1).

Maintenance dosing
The recommended maintenance dose is 0,15 mg ROCURONIUM 50 IV BIOTECH per kg body mass.
In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg ROCURONIUM 50 IV BIOTECH.
The maintenance doses should best be given as a bolus when twitch height has recovered to 25 % of control twitch height, or when 2 to 3 responses to train-of-four (TOF) stimulation are present (see section 5.1).

No cumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

The duration of action of maintenance doses of 0,15 mg ROCURONIUM 50 IV BIOTECH per kg body mass will be longer under enflurane and isoflurane anaesthesia in elderly 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).

Continuous infusion
If ROCURONIUM 50 IV BIOTECH is administered by continuous infusion, it is recommended to give a loading dose of 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass 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 to 0,6 mg/kg/h and under inhalation anaesthesia the infusion rate ranges from 0,3 to 0,4 mg/kg/h. Continuous monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Reversal of muscle relaxation
On completion of the surgical procedure where ROCURONIUM 50 IV BIOTECH was administered, anti-cholinesterase medicines such as neostigmine, pyridostigmine or edrophonium is used to reverse and decrease the duration of competitive neuromuscular blockade. A muscarinic antagonist (atropine or glycopyrrolate) is used concomitantly to prevent stimulation of muscarinic receptors and thereby to avoid slowing of the heart rate.

Administration of sugammadex (a chelating agent specific for rocuronium and vecuronium) at doses > 2 mg/kg is able to reverse neuromuscular blockade from ROCURONIUM 50 IV BIOTECH within 3 minutes. In patients with impaired renal function, sugammadex clearance is markedly reduced and this medicine should be avoided.

Before administering a neuromuscular antagonist, the train-of-four count should be at least 3.
The TOF count should preferably be done with a monitoring device.

Dosing in paediatric patients
Children (1 to 14 years) and infants (1 to 12 months) under halothane anaesthesia manifest similar sensitivity to ROCURONIUM 50 IV BIOTECH as adults. Onset of action is faster in infants and children than in adults. Clinical duration is shorter in children than in adults.

For infants (28 days to 23 months), children (2 to 14 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 1 or 2 responses to train of four stimulation during the procedure.
The experience with ROCURONIUM 50 IV BIOTECH in rapid sequence induction in paediatric patients is limited. ROCURONIUM 50 IV BIOTECH is therefore not recommended, for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure
The standard intubation dose for elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0,6 mg/kg ROCURONIUM 50 IV BIOTECH.
Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg ROCURONIUM 50 IV BIOTECH and the recommended infusion rate is 0,3 to 0,4 mg/kg/h (see 'Continuous infusion').

Dosing in overweight and obese patients
When used in overweight or obese patients (defined as patients with a body mass of 30 % or more above ideal body mass) doses should be reduced taking into account a lean body mass.

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 50 IV BIOTECH per kg body mass 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 (TOF) 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 % (1 to 2 twitches to train-of-four (TOF) stimulation) in adult patients is 0,3 to 0,6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6 to 12 hours, according to individual response.

Thereafter, individual dose requirements remain relatively constant.
A large between patient variability in hourly infusion rates has been found, with mean hourly infusion rates ranging from 0,2 to 0,5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal and individual patient control, monitoring of neuromuscular transmission is strongly recommended. Safety and efficacy beyond 3 days has not been established.
Following continuous infusion in the Intensive Care Unit, the time to recovery of the train-of-four ration to 0,7 depends on the level of block at the end of the infusion. After a continuous infusion of 20 hours or more, the median (range) time between return of T2 to train-of-four stimulation and recovery of the train-of-four ration to 0,7 approximates 1,5 (1 to 5) hours in patients without multiple organ failure and 4 (1 to 25) hours in patients with multiple organ failure.
Spontaneous respiration is only recommended when the TOF is 0,9.

Special populations

ROCURONIUM 50 IV BIOTECH is not recommended for the facilitation of mechanical ventilation in the Intensive Care Unit (ICU) in elderly patients due to a lack of data on safety and efficacy (see section 4.3).
For dosing in elderly patients or overweight and obese patients during surgical procedures, see 'Surgical procedures'.

Paediatric population

ROCURONIUM 50 IV BIOTECH is not recommended for the facilitation of mechanical ventilation in the Intensive Care Unit (ICU) in paediatric patients due to a lack of data on safety and efficacy (see section 4.3).
For dosing in paediatric patients during surgical procedures, see 'Surgical procedures'.

Method of administration

ROCURONIUM 50 IV BIOTECH is for single use only.
ROCURONIUM 50 IV BIOTECH is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6 for compatible infusion fluids).
Also refer to incompatibilities under section 6.2

For instructions on dilution of ROCURONIUM 50 IV BIOTECH before administration, see section 6.6.

4.3 Contraindications

ROCURONIUM 50 IV BIOTECH is contraindicated in:
- Hypersensitivity to rocuronium bromide, or the bromide ion, or to any of the ingredients included in ROCORONIUM 50 IV BIOTECH (see section 6.1).
- Neonates (0 to 1 month). There is inadequate data to support the use of ROCURONIUM 50 IV BIOTECH in neonates (0 to 1 month).
- For the facilitation of mechanical ventilation in the Intensive Care Unit (ICU) in paediatric and elderly patients due to a lack of data on safety and efficacy.
- Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Since ROCURONIUM 50 IV BIOTECH causes paralyses of respiratory muscles, ventilatory support is mandatory for patients treated with ROCURONIUM 50 IV BIOTECH until adequate spontaneous respiration is restored. It is important to anticipate intubation difficulties particularly when used as part of a rapid sequence induction technique.

Hypersensitivity/ anaphylaxis:
Severe anaphylactic and anaphylactoid reactions, which may be fatal, may occur. Precautions for treating such reactions should always be taken, particularly in the case of previous anaphylactic reactions to neuromuscular blocking medicines, since allergic cross-reactivity to neuromuscular blocking medicines has been reported.
Therefore, where possible, before administering ROCURONIUM 50 IV BIOTECH, hypersensitivity to other neuromuscular blocking medicines should be excluded. ROCURONIUM 50 IV BIOTECH should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

Histamine release and histaminoid reactions:
Since neuromuscular blocking medicines, such as ROCURONIUM 50 IV BIOTECH, are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see section 4.8), should always be taken into consideration when administering ROCURONIUM 50 IV BIOTECH.

Residual neuromuscular blockade:
Residual neuromuscular blockade has been reported for ROCURONIUM 50 IV BIOTECH (see section 4.8).
In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Elderly patients (65 years or older) may be at increased risk for residual neuromuscular block. Other factors which could cause residual neuromuscular blockade after extubation in post-operative phase (such as medicine interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal medicine should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur (see section 4.2). It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

Cardiac effects:
ROCURONIUM 50 IV BIOTECH may increase the heart rate (see section 4.8). Dose levels higher than 0,9 mg per kg body mass may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic medicines or by vagal stimulation.

Prolonged neuromuscular blockage:
Following long term treatment of muscle relaxants in the Intensive Care Unit (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 ROCURONIUM 50 IV BIOTECH.
Patients should receive adequate analgesia and sedation.
Furthermore, ROCURONIUM 50 IV BIOTECH should be titrated to effect in the individual patients by, or under supervision of, experienced medical practitioners who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy:
Myopathy after long-term administration of ROCURONIUM 50 IV BIOTECH in the ICU, in combination with corticosteroid therapy, has been reported. Therefore, for patients receiving both ROCURONIUM 50 IV BIOTECH and corticosteroids, the period of use of ROCURONIUM 50 IV BIOTECH should be limited as much as possible.

Suxamethonium:
If suxamethonium is used for intubation, the administration of ROCURONIUM 50 IV BIOTECH should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium (see section 4.5).

Malignant hyperthermia:
Because ROCURONIUM 50 IV BIOTECH is always used with other medicines and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering factors, medical practitioners should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia. Cases of malignant hyperthermia with rocuronium, as contained in ROCURONIUM 50 IV BIOTECH, have been reported during post-marketing surveillance; however, the causal association has not been proven.

Risk of death due to medicine errors:
Administration of ROCURONIUM 50 IV BIOTECH 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 50 IV BIOTECH:

Hepatic and/or biliary tract disease and renal failure:
Because rocuronium is excreted in urine and bile, ROCURONIUM 50 IV BIOTECH should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0,6 mg/kg ROCURONIUM 50 IV BIOTECH.

Prolonged circulation time:
Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and oedematous states resulting in an increased volume of distribution, may contribute to a slower onset of the effect. The duration of action may also be prolonged due to reduced plasma clearance.

Neuromuscular disease:
ROCURONIUM 50 IV BIOTECH should be used with extreme caution in patients with neuromuscular disease or after poliomyelitis, since the response to neuromuscular blocking medicines 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 50 IV BIOTECH may have profound effects and ROCURONIUM 50 IV BIOTECH should be titrated to the response.

Hypothermia:
In surgery under hypothermic conditions, the neuromuscular blocking effect of ROCURONIUM 50 IV BIOTECH is increased and the duration prolonged.

Obesity:
ROCURONIUM 50 IV BIOTECH may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, when the administered doses are calculated on actual body mass.

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

Conditions which may increase the effects of ROCURONIUM 50 IV BIOTECH:

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

Excipients:
ROCURONIUM 50 IV BIOTECH contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

Paediatric population

The same warnings and precautions as for adults should be taken into consideration.

4.5 Interaction with other medicines and other forms of interaction

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

Effect of other medicines on ROCURONIUM 50 IV BIOTECH:

Increased effect:
- Halogenated volatile anaesthetics potentiate the neuromuscular block of ROCURONIUM 50 IV BIOTECH. The effect only becomes apparent with maintenance dosing (see section 4.2, 'Surgical procedures, Maintenance dosing'). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.4).
- Long-term concomitant use of corticosteroids and ROCURONIUM 50 IV BIOTECH in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).
- High doses of thiopental, methohexital, ketamine, fentanyl, gamma-hydroxybutyrate, etomidate and propofol.

Other medicines:
- Antibiotics: aminoglycosides, lincosamide (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, high doses of metronidazole.
- Diuretics, thiamine, mono-amine oxidase (MAO) inhibiting medicines, quinidine, quinine, protamine, adrenergic blocking medicines, magnesium salts, calcium channel blocking medicines, lithium salts, local anaesthetics (lidocaine I.V., bupivacaine epidural) and acute administration of phenytoin or ß-blocking medicines.

Recurarisation (increase in neuromuscular block after a variable period of recovery) 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.
- Calcium chloride, potassium chloride, norepinephrine (noradrenaline), azathioprine (only transient and limited effect) and theophylline.
- Protease inhibitor homologues (such as gabexate and ulinastatin).
- Neostigmine, edrophonium, pyridostigmine and aminopyridine derivatives.

Variable effect:
- Administration of other non-depolarising neuromuscular blocking medicines in combination with ROCURONIUM 50 IV BIOTECH may produce attenuation or potentiation of neuromuscular block, depending on the order of administration and the neuromuscular blocking medicine used.
- Suxamethonium given after administration of ROCURONIUM 50 IV BIOTECH may produce potentiation or attenuation of neuromuscular blocking effects of ROCURONIUM 50 IV BIOTECH.

Effect of ROCURONIUM 50 IV BIOTECH on other medicines:
ROCURONIUM 50 IV BIOTECH combined with lidocaine (lignocaine) may result in a quicker onset of action of lidocaine.

Paediatric population
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 be taken into account for paediatric patients.

4.6 Fertility, pregnancy and lactation
Pregnancy
Safety in pregnancy has not been established (see section 4.3).

Caesarean section:
In patients undergoing Caesarean section, ROCURONIUM 50 IV BIOTECH can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic medicine is administered or following suxamethonium facilitated intubation.
However ROCURONIUM 50 IV BIOTECH, administered in doses of 0,6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in patients undergoing Caesarean section. ROCURONIUM 50 IV BIOTECH does not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation.
From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs, which does not lead to the observation of clinical adverse effects in the newborn. Doses of 1,0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients.
Therefore, only a dose of 0,6 mg/kg is recommended in this patient group.
Reversal of neuromuscular block, induced by neuromuscular blocking medicines 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 50 IV BIOTECH should be reduced and be titrated to twitch response.

Breastfeeding
Safety in breastfeeding has not been established (see section 4.3).

Fertility
There is no data available on fertility with ROCURONIUM 50 IV BIOTECH.

4.7 Effects on ability to drive and use machines
ROCURONIUM 50 IV BIOTECH has a major influence on the ability to drive and use machines.
Patients should be warned not to handle potentially dangerous machinery or drive a car within 24 hours after the full recovery from the neuromuscular blocking action of ROCURONIUM 50 IV BIOTECH.

4.8 Undesirable effects
a) Summary of the safety profile
The most frequently 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 in section c).

b) Tabulated list of adverse reactions

MeDRA System Organ Class (SOC)	Frequency [1]	Side effects
Immune system disorders	*Less frequent*	Hypersensitivity, anaphylactic reaction (sometimes fatal), anaphylactic shock, anaphylactoid reaction (see section 4.4), anaphylactoid shock, angioedema.
Nervous system disorder	*Less frequent*	Flaccid paralysis.
Eye disorders	*Frequency unknown*	Mydriasis[2,3], fixed pupils[2,3].
Cardiac disorders	*Less frequent*	Dysrhythmia, tachycardia.
	Frequency unknown	Kounis syndrome.
Vascular disorders	*Less frequent*	Hypotension, hypertension, circulatory collapse and shock, flushing.
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Bronchospasm, wheezing.
	Frequency unknown	Apnoea, respiratory failure.
Gastrointestinal disorders	*Less frequent*	Hiccups; nausea; vomiting.
Skin and subcutaneous tissue disorders	*Less frequent*	Urticaria, rash, erythematous rash, pruritus (itching), angioedema.
Musculoskeletal, connective tissue and bone disorders	*Less frequent*	Muscular weakness[4], steroid myopathy[4] (see section 4.4)
General disorders and administrative site conditions	*Less frequent*	Medicine ineffective, decreased medicine effect/therapeutic response, increased medicine effect/therapeutic response, injection site pain, injection site reaction, facial oedema.
	Frequency unknown	Malignant hyperthermia.
Investigations	*Less frequent*	Increase in mean plasma histamine.
Injury, poisoning	*Less frequent*	Prolonged neuromuscular block (see section 4.4), delayed recovery from anaesthesia, airway complication of anaesthesia.

1. Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
2. Post-marketing surveillance data cannot give precise incidence figures.
3. In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB).
4. After long-term use in the ICU.

c) Description of selected adverse reactions
Anaphylaxis:
Severe anaphylactic reactions to ROCURONIUM 50 IV BIOTECH have been reported less frequently. 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, the necessary precautions should always be taken in anticipation thereof.

Clinical study reports mention a slight increase in mean plasma histamine level following rapid bolus administration of 0,3 to 0,9 mg rocuronium bromide per kg body mass.

Histamine release:
See section 4.4.

Prolonged neuromuscular block:
The most frequent adverse reaction to ROCURONIUM 50 IV BIOTECH consists of an extension of the medicine's pharmacological action beyond the time period required. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea (see section 4.4).

Myopathy:
Myopathy has been reported in the ICU after the use of ROCURONIUM 50 IV BIOTECH in combination with corticosteroids (see section 4.4).

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 for induction. Clinical study reports mention pain on injection 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.

Paediatric population
A meta-analysis of 11 clinical studies in paediatric patients (n=704) with rocuronium bromide as contained in ROCORONIUM 50 IV BIOTECH (up to 1 mg/kg) showed that tachycardia was identified as an adverse medicine 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose
The acute effects of an overdose are apnoea and prolonged paralysis.
In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive controlled ventilation and sedation until spontaneous recovery. At the start of spontaneous recovery acetyl-cholinesterase inhibitors (pyridostigmine, neostigmine, edrophonium) should be administered in adequate doses. If these medicines fail to reverse the neuromuscular block of ROCURONIUM 50 IV BIOTECH, ventilation should be continued until spontaneous breathing is restored. Repeated doses of acetylcholinesterase inhibitors can be dangerous.
Further treatment should be supportive and symptomatic.
In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED90 135 mg/kg was administered.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamics properties
Pharmacological category and class: A.17.1 Peripherally acting muscle relaxants.
Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents.
ATC code: M03AC09.

Mechanism of action:
Rocuronium is a non-depolarising neuromuscular blocking medicine. It acts by competing for nicotinic acetylcholine (ACh) receptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

Pharmacodynamic effects:
The ED90 (dose required to produce 90 % depression of the twitch response of the thumb to stimulation of the ulnar nerve) during balanced anaesthesia is approximately 0,3 mg/kg. The ED90 in infants is lower than in adults and children (0,25; 0,35 and 0,40 respectively).
The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg/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 0,6 mg/kg rocuronium bromide is 14 minutes.
With lower dosages of 0,3 to 0,45 mg/kg rocuronium bromide (1 to 1,5 xED90), onset of action is slower and duration of action is shorter (13 and 26 minutes). With high doses of 2 mg/kg the clinical duration is 110 minutes.

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 an increase in heart rate up to 9 %, and an increase in mean arterial blood pressure up to 16 % from the control values.

Reversal of muscle relaxation:
Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T2 or at the first signs of clinical recovery, antagonises the action of rocuronium bromide.

Paediatric population
The 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.

5.2 Pharmacokinetics properties
Absorption and distribution:
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 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/min.

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 variability between patients is found in controlled clinical studies, related to nature 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.

Elimination:
Rocuronium is excreted in urine and bile. Excretion in urine approaches 40 % within 12 to 24 hours. After injection of a radio-labelled dose of rocuronium bromide, excretion of the radio-labelled is on average 47 % in urine and 43 % in faeces after 9 days.
Approximately 50 % is recovered as the parent compound.

Special populations
Elderly patients and patients with renal or hepatic disease:
The plasma clearance in elderly patients and in patients with renal dysfunction was reduced, in most studies however without reaching the level of statistical significance. In patients with hepatic disease, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 mL/kg/min.

Paediatric population
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 towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

5.3 Preclinical safety data
Not applicable.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Sodium acetate (E262) (for pH adjustment)
Sodium chloride
Glacial acetic acid (E260) (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injection.
No preservative has been added.

6.2 Incompatibilities
Physical incompatibilities has been documented for ROCURONIUM 50 IV BIOTECH when added to solutions containing the following medicines: amphotericin, amoxycillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. ROCURONIUM 50 IV BIOTECH is also incompatible with Intralipid®.
ROCURONIUM 50 IV BIOTECH must not be mixed with other medicines except those mentioned in section 6.6.
ROCURONIUM 50 IV BIOTECH 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 50 IV BIOTECH and medicines, for which incompatibility with ROCURONIUM 50 IV BIOTECH has been demonstrated, or for which compatibility with ROCURONIUM 50 IV BIOTECH has not been established.

6.3 Shelf life
ROCURONIUM 50 IV BIOTECH has a shelf life of 2 years (24 months), provided it is stored under the prescribed conditions (see section 6.4).
Since ROCURONIUM 50 IV BIOTECH does not contain a preservative, the solution should be used immediately after opening the vial and any unused solution should be discarded.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
Store in a refrigerator (2 to 8 °C). Do not freeze. Protect from light.
Keep vial in outer carton until required for use.

6.5 Nature and contents of container
ROCURONIUM 50 IV BIOTECH is filled into a 5 mL clear Type I glass vial with 13 mm bromobutyl rubber stopper and aluminium flip-off seal with green colour button.
Pack size: 12 x 5 mL, 10 x 5 mL or 1 x 5 mL vials per outer carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling
Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0,5 mg/mL and 2 mg/mL ROCURONIUM 50 IV BIOTECH has been shown to be compatible with: 0,9 % NaCl, 5 % dextrose, 5 % dextrose in saline, sterile water for injection and Lactated Ringer's.

ROCURONIUM 50 IV BIOTECH can be injected into the intravenous line of a running infusion with solution of the following intravenous medicines: epinephrine (adrenaline), alcuronium, alfentanil, aminophylline, atracurium, atropine, ceftazidime, cefuroxime, cimetidine, clemastine, clindamycin, clomethiazole, clonazepam, clonidine, danaparoid, dobutamine, dopamine, dehydrobenzperidol, ephedrine, ergometrine, esmolol, etomidate, fentanyl, flucytosine, gentamycin, glucose 40 %, glycopyrronium bromide, heparin, isoprenaline, ketamine, labetalol, lignocaine, mannitol 20 %, metoclopramide, metoprolol, metronidazole, midazolam, milrinone, morphine, nifedipine, nimodipine, nitroglycerine, norepinephrine (noradrenaline), oxytocin, pancuronium, pethidine, pipecuronium, potassium chloride, promethazine, propranolol, propofol, ranitidine, salbutamol, sodium carbonate, sodium nitroprusside, sufentanil, suxamethonium, vecuronium and verapamil.

Administration should begin immediately after mixing, and should be completed within 24 hours.
For single use only. Unused solutions should be discarded.
Do not use ROCURONIUM 50 IV BIOTECH if you notice that the solution is not clear or free from particles.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION
Biotech Laboratories (Pty) Ltd.
Ground Floor, Block K West, Central Park
400 16th Road, Randjespark, Halfway House
Midrand, 1685
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8. REGISTRATION NUMBER
44/17.1/0188

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTORISATION
Date of registration: 25 November 2016

10. DATE OF REVISION OF THE TEXT
27 January 2025