SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC.

Each vial contains Rocuronium bromide 50 mg equivalent to 50 mg/5 mL solution for injection.

Sugar free

For full list of excipients, (See section 6.1)

3. PHARMACEUTICAL FORM

Glass vials -

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC is available as sterile, non-pyrogenic, isotonic solution that is clear colourless to yellow or orange solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC 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.

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC is also indicated as an adjunct in the Intensive Care Unit to facilitate intubation and mechanical ventilation for up to 3 days in adults 18 to 65 years.

4.2. Posology and method of administration

Dosage: ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC should only be administered by, or under supervision of, experienced doctors who are familiar with the action and use of these medicines.

The dosage should be individualised in each patient. The 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, and the condition of the patient should be considered when determining the dose.

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

Inhalational anaesthetics potentiate the neuromuscular blocking effects of ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC. Potentiation, however, becomes clinically relevant during anaesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see “section 4.5”).

Risk of Medication Errors: Accidental administration of neuromuscular blocking agents may result in serious adverse events, including fatal outcomes. Store ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC with the cap and ferrule intact and in a manner that minimizes 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 routine anaesthesia is 0,6 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC 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.

Higher doses

Should there be reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC decreases the onset time and increases the duration of action (see “section 5.1”).

Maintenance dosing

The recommended maintenance dose is 0,15 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC. 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 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.

Continuous infusion

If ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC is administered by continuous infusion it is recommended to give a loading dose of 0,6 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC 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 inhalational anaesthesia the infusion rate ranges from 0,3 to 0,4 mg/kg/h. Continuous monitoring of neuromuscular block are recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Special population

Paediatric patients

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 like 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 BROMIDE INJECTION, 50 mg/5 mL RBC in rapid sequence induction in paediatric patients is limited. ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC 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 BROMIDE INJECTION, 50 mg/5 mL RBC.

Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC, and the recommended infusion rate is 0,3 to 0,4 mg/kg/h (see “Continuous infusion”, See “section 4.4”).

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 considering an ideal body weight.

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/kg ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC 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 stimulations. 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 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 medicine and individual patient characteristics. To provide optimal 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 ratio to 0,7 depends on the level of block at the end of the infusion. After a continuous infusion for 20 hours or more the median (range) time between return of T2 to train of four stimulation and recovery of the train of four ratio to 0,7 approximates 1,5 (1 to 5) hours in patients without multiple organ failure and 4 (1 to 25) hours in patients with multiple organ failure.

Method of Administration

ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC is administered intravenously either as a bolus injection or as a continuous infusion.

Compatibilities

Compatibility studies with the following infusion fluids have been performed. In nominal concentrations of 0,5 mg/mL and 2 mg/mL ROCURONIUM BROMIDE INJECTION, 50 mg/5 mL RBC has been shown to be compatible with: 0,9 % NaCl, 5 % Dextrose, 5 % Dextrose in saline, Sterile water for injection, Lactated Ringer's and Haemaccel.

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

Incompatibilities

Physical incompatibility has been documented for ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC when added to solutions containing the following medicines: Amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, frusemide, hydrocortisone
sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim, and vancomycin. ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC is also incompatible with Intralipid.

ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC must not be mixed with other medicines except those mentioned above.

If ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC 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 BROMIDE INJECTION 50 mg/5 mL RBC and medicines, for which incompatibility with ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC has been demonstrated, or for which compatibility with has not been established.

4.3. Contraindications

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

There is insufficient data to support recommendations for the use of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC in neonates (0 to 1 month).

ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and elderly patients due to a lack of data on safety and efficacy.

Safety in pregnancy and lactation has not been demonstrated (see “section 4.6”).

4.4. Warnings and Special Precautions

Since ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine until adequate spontaneous respiration is restored. As with all neuromuscular blocking agents, it is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

As with other neuromuscular blocking agents, residual neuromuscular blockade has been reported for ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC. 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 the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent (such as sugammadex or cetylcholinesterase inhibitors) should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

High rates of cross-sensitivity between neuromuscular blocking agents have been reported. Therefore, where possible, before administering ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC, hypersensitivity to other neuromuscular blocking agents should be excluded.

ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC 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.

Rocuronium may increase the heart rate.

In general, following long-term use of neuromuscular blocking agents in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of neuromuscular blocking agents. In addition, patients should receive adequate analgesia and sedation. Furthermore, neuromuscular blocking agents should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long-term administration of other non-depolarising neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported regularly. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

If suxamethonium is used for intubation, the administration of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Because rocuronium bromide is always used with other medicines and because of the risk of malignant hyperthermia during anesthesia, even in the absence of known triggering factors, physicians should be aware of the early symptoms, confirmatory diagnosis, and treatment of malignant hyperthermia prior to the start of anesthesia. Animal studies have shown that

rocuronium bromide is not a triggering factor for malignant hyperthermia. Rare cases of malignant hyperthermia with ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC have been observed thru post-marketing surveillance; however, the causal association has not been proven.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC:

Hepatic and/or biliary tract disease and renal failure

Because rocuronium is excreted in urine and bile, it should be used with caution in patients with clinically significant hepatic and/or biliary diseases and/or renal failure. In these patient groups prolongation of action has been observed with doses of 0.6 mg/kg rocuronium bromide.

Prolonged circulation time

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

Neuromuscular disease

Like other neuromuscular blocking agents, ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC should be used with extreme caution in patients with a neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC may have profound effects and ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients when the administered doses are calculated on actual body weight.

Burns

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

Conditions which may increase the effects of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC

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 with known effect

Sodium

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

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 agents.

Effect of other medicines on ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC

Increased effect:

• Halogenated volatile anaesthetics potentiate the neuromuscular block of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC. The effect only becomes apparent with maintenance

dosing (see section 4.2). 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 BROMIDE INJECTION 50 mg/5 mL RBC in the ICU may result in prolonged duration of neuromuscular block or myopathy (see sections 4.4 and 4.8).

Other medicines:

• Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics.

• Diuretics, quinidine and its isomer quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anaesthetics (lidocaine (lignocaine) i.v, bupivacaine epidural) and acute administration of phenytoin or B-blocking agents.

Recurarisation 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 phenytoin or carbamazepine.

• Calcium chloride, potassium chloride.

• Protease inhibitors (gabexate, ulinastatin).

Variable effect:

• Administration of other non-depolarising neuromuscular blocking agents in combination with ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.

• Suxamethonium given after the administration of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC may produce potentiation or attenuation of the neuromuscular blocking effect of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC.

Effect of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC on other medicines

ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC combined with lidocaine (lignocaine) may result in a quicker onset of action of lidocaine (lignocaine).

Paediatric population

No formal interaction studies have been performed. The above-mentioned interactions for adults (see section 4.4) should be considered for paediatric patients.

4.6. Fertility, pregnancy, and lactation

Pregnancy

For rocuronium bromide, no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development.

Safety in pregnancy has not yet been demonstrated.

Caesarean section

In patients undergoing Caesarean section, ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic agent is administered or following suxamethonium facilitated intubation. However, ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC, 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 parturient undergoing Caesarean section. ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC 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.

Note 1: 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.

Note 2: Reversal of neuromuscular block induced by neuromuscular blocking agents may be inhibited or unsatisfactory in patients receiving magnesium salts for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC should be reduced and be titrated to twitch response.

Breast-feeding

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk.

Insignificant levels of rocuronium bromide were found in the milk of lactating rats. There are no human data on the use of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC during lactation.

Safety in breastfeeding has not been established.

4.7. Effects on ability to drive and use machines

Since ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia should be taken for ambulatory patients.

4.8 Undesirable effects

{Frequency to change to Frequent, Less frequent and Frequency unknown}.

Adverse reactions frequency is defined using the following convention:

Frequent - Very common (≤1/10); common (≤1/100 to <1/10); Less frequent - uncommon (≤1/1,000 to <1/100); rare (≤1/10,000 to<1/1,000); very rare (<1/10,000); Frequency not known

- (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

The most commonly occurring adverse drug reactions include injection site pain/reaction, changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance is 'anaphylactic and anaphylactoid reactions' and associated symptoms

a. Tabulated list of adverse reactions

SYSTEM ORGAN CLASS	
Immune system disorders	
Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	Less frequent
Nervous system disorders	
Flaccid paralysis	Less frequent
Cardiac disorders	
Tachycardia	Less frequent
Kounis syndrome	Frequency not known
Vascular disorders	
Hypotension	Frequent
Circulatory collapse and shock Flushing	Less frequent
Respiratory, Thoracic, and mediastinal disorders:	
Bronchospasm	Less frequent
Skin and subcutaneous tissue disorders	

Angioneurotic oedema Urticaria Rash Erythematous rash	Less frequent
Musculoskeletal and connective tissue disorders	
Muscular weakness[3] Steroid myopathy[3]	Less frequent
General disorders and administration site conditions:	
Medicine ineffective Medicine effect/ therapeutic response decreased Medicine effect/ therapeutic response increased Injection site pain Injection site reaction Malignant hypothermia	Frequent
Face oedema	Less frequent
Injury, poisoning, and procedural complications	
Prolonged neuromuscular block Delayed recovery from anaesthesia	Frequent
Airway complication of anesthesia	Less frequent

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC, have been reported. Anaphylactic/anaphylactoid reactions are bronchospasm, cardiovascular changes (e.g., hypotension, tachycardia, circulatory collapse - shock), and cutaneous changes (e.g., angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume they may occur and take the necessary precautions.

Since neuromuscular blocking agents 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 reaction at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these medicines.

In studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0,3 to 0,9 mg/kg rocuronium bromide.

Prolonged neuromuscular block

The most frequent adverse reaction to nondepolarising blocking agents as a class consists of an extension of the medicine's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea.

Myopathy:

Myopathy has been reported after the use of various neuromuscular blocking agents in the ICU 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 as the induction agent. In studies, pain on injection has been noted in 16 % of the patients who underwent rapid sequence induction of anaesthesia with propofol and in less than 0,5 % of the patients who underwent rapid sequence induction of anaesthesia with fentanyl and thiopental.

Paediatric Population

A meta-analysis of 11 studies in paediatric patients (n=704) with rocuronium bromide (up to 1 mg/kg) showed that tachycardia was identified as adverse drug reaction with a frequency of 1,4 %.

f. 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 professionals are asked to report any suspected adverse reactions to SAHPRA via The '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications:

https://www/sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. At the start of spontaneous recovery an acetylcholinesterase inhibitor (e.g., neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

In animal studies, severe depression of cardiovascular function, ultimately leading to cardiac collapse did not occur until a cumulative dose of 750 x ED_{90} (135 mg/kg rocuronium bromide) was administered.

Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, ATC code: M03AC09.

Pharmacological Classification: A.17.1 Peripherally acting muscle relaxants

Mechanism of action

Rocuronium bromide is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of medicines (curariform). It acts by competing for nicotinic cholinoceptors at the motor endplate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

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 rocuronium bromide. The ED_{90} 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 rocuronium bromide 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 x ED_{90}), onset of action is slower and duration of action is shorter (13 to 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.

Special populations

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.

Reversal of muscle relaxation

Administration of acetylcholinesterase inhibitors, (neostigmine, pyridostigmine or edrophonium) at reappearance of T_2 or at the first signs of clinical recovery, antagonises the action of rocuronium bromide.

5.2. Pharmacokinetic properties

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time course runs in three exponential phases. In normal adults, the mean (95 % CI) elimination half-life is 73 (66 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.

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.
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.

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 studies, related to

nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (+/- SD) elimination half-life of 21,5 (+/- 3,3) hours, a (apparent) volume of distribution at steady state of 1,5 (+/- 0,8) l/kg and a plasma clearance of 2,1 (+/- 0,8) mL/kg/min were found.

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-label is on average 47 % in urine and 43 % in faeces after 9 days. Approximately 50 % is recovered as the parent compound.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Glacial Acetic Acid

Nitrogen

Sodium Acetate Trihydrate

Sodium Chloride

Sodium Hydroxide

Water for Injection

6.2. Incompatibilities

Not Applicable

6.3. Shelf life

Proposed shelf-life: 24 months.

6.4. Special precautions for storage

“Store in refrigerator, 2 to 8 °C (36 to 46 °F)”.

Do not Freeze.

6.5. Nature and contents of container

PACK SIZE 10's: ROCURONIUM BROMIDE INJECTION 50 mg/5 mL RBC is a 13 mm Fiolax clear tubular type I glass vial with European blow back closed with a 13 mm Grey bromobutyl uncoated rubber stopper and sealed with 13 mm Aluminium seals assembled with a bridged portion on top with yellow colour (3772) matte finish plastic button.

10 vials of 5 mL are packed into a printed carton along with a printed patient information leaflet.

6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

No special requirements for disposal.

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

7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

RBC PHARMACEUTICALS (PTY)LTD

23 Kiaat Street, ERF 926, Extension 7,

Noordwyk, Midrand,

1687, South Africa.

8. REGISTRATION NUMBER

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