SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROCURONIUM 50 IV BIOTECH 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.

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 - 65 years.

4.2 Posology and method of administration

Posology

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 agents 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).

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 ICU.

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 (TOF) of 1 or less must be obtained prior to intubation. Disappearance of the TOF will correspond to optimal intubation conditions.

Maintenance dosing

The recommended maintenance dose is 0,15 mg ROCURONIUM 50 IV BIOTECH per kg body mass. 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 TOF stimulation are present.

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 (IV) 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 – 0,6 $mg.kg^{-1}.h^{-1}$ and under inhalation anaesthesia the infusion rate ranges from 0,3 - 0,4 $mg.kg^{-1}.h^{-1}$. 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 agents 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 agent should be avoided.

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

Dosing in paediatric patients

Children (1 - 14 years) and infants (1 - 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.

Dosing in overweight and obese patients

When used in overweight or obese patients (defined as patients with a body weight of 30 % or more above ideal body 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.

Dosing to facilitate mechanical ventilation

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 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 - 90 % (1 to 2 twitches to TOF stimulation) in adult patients is 0,3 - 0,6 $mg.kg^{-1}.h^{-1}$ during the first hour of administration, which will need to be decreased during the following 6 - 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 - 0,5 $mg.kg^{-1}.h^{-1}$ 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 ICU, the time to recovery of the TOF 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 T_2 to TOF stimulation and recovery of the TOF ration 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. Spontaneous respiration is only recommended when the TOF is 0,9.

Special populations

For dosing in overweight and obese patients during surgical procedures, see Surgical procedures.

Paediatric population

For dosing in paediatric patients during surgical procedures, see Surgical procedures.

Method of administration

ROCURONIUM 50 IV BIOTECH is administered IV either as a bolus injection or as a continuous infusion.

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, Lactated Ringer's.

Administration should begin immediately after mixing, and should be completed within 24 hours. Unused solutions should be discarded.

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.

Also refer to incompatibilities under section 6.2.

4.3 Contraindications

ROCURONIUM 50 IV BIOTECH is contraindicated in:

- Patients hypersensitive to rocuronium or the bromide ion.
- Neonates (0 - 1 month).
- ICU circumstances for the facilitation of mechanical ventilation in paediatric and geriatric patients.
- Pregnancy and lactation.

- Caesarean section.

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.

Severe anaphylactic reactions to rocuronium, as in ROCURONIUM 50 IV BIOTECH have been reported. These reactions have, in some cases been fatal. Due to the possible severity of these reactions, it should be assumed that they may occur and the necessary precautions should be taken. Cross-sensitivity reactions to similar neuromuscular blocking agent may occur. Since ROCURONIUM 50 IV BIOTECH is capable of inducing histamine release both locally at the site of injection and systemically, possible occurrence of itching and erythematous reactions at the site of injection and/or general generalised histaminic-release reactions should be taken into consideration when administering ROCURONIUM 50 IV BIOTECH. The most frequent reaction to ROCURONIUM 50 IV BIOTECH 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.

Neuromuscular blocking agents are known to be capable of inducing histamine release both locally and systemically. This should be taken into consideration when administering ROCURONIUM 50 IV BIOTECH due to the possible occurrence of itching and erythematous reactions at the injection site, and/ or general anaphylactoid reaction (bronchospasm and cardiovascular changes).

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 with TOF of 0,9 or above.

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, especially in those cases where residual neuromuscular blockade is more likely to occur (see section 4.2).

Muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced doctors who are familiar with their actions and with appropriate neuromuscular monitoring techniques.

Adequate analgesia and sedation should be given to the patients.

Prolonged paralysis and/ or skeletal muscle weakness has been noted following long-term treatment of muscle relaxants in the ICU. It is strongly recommended that neuromuscular transmission be monitored throughout the treatment period in order to help preclude possible prolongation of neuromuscular block and/ or overdosage.

ROCURONIUM 50 IV BIOTECH is always used concurrently with other agents and malignant hyperthermia can occur during anaesthesia (even in the absence of known triggering agents). Therefore, the doctor should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of ROCURONIUM 50 IV BIOTECH.

Prolonged circulation time:

Conditions (such as cardiovascular disease, old age, and oedematous state resulting in an increased volume of distribution) that prolongs circulation time, may contribute to a slower onset of action.

Hepatic and/or biliary tract disease and renal failure:

Special caution is advised when administering ROCURONIUM 50 IV BIOTECH to patients with hepatic and/

or biliary diseases and/or renal failure. As ROCURONIUM 50 IV BIOTECH is excreted in urine and bile, prolongation of action has been observed with doses of 0,6 mg ROCURONIUM 50 IV BIOTECH per kg body mass.

Hypothermia:

The neuromuscular blocking effect of ROCURONIUM 50 IV BIOTECH is increased and prolonged during surgery under hypothermic conditions.

Burns:

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

Neuromuscular disease:

Extreme caution is advised in patients with neuromuscular disease or after poliomyelitis, as the response to neuromuscular blocking agents can be altered in these cases. The magnitude and direction of the alteration may vary widely. Small doses of ROCURONIUM 50 IV BIOTECH in patients with myasthenia gravis or with the myasthenic syndrome, can have profound effects. ROCURONIUM 50 IV BIOTECH should be titrated to the response.

Obesity:

A prolonged duration and prolonged spontaneous recovery in obese patients are exhibited when the administered doses are calculated on actual body mass.

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

Hypokalaemia, hypermagnesaemia, hypocalcaemia, hypoproteinaemia, dehydration, acidosis, hypercapnoea, cachexia. Altered blood pH, dehydration and severe electrolyte disturbances should therefore be corrected when possible.

4.5 Interaction with other medicines and other forms of interaction

The neuromuscular blocking activity of aminoglycosides, bacitracin, colistin, polymyxins, sodium colistimethate, tetracyclines or vancomycin may be additive to that of ROCURONIUM 50 IV BIOTECH.

Concurrent administration of inhalation halogenated anaesthetics with ROCURONIUM 50 IV BIOTECH, results in additive neuromuscular blocking activity. The infusion rate of ROCURONIUM 50 IV BIOTECH should be reduced by 40 % when used concurrently with enflurane and isoflurane.

The following agents will also enhance the neuromuscular blockade of ROCURONIUM 50 IV BIOTECH:

- Large doses magnesium salt
- High doses of thiopentone, methohexitone, ketamine, fentanyl, etomidate and propofol
- Other antibiotics (lincosamide, polypeptide antibiotics, acylaminopenicillin, high doses metronidazole)
- Diuretics, thiamine, mono-amine oxidase (MAO) inhibiting agents, quinidine, protamine, α-adrenergic blocking agents, calcium channel blocking agents and lithium salts.

Variable effects:

- Administration of other non-depolarising neuromuscular blocking agents 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 agent used.
- Suxamethonium given after administration given after administration of ROCURONIUM 50 IV BIOTECH may produce potentiation or attenuation of neuromuscular blocking effects of ROCURONIUM 50 IV BIOTECH.

A decrease in the neuromuscular blockade of ROCURONIUM 50 IV BIOTECH occurs when the following agents are used concurrently:

- Prior chronic treatment with corticosteroids, phenytoin or carbamazepine.

- Theophylline, potassium chloride, calcium chloride, norepinephrine (noradrenaline) and azathioprine.
- Aminopyridine derivatives, pyridostigmine, edrophonium and neostigmine.
- Protease inhibitors.

4.6 Fertility, pregnancy and lactation

Pregnancy

ROCURONIUM 50 IV BIOTECH is contraindicated during pregnancy (see section 4.3).

Breastfeeding

ROCURONIUM 50 IV BIOTECH is contraindicated during breastfeeding.

4.7 Effects on ability to drive and use machines

The use of potentially dangerous machinery or driving a car is not recommended within 24 hours after the full recovery from the neuromuscular blocking action.

4.8 Undesirable effects

Immune system disorders

Less frequent: Anaphylactic reaction; anaphylactic shock; anaphylactoid reaction; anaphylactoid shock; hypersensitivity; angioedema; increase in mean plasma histamine.

Nervous system disorders

Less frequent: Flaccid paralysis.

Cardiac disorders

Less frequent: Dysrhythmia; tachycardia.

Frequency unknown: Kounis syndrome

Vascular disorders

Less frequent: Hypertension; hypotension; flushing; circulatory collapse and shock

Respiratory, thoracic and mediastinal disorders

Less frequent: Bronchospasm; wheezing.

Skin and subcutaneous tissue disorders

Less frequent: Pruritus; angioneurotic oedema; urticaria; skin rash; erythematous rash.

General disorders and administrative site conditions

Frequent: Pain at injection site.

Less frequent: Injection site reaction; facial oedema; medicine ineffective; medicine effect/therapeutic response decrease or increase.

Gastrointestinal disorders

Less frequent: Hiccups; nausea; vomiting.

Musculoskeletal disorders

Frequent: Muscle weakness, myopathy

Less frequent: Steroid myopathy.

Injury, poisoning and procedural complications

Less frequent: Prolonged neuromuscular block, delayed recovery from anaesthesia, airway complication of anaesthesia.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued

monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to SAHPRA via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

The acute effects of an overdose are apnoea and prolonged paralysis.

The patient should continue to receive controlled ventilation and sedation until spontaneous recovery. Acetylcholinesterase inhibitors (pyridostigmine, neostigmine, edrophonium) should be administered in adequate doses. If these agents 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties:

Pharmacotherapeutic group: A.17.1 Peripherally acting muscle relaxants.

Rocuronium is a non-depolarising neuromuscular blocking agent. It acts by binding with the nicotinic acetylcholine receptor at the motor end-plate.

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 0,3 mg per body mass.

The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg per kg body mass 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 - 75 % (recovery index) after a bolus dose of 0,6 mg rocuronium bromide per kg body mass is 14 minutes. With lower dosages of 0,3 - 0,45 rocuronium bromide per kg body mass (1 - 1,5 xED_{90}), onset of action is slower and duration of action is shorter (13 and 26 minutes).

5.2 Pharmacokinetics properties:

After IV 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 % Cl) elimination half-life is 73 (66 - 80) minutes; the (apparent) volume of distribution at steady state conditions is 203 (193 - 214) $ml.kg^{-1}$ and plasma clearance is 3,7 (3,5 - 3,9) $mL.kg^{-1}.min^{-1}$. 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 diseases, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 $mL.kg^{-1}.min^{-1}$. 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 extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean ($_{\pm}$SD) elimination half-life of 21,5 (± 3,3) hours, a (apparent) volume of distribution at steady state of 1,5 (± 0,8) $L.kg^{-1}$ and a plasma clearance of 2,1 (± 0,8) $mL.kg^{-1}.min^{-1}$ was found.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium acetate

Sodium chloride

Water for injection

6.2 Incompatibilities

Physical incompatibilities have been noted for ROCURONIUM 50 IV BIOTECH when added to solutions containing the following: 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®.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store between 2-8 °C. Protect from light.

Do not freeze.

Keep vial in outer carton until required for use.

Since ROCURONIUM 50 IV BIOTECH does not contain any preservative, it should be used immediately after first opening the container and any unused solution should be discarded.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

ROCURONIUM 50 IV BIOTECH is filled into a clear Type I glass vials with dark grey rubber stopper and aluminium cap. 12 x 5 mL, 10 x 5 mL or 1 x 5 mL vials per outer carton.

7 HOLDER OF CERTIFICATE OF REGISTRATION

BIOTECH LABORATORIES (PTY) LTD.

Block K West, Central Park

400 16th Road, Halfway House

Midrand, 1685

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

18 March 2021