PROFESSIONAL INFORMATION FOR HUMAN MEDICINES

SCHEDULING STATUS

S5

1. NAME OF THE MEDICINE

ROCURONIUM 50 mg B Braun, Intravenous

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROCURONIUM 50 mg B Braun, Intravenous solution for injection

Each 5ml vial contains 50 mg Rocuronium bromide

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ROCURONIUM 50 mg B Braun, Intravenous solution for injection

Clear solution free from visible particles

pH of the solution: 3.8 to 4.2

Osmolality: 270– 310 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ROCURONIUM 50 mg B Braun 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 50 mg B Braun** 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

ROCURONIUM 50 mg B Braun should only be administered by, or under supervision of, experienced medical practitioners who are familiar with the action and use of these medicines.

Posology

The dosage of **ROCURONIUM 50 mg B Braun** 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 taken into account 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 50 mg B Braun**. 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 mg B Braun** should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of **ROCURONIUM 50 mg B Braun** during long lasting procedures (longer than 1 hour) under inhalational anaesthesia *(see section 4.5)*

Risk of Medication Errors: Accidental administration of neuromuscular blocking medicines may result in serious adverse events, including fatal outcomes. Store ROCURONIUM 50 mg B Braun with the cap and ferrule intact and in a manner that minimises the possibility of selecting the wrong medicine *(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 50 mg B Braun**, after which adequate intubation conditions are established within 90 seconds.

A dose of 1 mg/kg **ROCURONIUM 50 mg B Braun** 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 50 mg B Braun** have been administered during surgery without adverse cardiovascular effects being noted. The use of these high dosages of **ROCURONIUM 50 mg B Braun** 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 50 mg B Braun**. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to 0,1 mg/kg **ROCURONIUM 50 mg B Braun**. 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 50 mg B Braun** is administered by continuous infusion it is recommended to give a loading dose of 0,6 mg/kg **ROCURONIUM 50 mg B Braun** 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 is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

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 similar to those in adults.

For continuous infusion in paediatrics the infusion rates, with exception of children, are the same as for adults. For children higher infusion rates might be necessary. For children the same initial infusion rates as for adults are recommended, and this should be adjusted to maintain twitch response at 10 % of control twitch height, or to maintain 1 or 2 responses to train of four stimulation during the procedure.

The experience with **ROCURONIUM 50 mg B Braun** in rapid sequence induction in paediatric patients is limited. **ROCURONIUM 50 mg B Braun** is therefore not recommended, for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure

The standard intubation dose for elderly patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0,6 mg/kg **ROCURONIUM 50 mg B Braun**.

Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg **ROCURONIUM 50 mg B Braun**, and the recommended infusion rate is 0,3 to 0,4 mg/kg/h (see "Continuous infusion"). (See also 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 taking into account 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 50 mg B Braun** 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 stimulation. Dosage should always be titrated to effect in the individual patient. The recommended initial infusion rate for the maintenance of a neuromuscular block of 80 to 90 % (1 to 2 twitches to train of four stimulation) in adult patients is 0,3 to 0,6 mg/kg/h during the first hour of administration, which will need to be decreased during the following 6 to 12 hours, according to individual response. Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found, with mean hourly infusion rates ranging from 0,2 to 0,5 mg/kg/h depending on nature and extent of organ failure(s), concomitant medication and individual patient characteristics. To provide optimal 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 T_2 to train of four stimulation

and recovery of the train of four ratio to 0,7 approximates 1,5 (1 to 5) hours in patients without multiple organ failure and 4 (1 to 25) hours in patients with multiple organ failure.

Method of administration

ROCURONIUM 50 mg B Braun is administered intravenously either as a bolus injection or as a continuous infusion (see sections 6.2 and 6.6).

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

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 50 mg B Braun** when added to solutions containing the following medicines: Amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, methohexital, methylprednisolone, prednisolone sodium succinate, thiopental, trimethoprim and vancomycin. **ROCURONIUM 50 mg B Braun** is also incompatible with Intralipid.

ROCURONIUM 50 mg B Braun must not be mixed with other medicinal products except those mentioned above.

If **ROCURONIUM 50 mg B Braun** 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 % NaCI) between administration of **ROCURONIUM 50 mg B Braun** and medicines, for which incompatibility with **ROCURONIUM 50 mg B Braun** has been demonstrated, or for which compatibility with **ROCURONIUM 50 mg B Braun** has not been established.

4.3. Contraindications

ROCURONIUM 50 mg B Braun is contraindicated:

- Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients of **ROCURONIUM 50 mg B Braun** listed in section 6.1.
- There is insufficient data to support recommendations for the use of **ROCURONIUM 50 mg B Braun** in neonates (0 to 1 month).
- **ROCURONIUM 50 mg B Braun** 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. Special warnings and precautions for use

Hypersensitivity/Anaphylaxis

Severe anaphylactic and anaphylactoid reactions which may be fatal may occur after administration of **ROCURONIUM 50 mg B Braun**.

High rates of cross-sensitivity between neuromuscular blocking medicines have been reported. Therefore, where possible, before administering **ROCURONIUM 50 mg B Braun**, hypersensitivity to other neuromuscular blocking medicines should be excluded.

ROCURONIUM 50 mg B Braun should only be used when absolutely essential in susceptible patients. Patients who experience a hypersensitivity reaction under general anaesthesia should be tested subsequently for hypersensitivity to other neuromuscular blockers.

Histamine Release and Histaminoid Reactions

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

In clinical 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, as in **ROCURONIUM 50 mg B Braun**.

Appropriate Administration and Monitoring

Since **ROCURONIUM 50 mg B Braun** causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine until adequate spontaneous respiration is restored. It is important to anticipate intubation difficulties, particularly when used as part of a rapid sequence induction technique.

Residual Curarisation

Residual curarisation has been reported for rocuronium, as in **ROCURONIUM 50 mg B Braun**. In order to prevent complications resulting from residual curarisation, 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 curarisation after extubation in the post-operative phase (such as medicine interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal medicine should be considered, especially in those cases where residual curarisation is more likely to occur.
Rocuronium may increase the heart rate.

Long-Term Use in an Intensive Care Unit

Following long term use of rocuronium, as in **ROCURONIUM 50 mg B Braun**, in the Intensive Care Unit, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of **ROCURONIUM 50 mg B Braun**.

Patients should receive adequate analgesia and sedation. Furthermore, rocuronium, as in **ROCURONIUM 50 mg B Braun**, should be titrated to effect in the individual patients by, or under supervision of, experienced doctors who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy

Myopathy after long-term administration of rocuronium as in **ROCURONIUM 50 mg B Braun** in the Intensive Care Unit, in combination with corticosteroid therapy, has been reported. Therefore, for patients receiving both **ROCURONIUM 50 mg B Braun** and corticosteroids, the period of use of **ROCURONIUM 50 mg B Braun** should be limited as much as possible.

Use with Suxamethonium

If suxamethonium is used for intubation, the administration of **ROCURONIUM 50 mg B Braun** should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium (see section 4.5).

Risk of Death due to Medication Errors

Administration of rocuronium, as in **ROCURONIUM 50 mg B Braun**, results in paralysis, which may lead to respiratory arrest and death, a progression that may be more likely to occur in a patient for whom it is not intended. Confirm proper selection of intended medicine and avoid confusion with other injectable solutions that are present in critical care and other clinical settings. If another healthcare provider is administering the medicine, ensure that the intended dose is clearly labelled and communicated.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuronium as in ROCURONIUM 50 mg B Braun:

Hepatic and/or biliary tract disease and renal failure

Because rocuronium is excreted in urine and bile, **ROCURONIUM 50 mg B Braun** 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 as in **ROCURONIUM 50 mg B Braun**.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular disease, old age and oedematous states 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 reduced plasma clearance.

Neuromuscular disease

ROCURONIUM 50 mg B Braun should be used with extreme caution in patients with neuromuscular disease or after poliomyelitis, since the response to neuromuscular blocking medicines may be considerably altered in these cases. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or with the myasthenic (Eaton-Lambert) syndrome, small doses of **ROCURONIUM 50 mg B Braun** may have profound effects and **ROCURONIUM 50 mg B Braun** should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of **ROCURONIUM 50 mg B Braun** is increased and the duration prolonged.

Malignant hyperthermia

Because rocuronium bromide as in **ROCURONIUM 50 mg B Braun** is always used with other medicines and because of the risk of malignant hyperthermia during anaesthesia, even in the absence of known triggering factors, medical practitioners should be aware of the early symptoms, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of anaesthesia.

Obesity

Rocuronium, as in **ROCURONIUM 50 mg B Braun**, 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 medicines. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of rocuronium, as in ROCURONIUM 50 mg B Braun:

Hypokalaemia (e.g. after severe vomiting, diarrhoea and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnoea, cachexia.

Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5. Interaction with other medicines and other forms of interaction

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

Effect of other medicines on **ROCURONIUM 50 mg B Braun**

Increased effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of rocuronium as in **ROCURONIUM 50 mg B Braun**. The effect only becomes apparent with maintenance dosing (see section 4.2 “Surgical Procedures, Maintenance dosing"). Reversal of the block with anticholinesterase inhibitors could also be inhibited.
- After intubation with suxamethonium (see section 4.2).

- Long-term concomitant use of corticosteroids and **ROCURONIUM 50 mg B Braun** in the Intensive Care Unit 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, acylaminopenicillin antibiotics.

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

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 inhibitor homologues (such as gabexate and ulinastatin).

Variable effect

- Administration of other non-depolarising neuromuscular blocking medicines in combination with **ROCURONIUM 50 mg B Braun** 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 50 mg B Braun**, may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium as in **ROCURONIUM 50 mg B Braun** (see section 4.4).

Effect of ROCURONIUM 50 mg B Braun on other medicines

ROCURONIUM 50 mg B Braun 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 and their special warnings and precautions for use (see section 4.4) should be taken into account for paediatric patients.

4.6. Fertility, pregnancy and lactation

Safety in pregnancy and breastfeeding has not been demonstrated.

Caesarean Section

In patients undergoing Caesarean section, ROCURONIUM 50 mg B Braun can be used as part of a rapid sequence induction technique, provided no intubation difficulties are anticipated and a sufficient dose of anaesthetic medicine is administered or following suxamethonium facilitated intubation. However ROCURONIUM 50 mg B Braun, administered in doses of 0,6 mg/kg may not produce adequate conditions for intubation until 90 seconds after administration. This dose has been shown to be safe in patients undergoing Caesarean section. Rocuronium, as in **ROCURONIUM 50 mg B Braun**, does not affect Apgar score, foetal muscle tone or cardiorespiratory adaptation.

From umbilical cord blood sampling it is apparent that only limited placental transfer of rocuronium bromide occurs, which does not lead to the observation of clinical adverse effects in the newborn.

Doses of 1,0 mg/kg have been investigated during rapid sequence induction of anaesthesia, but not in Caesarean section patients. Therefore, only a dose of 0,6 mg/kg is recommended in this patient group.

Reversal of neuromuscular block, induced by neuromuscular blocking medicines may be inhibited or unsatisfactory in patients receiving magnesium salts for toxaemia of pregnancy,

because magnesium salts enhance neuromuscular blockade. Therefore, in these patients the dosage of rocuronium, as in **ROCURONIUM 50 mg B Braun**, should be reduced and be titrated to twitch response.

Breastfeeding

The safety of rocuronium in breastfeeding has not been established.

There are no data with regard to effects of rocuronium bromide on fertility.

4.7. Effects on ability to drive and use machines

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after the full recovery from the neuromuscular blocking action of rocuronium as in **ROCURONIUM 50 mg B Braun.**

Since rocuronium bromide 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

a. *Summary of the safety profile*

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

The following side effects have been reported and the frequencies indicators are as follows:

b. *Tabulated list of adverse reactions*

System Organ Class	**Frequency Category**
Immune system disorders:	
Hypersensitivity, anaphylactic reaction,	

anaphylactoid reaction, anaphylactic shock,	Less frequent
anaphylactoid shock	
Nervous system disorders:	
Flaccid paralysis	Less frequent
Cardiac disorders :	
Tachycardia	Less frequent
Kounis syndrome	Frequency unknown
Vascular disorders :	
Hypotension	Less frequent
Circulatory collapse and shock, flushing	
Respiratory, thoracic and mediastinal disorders:	
Bronchospasm	Less frequent
Skin and subcutaneous tissues disorders:	
Angioedema, urticarial, rash, erythematous	Less frequent
rash	
Musculoskeletal and connective tissue disorder	
After long-term use in the Intensive Care Unit muscular weakness and a few cases of steroid myopathy have been reported (see section 4.4)	Less frequent
General disorders and administration site conditions:	
Medicine ineffective, decreased medicine effect/ therapeutic response, increased medicine effect/ therapeutic response, injection site pain, injection site reaction	Less frequent
Facial oedema, malignant hyperthermia	
Injury, poisoning and procedural complications	
Prolonged neuromuscular block, delayed recovery	Less frequent
from anaesthesia	
Airway complication of anaesthesia	

c. Description of selected adverse reactions

Anaphylaxis

Although less frequent, severe anaphylactic reactions to rocuronium 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, the necessary precautions should always be taken in anticipation thereof.

Histamine release

Since neuromuscular blocking medicines 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 (see section 4.4).

Prolonged neuromuscular block

The most frequent adverse reaction to non-depolarising blocking medicines as a class, including rocuronium as contained in **ROCURONIUM 50 mg B Braun**, consists of an extension of the medicine's pharmacological action beyond the time period required. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea.

Myopathy

Myopathy has been reported in the Intensive Care Unit after the use of various neuromuscular blocking medicines, including rocuronium as contained in **ROCURONIUM 50 mg B Braun**, in combination with corticosteroids (see section 4.4)

Local injection site reactions

Pain on injection has been noted in patients who underwent rapid sequence induction of anaesthesia.

Paediatric population

Clinical studies in paediatric patients with rocuronium bromide showed that tachycardia was identified as a frequent adverse drug reaction.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. 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

Symptoms and treatment

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 medicine fails to reverse the neuromuscular effects of rocuronium, as in **ROCURONIUM 50 mg B Braun**, 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 ED90 135 mg/kg was administered.

Further treatment is symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Category and class: A.17.1 Peripherally acting muscle relaxants

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, other quaternary ammonium compounds.

ATC code: M03AC09

Mechanism of action

Rocuronium bromide is a non-depolarising neuromuscular blocking agent. It acts by competing for nicotinic cholinoceptors at the motor end-plate. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine, edrophonium and pyridostigmine.

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/kg rocuronium bromide. The ED90 in infants is lower than in adults and children (0,25, 0,35 and 0,40 respectively).

The clinical duration (the duration until spontaneous recovery to 25 % of control twitch height) with 0,6 mg/kg 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 ED90), 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.

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.

Special populations

Paediatric 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.

5.2. Pharmacokinetic properties

Distribution

After intravenous administration of a single bolus dose of rocuronium bromide the plasma concentration time course runs in three exponential phases.

In normal adults, the mean (95 % CI) elimination half-life is 73 (66 to 80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193 to 214) mL/kg and plasma clearance is 3,7 (3,5 to 3,9) mL/kg/min.

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large between patient variability is found in controlled clinical studies, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure a mean (± SD) elimination half-life of 21,5 (± 3,3) hours, 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.

Biotransformation

No metabolites are detected in the plasma.

Elimination

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

Special Populations

Distribution

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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Gluconolactone, sodium acetate trihydrate, sodium citrate (pH-adjustment), water for injection

6.2. Incompatibilities

ROCURONIUM 50 mg B Braun must not be mixed with other medicinal products except those mentioned in section 4.2 above.

6.3. Shelf life

Unopened ampoule: 18 months.

After first opening: The product should be used immediately after opening the ampoule.

Chemical and physical in-use stability of a 5.0 mg/ml and 0.1 mg/ml solution (diluted with sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5%) solution for infusion) has been demonstrated for 24 hours at room temperature exposed to room light in glass, PE and PVC. From the microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4. Special precautions for storage

Store at or below 25 °C.

For storage conditions after dilution of the medicinal product, see section 6.3.

Keep in original packaging until required for use.

6.5. Nature and contents of container

ROCURONIUM 50 mg B Braun

20 x 5 mL colourless Low Density Polyethylene (LDPE) ampoules.

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

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

The solution is to be visually inspected prior to use. Only clear solutions practically free from particles should be used.

ROCURONIUM 50 mg B Braun has shown to be compatible with: sodium chloride 9 mg/ml (0.9%) and glucose 50 mg/ml (5 %) solution for infusion.

If **ROCURONIUM 50 mg B Braun** is administered via the same infusion line with other medicinal products, it is important that the infusion line is adequately flushed (e.g. with sodium chloride 9 mg/ml (0.9 %) solution for infusion) between administration of **ROCURONIUM 50 mg B Braun** and medicinal products for which incompatibility with **ROCURONIUM 50 mg B Braun** has been demonstrated or for which compatibility with **ROCURONIUM 50 mg B Braun** has not been established.

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

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

B.Braun Medical (Pty) Ltd

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8. REGISTRATION NUMBER

46/17.1/0585

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