SCHEDULING STATUS
S4

PROPRIETARY NAME AND DOSAGE FORM
ROCURONIUM 50 IV BIOTECH (injection)

COMPOSITION
ROCURONIUM 50 IV BIOTECH: Each 5 ml vial contains 50 mg rocuronium bromide.
Inactive ingredients: Sodium acetate, sodium chloride, glacial acetic acid, sodium hydroxide and water for injection.

PHARMACOLOGICAL CLASSIFICATION
A.17.1 Peripherally acting muscle relaxants.

PHARMACOLOGICAL ACTION
Pharmacodynamics:
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).

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 % CI) 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 (± 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.

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

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 18 – 65 years of age.

CONTRA-INDICATIONS
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.

WARNINGS and SPECIAL PRECAUTIONS

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 train-of-four (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 "Dosage and Directions for use").

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 of 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.

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.

INTERACTIONS
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 of magnesium salt
- High doses of thiopentone, methohexitone, ketamine, fentanyl, etomidate and propofol
- Other antibiotics (linacosamide, 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 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.

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®.

PREGNANCY AND LACTATION
ROCURONIUM 50 IV BIOTECH is contraindicated during pregnancy and lactation (see "Contraindications").

DOSAGE AND DIRECTIONS FOR USE
Dosage
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 "Interactions").

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 (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 train-of-four (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 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 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 – 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

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 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 – 90 % (1 to 2 twitches to train-of-four (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 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 T_1 to train-of-four stimulation and recovery of the train-of-four 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.

Administration
ROCURONIUM 50 IV BIOTECH is administered intravenously 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 header under "Interaction" section.

SIDE EFFECTS
Immune system disorders
Less frequent: Anaphylactic reaction; hypersensitivity; angioedema; increase in mean plasma histamine.

Cardiac disorders
Less frequent: Dysrhythmia; tachycardia.

Vascular disorders
Less frequent: Hypertension; hypotension; flushing.

Respiratory, thoracic and mediastinal disorders
Less frequent: Bronchospasm; wheezing.

Skin and subcutaneous tissue disorders
Less frequent: Pruritus; skin rash; erythematous rash.

General disorders and administrative site conditions
Frequent: Pain at injection site.
Less frequent: Swelling at injection site; facial oedema.

Gastrointestinal disorders
Less frequent: Hiccups; nausea; vomiting.

Musculoskeletal disorders
Frequent: Muscle weakness, myopathy; injury, poisoning and procedural complications.
Less frequent: Prolonged neuromuscular block, delayed recovery from anaesthesia, airway complication of anaesthesia.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT
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.

IDENTIFICATION
A clear, colourless to yellow or orange solution.

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

STORAGE INSTRUCTIONS
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.

REGISTRATION NUMBER
44/17.1/0188

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EIENDOMSNAAM EN DOSEERVORM
ROCURONIUM 50 IV BIOTECH (inspuiting)

SAMESTELLING
ROCURONIUM 50 IV BIOTECH: Elke 5 ml flessie bevat 50 mg rokuroniumbromied.
Onaktiewe bestanddele: Natriumasetaat, natriumchloried , ysasynsuur, natriumhidroksied en water vir inspuiting.

FARMAKOLOGIESE KLASSIFIKASIE
A.17.1 Perifeer-werkende spierontspanners.

FARMAKOLOGIESE WERKING
Farmakodinamika:
Rokuroniumbromied is 'n nie-depolariserende neuromuskulêre blokkeermiddel. Dit werk deur aan die nikotiniese asetielcholienreseptore by die motoriese eindplaat te bind.
Die ED_{90} (dosis wat vereis word om 90 %-onderdrukking van die spiertrekkingsreaksie van die duim op stimulasie van die ulnarissenuwee te produseer) gedurende gebalanseerde anestesie, is ongeveer 0,3 mg/kg rokuroniumbromied. Die kliniese duur (die duur tot spontane herstel tot 25 % van kontrole-spiertrekkingshoogte) met 0,6 mg/kg rokuroniumbromied is 30 tot 40 minute. Die totale duur (tyd tot spontane herstel van 90 % kontrole-spiertrekkingshoogte) is 50 minute. Die gemiddelde tyd tot spontane herstel van spiertrekkingsreaksie vanaf 25 tot 75 % (herstelindeks) na 'n bolusdosis van 0,6 mg rokoroniumbromied per kg liggaamsmassa is 14 minute. Met laer doserings van 0,3 – 0,45 rokuroniumbromied per kg liggaamsmassa (1 – 1,5 xED_{90}) is die aanvang van werking stadiger en die duur van werking korter (13 tot 26 minute).

Farmakokinetika:
Na intraveneuse toediening van 'n enkele bolusdosis van rokuroniumbromied, loop die tyd van plasmakonsentrasie in drie eksponensiële fases. In normale volwassenes is die gemiddelde (95 % CI) uitskeidingshalfleeftyd 73 (66 - 80) minute; is die (oënskynlike) volume van verspreiding teen 'n bestendige staat van 203 (193 tot 214) ml.kg^{-1} en is plasma-opruiming 3,7 (3,5 – 3,9) ml.kg^{-1}.min^{-1}. Die plasmaopruiming in geriatriese pasiënte en in pasiënte met renale disfunksie was in die meeste studies minder maar sonder om 'n vlak van statistiese betekenis te bereik. In pasiënte met hepatiese siekte word die gemiddelde uitskeidingshalfleeftyd met 30 minute verleng en word die gemiddelde plasma-opruiming met 1 ml.kg^{-1}.min^{-1} verminder.
Waar dit as 'n aanhoudende infusie toegedien word om meganiese ventilasie vir 20 uur of langer te bewerkstellig, word die gemiddelde uitskeidingshalfleeftyd en die gemiddelde (oënskynlike) volume van verspreiding teen bestendige staat verhoog.

'n Groot veranderlikheid tussen pasiënte is in gekontroleerde kliniese studies teëgekom, verwant aan die aard en omvang van (veelvoudige) orgaanversaking en individuele pasiëntkenmerke. In pasiënte met veelvoudige orgaanversaking is 'n gemiddelde ($\pm$SD) uitskeidingshalfleeftyd van 21,5 ($\pm$ 3,3) uur, 'n (oënskynlike) volume van verspreiding teen bestendige staat van 1,5 ($\pm$ 0,8) ml.kg^{-1} en 'n plasma-opruiming van 2,1 ($\pm$ 0,8) ml.kg^{-1}.min^{-1} bevind.

Rokuronium word in die urien en gal uitgeskei. Uitskeiding in urien nader 40 % binne 12 – 24 uur. Na inspuiting van die radio-gemerkte dosis van rokuroniumbromied, word rokuronium gemiddeld 47 % in die uriene en 43 % in ontlasting na 9 dae uitgeskei. Ongeveer 50 % word as die moederverbinding verhaal.

INDIKASIES
ROCURONIUM 50 IV BIOTECH word aangewys as 'n byvoeging tot:
- algemene anestesie om trageale intubasie gedurende roetine en vinnige opvolginduksie te fasiliteer, en om skeletale spierontspanning gedurende chirurgie te bewerkstellig.
- die Intensiewe Sorgeenheid om intubasie en meganiese ventilasie vir tot 3 dae in volwassenes van 18 tot 65 jaar te vergemaklik.

KONTRAINDIKASIES
ROCURONIUM 50 IV BIOTECH is teenaangedui in:
- Pasiënte wat hipersensitief/allergies is vir rokuronium of vir die bromiedioon.
- Pasgeborenes (0 – 1 maand).
- Intensiewe Sorg omstandighede vir die fasilitering van meganiese ventilasie in pediatriese en geriatriese pasiënte.
- Swangerskap en borsvoeding.
- 'n Keisersnit.

WAARSKUWINGS en SPESIALE VOORSORGMAATREËLS

Aangesien ROCURONIUM 50 IV BIOTECH verlamming van die respiratoriese spiere veroorsaak, is ventilasie-ondersteuning verpligtend vir pasiënte wat met ROCURONIUM 50 IV BIOTECH behandel word, totdat toereikende spontane asemhaling hervat word. Dit is belangrik om bedag te wees op intubasieprobleme, veral waar dit as deel van 'n vinnige opvolginduksie-tegniek gebruik word.

Hewige anafilaktiese reaksies teenoor rokuronium, soos in ROCURONIUM 50 IV BIOTECH is aangemeld. Hierdie reaksies was in sommige gevalle noodlottig gewees. As gevolg van die moontlike erns van hierdie reaksies, moet dit aanvaar word dat hulle kan ontstaan en die nodige voorsorgmaatreëls moet getref word. Kruis-sensitiwiteitsreaksies teenoor soortgelyke neuromuskulêre blokkeringsmiddels kan ontstaan. Aangesien ROCURONIUM 50 IV BIOTECH daarvoor bekend is dat dit histamien-vrystelling kan induseer, beide plaaslik, by die plek van inspuiting en sistemies, moet die moontlike voorkoms van jeuk en eritemateuse reaksies by die plek van die inspuiting en/of veralgemeende histaminoïed- (anafilaktoïed) reaksies altyd in aanmerking geneem word wanneer ROCURONIUM 50 IV BIOTECH toegedien word. Die mees algemene reaksie teenoor ROCURONIUM 50 IV BIOTECH bestaan uit 'n verlenging van die farmakologiese werking daarvan, buite die tydperk wat nodig is. Die reaksies kan wissel van skeletspierswakheid na diepgaande en langdurige skeletspier verlamming wat respiratoriese ontoereikendheid en apnee tot gevolg kan hê.

Neuromuskulêre blokkeringsmiddels is daarvoor bekend dat hulle histamien-vrystelling kan induseer, beide plaaslik, by die plek van inspuiting en sistemies. Die moontlike voorkoms van jeuk en eritemateuse reaksies by die plek van die inspuiting en/of veralgemeende anafilaktoïede reaksies (brongospasma en kardiovaskulêre veranderings) moet altyd in aanmerking geneem word wanneer ROCURONIUM 50 IV BIOTECH toegedien word.

Ten einde komplikasies as gevolg van oorblywende neuromuskulêre blokkade te voorkom, word dit aanbeveel om eers te ekstubeer nadat die pasiënt voldoende herstel het van neuromuskulêre blok met 'n reeks-van-vier-stimulus (TOF) van 0,9 of hoër. Ander faktore wat residuele kurarisasie na ekstubasie in die post-operatiewe fase kan veroorsaak (soos medisyne-interaksies of die pasiënt se toestand) moet ook in aanmerking geneem word, veral in gevalle waar residuele kurarisasie meer waarskynlik is om in te tree (sien "Dosis- en Gebruiksaanwysings").

Spierverslappers moet getitreer word na gelang van individuele pasiënte deur of onder die toesig van ervare dokters wat vertroud is met die werking daarvan en met geskikte neuromuskulêre moniteringstegnieke.

Voldoende verdowing en sedasie moet aan hierdie pasiënte gegee word.
Na lantermyngebruik van spierverslappers in die Intensiewe Sorgeenheid, is verlengde verlamming en/of skeletale spierswakheid al opgemerk. Ten einde die moontlike verlenging van neuromuskulêre blok en/of oordosering uit te skakel, word daar ten sterkste aanbeveel dat neuromuskulêre transmissie dwarsdeur die gebruik gemoniteer word.

ROCURONIUM 50 IV BIOTECH word altyd tesame met ander middels gebruik en maligne hipertermie kan voorkom tydens anestesie (selfs in die afwesigheid van bekende middels wat aanleiding kan gee daartoe). Daarom moet die dokter bekend wees met die vroeë tekens, bevestigende diagnose en behandeling van maligne hipertermie voor die aanvang van enige narkose.

Die volgende toestande kan die farmakokinetika en/of farmakodinamika van ROCURONIUM 50 IV BIOTECH beïnvloed.

Verlengde sirkulasietyd:
Toestande (soos kardiovaskulêre siekte, bejaarde ouderdom en edemateuse toestande wat 'n verhoogde volume van verspreiding tot gevolg het) wat sirkulasietyd verleng, mag bydra tot 'n stadiger aanvang van werking.

Hepatiese en/of bilière kanaalsiekte en nierversaking:
Spesiale voorsorg word aanbeveel wanneer ROCURONIUM IV BIOTECH toegedien word aan pasiënte met hepatise en/of billière kanaalsiekte en/of nierversaking. Omdat ROCURONIUM 50 IV BIOTECH in die urien en gal uitgeskei word, is verlengde werking waargeneem met dosisse van 0,6 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa.

Hipotermie:
Die neuromuskulêre blokkerende uitwerking van ROCURONIUM 50 IV BIOTECH word verhoog en verleng gedurende chirurgie onder hipotermiese kondisies.

Brandwonde:
Dit is bekend dat pasiënte met brandwonde weerstand teen nie-depolariserende neuromuskulêre blokkeermiddels ontwikkel. Daar word aanbeveel dat die dosis volgens die reaksie daarop aangepas word.

Neuromuskulêre siekte:
Uiterse sorg word aanbeveel in die behandeling van pasiënte met neuromuskulêre siekte of na poliomiëlitis aangesien reaksie op neuromuskulêre blokkeermiddels in hierdie gevalle aansienlik verander mag word. Die omvang en rigting van hierdie verandering mag aansienlike uiteenlopende gevolge hê. Klein dosisse van ROCURONIUM 50 IV BIOTECH wat toegedien word aan pasiënte met *myasthenia gravis* of met die miasteniese sindroom, kan ernstige gevolge hê. ROCURONIUM 50 IV BIOTECH moet volgens die reaksie getitreer word.

Vetsug:
Wanneer die toegediende dosisse uitgewerk word volgens die pasiënt se werklike liggaamsmassa, mag dit 'n uitgerekte duur en verlengde spontane herstel tot gevolg hê in vetsug pasiënte

Toestande wat die uitwerking van ROCURONIUM 50 IV BIOTECH verhoog:
Hipokalemie, hipermagnesemie, hipoproteïenemie, dehidrasie, asidose, hiperkapnee, kageksie. Verandering in bloed pH, dehidrasie en erge elektrolietversteurings moet dus waar moontlik reggestel word.

Uitwerking op die vermoë om te bestuur en die gebruik van masjienerie
Die gebruik van moontlike gevaarlike masjienerie of die bestuur van 'n motor word nie aanbeveel binne 24 uur na die volledige herstel van die neuromuskulêre blokkerende werking nie.

INTERAKSIE
Die neuromuskulêre blokkeringsaktiwiteit van anminoglikosiede, bakitrasien, kolistien, polimiksien, natrium kolistimetaat, tetrasiklien of vankomisien mag aanvullend wees tot die effek van ROCURONIUM 50 IV BIOTECH.

Gelyktydige toediening van vlugtige halogeenanestetikum met ROCURONIUM 50 IV BIOTECH, het 'n verhoging in neuromuskulêre blokkeringsaktiwiteit tot gevolg. Die infusiedosis van Rokuronium 50 IV BIOTECH moet verminder word deur 40 % wanneer gelyktydig gebruik word met enfluraan en isofluraan.

Die volgende middels sal ook die neuromuskulêre blokkade van ROCURONIUM 50 IV BIOTECH versterk:
- Groot dosisse van magnesiumsout
- Hoë dosisse van tiopentoon, metoheksitoon, ketamien, fentaniel, etomidaat
- Ander antibiotikum (linakosamied, polipeptied antibiotika, asielaminopenisillien, hoë dosisse metronidasool)
- Diuretika, tiamien, mono-amien oksidase inhiberingsmiddels (MAOI), quinidien, protoamien, α-adrenergiese blokkeringsmiddels, kalsiumkanaal blokkeringsmiddels en litium sout.

Veranderlike uitwerking:
- Toediening van ander nie-depolariserende neuromuskulêre blokkeermiddels in kombinasie met ROCURONIUM 50 IV BIOTECH mag verswakking of versterking van die neuromuskulêre blok teweegbring, afhangende van die volgorde van toediening en die neuromuskulêre blokkeermiddels wat gebruik word.
- Suksametonium wat gegee word na afloop van toediening van ROCURONIUM 50 IV BIOTECH, mag versterking of verswakking van die neuromuskulêre blokkerende effek van ROCURONIUM 50 IV BIOTECH tot gevolg hê.

'n Afname in die neuromuskulêre blokkering van ROCURONIUM 50 IV BIOTECH vind plaas wanneer die volgende middels gelyktydig gebruik word:
- Vorige chroniese behandeling met kortikosteroïede, fenitoien of karbamasepien.
- Teofillien, kaliumchloried, kalsiumchloried, norepinefrien (noradrenalien) en azatioprien.
- Aminopiridien derivate, piridostigmien, edrofonium en neostigmien.
- Protease inhibeerders.

Onverenigbaarheid
Fisiese onverenigbaarhede is opgemerk in ROCURONIUM 50 IV BIOTECH wanneer dit by oplossings gevoeg word wat die volgende bevat: amfoterisien, amoksisillien, azatioprien, kafasolien, kloxasillien, deksametasoon, diasepam, enoximoon, eritromisien, famotidien, furosemied, hidrokortisoon, natrium suksinaat, insulien, metoheksital, metielprednisoloon, prednisoloon, natrium suksinaat, tiopental, trimetoprim en vankomisien. ROCURONIUM 50 IV BIOTECH is ook onverenigbaar met Intralipid®.

SWANGERSKAP EN BORSVOEDING
ROCURONIUM 50 IV BIOTECH word nie aangedui vir gebruik gedurende swangerskap en borsvoeding nie (sien "Kontraindikasies").

DOSIS EN GEBRUIKSAANWYSINGS
Dosering
Die dosis van ROCURONIUM 50 IV BIOTECH moet in elke pasiënt geïndividualiseer word.

Die volgende aspekte moet in ag geneem word wanneer die dosis vasgestel word:
- metode van anestesie en die verwagte duur van die chirurgie,
- die sedasiemetode en die verwagte duur van meganiese ventilasie,
- die moontlike interaksie met ander medikasie wat gelyktydig toegedien word,
- die toestand van die pasiënt.

Die gebruik van 'n gepaste neuromuskulêre moniteringstegniek word aanbeveel vir die evaluering van neuromuskulêre blok en herstel.

Inhallasie-anestetika versterk die neuromuskulêre blokkerende uitwerking van ROCURONIUM 50 IV BIOTECH. Versterking word egter eers klinies relevant gedurende die anestesie-proses, wanneer die vlugtige middels die weefselkonsentrasies bereik het wat vir hierdie interaksie vereis word. Gevolglik moet aanpassings met ROCURONIUM 50 IV BIOTECH gemaak word deur middel van:
- die toediening van kleiner instandhoudingsdosisse teen minder frekwente tussenposes of
- deur laer infusietempos van ROCURONIUM 50 IV BIOTECH gedurende langer prosedures (langer as 1 uur) onder inhalasie-anestesie te gebruik (sien "Interaksies").

In volwasse pasiënte dien die volgende doseringsaanbevelings as 'n algemene riglyn vir trageale intubasie en spierontspanning vir kort tot langdurige chirurgiese prosedures en vir gebruik in die Intensiewe Sorgeenheid.

Chirurgiese prosedures
Trageale intubasie
Die standard-intubasiedosis gedurende roetine anestesie is 0,6 mg ROCURONIUM 50 IV BIOTECH, waarna genoegsame intubasie-toestande binne 90 sekondes daargestel word.

'n Dosis van 1 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa word aanbeveel vir die fasilitering van trageale intubasie-toestande gedurende vinnige opvolginduksie van anestesie. Teen hierdie dosis word toereikende intubasie-toestande binne 60 sekondes in bykans alle pasiënte bewerkstellig.

'n Spiertrekkingshoogte van 90 % of 'n reeks-van-vier-stimulasie ("TOF") van 1 of minder voor intubasie moet verkry word. Verdwyning van die "TOF" sal ooreenstem met optimale intubasie toestande.

Instandhoudingsdosis
Die voorgestelde instandhoudingsdosis is 0,15 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa. Die instandhoudingsdosis behoort ten beste as 'n bolus toegedien word, wanneer spiertrekkingshoogte herstel het tot 25 % van kontrole-spiertrekkingshoogte, of wanneer 2 – 3 reaksies op reeks-van-vier-stimulasie aanwesig is.

Die werkingsduur van instandhoudingsdosisse van 0,15 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa sal meer onder enfluraan- en isofluraan-anestesie in bejaarde pasiënte, en in pasiënte met lewersiekte en/of niersiekte (ongeveer 20 minute) wees, as in pasiënte sonder inkorting van die funksies van die uitskeidingsorgane onder binneaarse anestesie (ongeveer 13 minute).

Aanhoudende infusie
Indien ROCURONIUM 50 IV BIOTECH deur middel van aanhoudende infusie toegedien word, word aanbeveel dat 'n ladingsdosis van 0,6 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa en wanneer neuromuskulêre blok begin herstel, om toediening deur middel van infusie te begin. Die tempo van infusie moet aangepas word om spiertrekkingsreaksie teen 10 % van die kontrole-spiertrekkingshoogte te handhaaf of om 1 tot 2 reaksies op reeks-van-vier-stimulasie te handhaaf. In volwassenes onder intraveneuse anestesie, wissel die infusietempo wat vereis word om neuromuskulêre blok teen hierdie vlak te handhaaf van 0,3 – 0,6 $mg.kg^{-1}.h^{-1}$ en onder inhalasie-anestesie wissel die infusietempo van 0,3 – 0,4 $mg.kg^{-1}.h^{-1}$. Voortdurende monitering van neuromuskulêre blok word aanbeveel, aangesien die infusietempo-vereistes van pasiënt tot pasiënt en met die anestetiese metode wat gebruik word, kan varieer.

Omkeer van spierontspanning
Na afloop van die chirurgiese prosedure waar ROCURONIUM 50 IV BIOTECH toegedien is word anti-cholienesterase middels soos neostigmien, piridostigmien of edrofonium gebruik om die duur van kompeterende neuromuskulêre blokkade te verminder of om te keer toegedien. In Muskariniese antagonis (atropien of glikopirrolaat) word gelyktydig gebruik om stimulasie van muskariniese reseptore te voorkom en om sodoende 'n verlangsaming van die hartklop te vermy.

Toediening van sugammadex ('n cheleermiddel spesifiek vir rokuronium en vekuronium) by dosisse van > 2 mg / kg wat staat is om neuromuskulêre blokkade van ROCURONIUM 50 IV BIOTECH binne 3 minute om te keer. Sugammadex opruiming word aansienlik verminder in pasiënte met ingekorte nierfunksie, en toediening van hierdie middel behoort vermy te word.

Die reeks-van-vier-stimulasie telling behoort ten minste 3 te wees alvorens 'n neuromuskulêre antagonis toegedien word.

Die reeks-van-vier-stimulasie telling moet verkieslik gedoen word met 'n moniteringstoestel.

Dosering in pediatriese pasiënte
Kinders (1 – 4 jaar) en babas (1 – 12 maande) onder halotaan-anestesie openbaar soortgelyke sensitiwiteit teenoor ROCURONIUM 50 IV BIOTECH as volwassenes. Kliniese duur is korter in kinders as in volwassenes.

Dosering in oorgewig- en vetsugtige pasiënte
Wanneer dit in oorgewig- of vetsugtige pasiënte (gedefinieer as pasiënte met 'n liggaamsmasssa van 30 % of meer bokant ideale liggaamsmassa) gebruik word, moet dosisse verminder word met inagneming van ideale liggaamsgewig.

Intensiewe sorg prosedures
Trageale intubasie
Vir trageale intubasie moet dieselfde dosisse gebruik word as wat hierbo onder chirurgiese prosedures beskryf word.

Dosering om meganiese ventilasie te fasiliteer
Die gebruik van 'n aanvanklike ladingsdosis van 0,6 mg ROCURONIUM 50 IV BIOTECH per kg liggaamsmassa word aanbeveel, gevolg deur aanhoudende infusie sodra spiertrekkingshoogte tot 10 % herstel, of tot herverskyning van 1 – 2 spiertrekkings op reeks-van-vier-stimulasie. Dosering moet altyd getitreer word na gelang van uitwerking op die individuele pasiënt. Die aanbevole aanvanklike infusietempo vir die instandhouding van 'n neuromuskulêre blok van 80 – 90 % (1 tot 2 spiertrekkings op reeks-van-vier-stimulasie) in volwasse pasiënte is 0,3 – 0,6 $mg.kg^{-1}.h^{-1}$ gedurende die eerste uur van toediening, wat gedurende die daaropvolgende 6 – 12 uur volgens individuele reaksie verminder moet word.

Daarna bly die individuele dosisvereistes relatief konstant.

'n Groot veranderlikheid tussen pasiënte in uurlikse infusietempos is bevind, met gemiddelde uurlikse infusietempos wat wissel van 0,2 – 0,5 $mg.kg^{-1}.h^{-1}$, afhangende van die aard en omvang van orgaanversaking(s), gelyktydige medikasie en individuele pasiëntkenmerke. Om optimale individuele beheer van pasiënte te verseker, word monitering van neuromuskulêre transmissie ten sterkste aanbeveel. Veiligheid en doeltreffend na oorskryding van 3 dae is nie vasgestel nie.

Na afloop van aanhoudende infusie in die Intensiewe Sorgeenheid, is die herstel tot reeks-van-vier-verhouding tot 0,7 afhanklik van die vlak van blok aan die einde van die infusie. Na 'n aanhoudende infusie vir 20 uur of meer, is die gemiddelde (omvang) tyd tussen terugkering van T_1 tot reeks-van-vier-stimulasie en herstel van die reeks-van-vier-verhouding tot 0,7 ongeveer 1,5 (1 – 5) uur in pasiënte sonder veelvoudige orgaanversaking en 4 (1 – 25) uur in pasiënte met veelvoudige orgaanversaking. Spontane asemhaling word slegs aanbeveel wanneer die reeks-van-vier-stimulasie 0,9 is.

Toediening
ROCURONIUM 50 IV BIOTECH word intravenous toegedien, hetsy as 'n bolus-inspuiting of as 'n aanhoudende infusie.

Verenigbaarheidstudies met die volgende infusie-vloeistowwe is uitgevoer. Teen nominale konsentrasies van 0,5 mg/ml and 2 mg/ml, is daar getoon dat ROCURONIUM 50 IV BIOTECH verenigbaar is met: 0,9 % NaCl, 5 % dekstrose, 5 % dekstrose in soutoplossing, sterile water vir inspuiting, Gelakteerde Ringer's.

Toediening moet onmiddelik na vermenging begin word en moet binne 24 uur voltooi word. Ongebruikte oplossings moet weggegooi word.

ROCURONIUM 50 IV BIOTECH kan ingespuit word in die intraveneuse lyn van 'n lopende infusie met 'n oplossing van die volgende binneaarse medikasie: epinefrien (adrenalien), alcuronium, alfentanil, aminofillien, atrakurium, atropien, keftasidiem, kefuroxime, simetidien, klemastien, klindamisien, klometiasool, clonasepam, clonidien, danaparoied, dobutamien, dopamien, dehidrobenzperidol, efedrien, ergometrien, esmolol, etomidaat, fentaniel, flukitosien, gentamisien, glukose 40 %, glicopirronium bromied, heparien, isoprenalien, ketamien, labetalol, lignocaine, mannitol 20 %, metoklopramied, metoprolol, metronidasool, midasolam, milrinoon, morfien, nifedipien, nimodipien, nitrogliserien, norepinefrien (noradrenalien), oksitosien, pankuronium, pethidien, pipekuronium, kaliumchloried, prometasien, propranolol, propofol, ranitidien, salbutamol, natriumkarbonaat, natrium nitroprussien, sufentaniel, suxametonium, vekuronium and verapamil.

Verwys ook na die onverenigbaarheid opskrif onder die "Interaksie" seksie.

NEWE EFFEKTE
Immuunsisteem versteurings
Minder algemeen: Anafilaktiese reaksie; hipersensitiwiteit; angioedeem; verhoging in gemiddelde plasma histamine.

Kardiale versteurings
Minder algemeen: Disritmie; tagikardie.

Vaskulêre versteurings
Minder algemeen: Hipertensie; hipotensie; warmgloede.

Respiratoriese, torakale en mediastinale versteurings
Minder algemeen: Brongospasma; hygende asemhaling.

Vel en subkutaneuse weefsel versteurings
*Minder algemeen:*Pruritus; veluitslag; eritemateuse uitslag.

Algemene versteurings en toestande by die plek van toediening
Algemeen: Pyn by die plek van inspuiting.
Minder algemeen: Swelling by die plek van inspuiting; gesigsedeem.

Gastroïntestinale versteurings
Minder algemeen: Hik; naarheid; braking.

Muskuloskeletale versteurings
Algemeen: Muskulêre swakheid, miopatie; besering, vergiftiging en komplikasies gedurende 'n prosedure.
Minder algemeen: Verlengde neuromuskulêre blok, vertraagde hetstel van narkose, lugweg komplikasies van narkose.

BEKENDE SIMPTOME VAN OORDOSERING EN BESONDERHEDE VIR DIE BEHANDELING DAARVAN
Die akute gevolge van oordosering is apnee en langdurige verlamming.

Die pasiënt moet steeds gekontroleerde ventilasie- en sedasie ondersteuning ontvang tot spontane herstel plaasvind. Asetielcholienesterase-inhibeerders (piridostigmien, neostigmine, edrofonium) moet in voldoende dosisse toegedien word. Ventilasie moet voortgesit word totdat spontane asemhaling herstel word indien hierdie middels nie daarin slaag om die neuromuskulêre blok van ROCURONIUM 50 IV BIOTECH om te keer nie. Herhaalde dosisse van 'n asetielcholienesterase-inhibeerder kan gevaarlik wees.

Verdere behandeling is simptomaties en ondersteunend.

IDENTIFIKASIE
'n Helder, kleurlose tot geel of oranje oplossing.

AANBIEDING
ROCURONIUM 50 IV BIOTECH word gevul binne-in helder Tipe I glas flessies met 'n donkergrys rubberprop en aluminium doppie. 10 x 5 ml of 1 x 5 ml flessies per buitenste kartonhouer.

BEWARINGSINSTRUKSIES
Bewaar tussen 2-8 °C. Beskerm teen lig.
Moet nie vries nie.
Hou die flessie in die buitenste kartonhouer totdat dit benodig word vir gebruik.
Aangesien ROCURONIUM 50 IV BIOTECH geen preserveermiddel bevat nie, moet dit dadelik gebruik word en enige ongebruikte oplossing vernietig word.
HOU BUITE DIE BEREIK VAN KINDERS.

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