Approved Professional Information for ROCURONIUM FRESENIUS

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROCURONIUM 25 mg/2,5 ml FRESENIUS

ROCURONIUM 50 mg/5 ml FRESENIUS

ROCURONIUM 100 mg/10 ml FRESENIUS

Solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains 10 mg rocuronium bromide.

(Osmolality 270 - 310 mOsmol/kg)

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection or infusion.

A clear, colourless to pale brownish-yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ROCURONIUM FRESENIUS 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
- an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation for up to 3 days in adults 18 - 65 years.

4.2 Posology and method of administration

Posology

ROCURONIUM FRESENIUS should only be administered by, or under supervision of, experienced doctors who are familiar with the action and use of these medicines.

The dosage of ROCURONIUM FRESENIUS 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 medicines that are 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 the neuromuscular block and recovery.

Inhalation anaesthetics potentiate the neuromuscular blocking effects of ROCURONIUM FRESENIUS (see section 4.5). This potentiation becomes clinically relevant during the course of anaesthesia when a certain tissue concentration of the volatile medicines is reached. Consequently, adjustments should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of ROCURONIUM FRESENIUS 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 FRESENIUS with the cap and ferrule intact and in a manner that minimises the possibility of selecting the wrong product (see section 4.4).

In adult patients the following dosage recommendations may serve as a general guidance 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 rocuronium bromide per kg body mass, which results in adequate intubation conditions within 90 seconds in nearly all patients.

A dose of 1,0 mg ROCURONIUM FRESENIUS per kg body mass is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are also established within 60 seconds in nearly all patients.

Higher doses

Should there be a reason for selection of larger doses in individual patients, initial doses up to 2 mg/kg ROCURONIUM FRESENIUS have been administered during surgery without adverse cardiovascular effects being noted. The use of these high doses of ROCURONIUM FRESENIUS decreases the onset time and increases the duration of action.

Maintenance dosage

The recommended maintenance dose is 0,15 mg ROCURONIUM FRESENIUS per kg body mass. In the case of long-term inhalational anaesthesia, this should be reduced to 0,075 to

0,1 mg/kg ROCURONIUM FRESENIUS. The maintenance doses should 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 (TOF) are present.

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

Continuous infusion

If ROCURONIUM FRESENIUS is administered by continuous infusion, it is recommended to give a loading dose of 0,6 mg ROCURONIUM FRESENIUS per kg body mass and, when the 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 the neuromuscular block at this level ranges from 0,3 – 0,6 mg/kg/h. Under inhalational anaesthesia the infusion rate ranges from 0,3 – 0,4 mg/kg/h.

Continuous monitoring of the neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosage in 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 FRESENIUS in rapid sequence induction in paediatric patients is limited. ROCURONIUM FRESENIUS 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 FRESENIUS.

Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0,075 to 0,1 mg/kg ROCURONIUM FRESENIUS and the recommended infusion rate is 0,3 to 0,4 mg/kg/h (see “Continuous infusion”).

Dosage 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 weight) doses should be reduced taking into account an ideal body mass.

Intensive care procedures

Tracheal intubation

For tracheal intubation, the same doses should be used as described above under surgical procedures.

Maintenance dosing

The use of an initial loading dose of 0,6 mg ROCURONIUM FRESENIUS 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 TOF stimulation) in adult patients is 0,3 - 0,6 mg/kg/h 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 interpatient variability in hourly infusion rates has been found, with mean hourly infusion rates ranging from 0,2 - 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 ICU, 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 - 5) hours in patients without multiple organ failure and 4 (1 - 25) hours in patients with multiple organ failure.

Method of administration

ROCURONIUM FRESENIUS is administered intravenously either as a bolus injection or as a continuous infusion.

4.3 Contraindications

ROCURONIUM FRESENIUS is contraindicated in:

- patients with hypersensitivity to rocuronium bromide or to the bromide ion or any of the ingredients of ROCURONIUM FRESENIUS (see section 6.1)
- neonates (0 - 1 month).

ROCURONIUM FRESENIUS is not recommended for the facilitation of mechanical ventilation in the intensive care unit (ICU) in paediatric and elderly patients due to a lack of data on safety and efficacy.

Safety in pregnancy and lactation has not been established (see section 4.6).

4.4 Special warnings and precautions for use

Appropriate administration and monitoring

Since ROCURONIUM FRESENIUS 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.

ROCURONIUM FRESENIUS should be administered only by an experienced doctor familiar with the use of neuromuscular blocking medicines. Adequate facilities and staff for endotracheal intubation and artificial ventilation have to be available for immediate use.

Hypersensitivity/anaphylaxis

Severe anaphylactic and anaphylactoid reactions, which may be fatal, can occur after the administration of ROCURONIUM FRESENIUS. Anaphylactic/anaphylactoid reactions include bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse, shock) and cutaneous changes (e.g. angioedema, urticaria). Precautions for treating such reactions should always be taken. Allergic cross-reactivity to neuromuscular blocking medicines has been reported. Therefore, particular care should be taken in cases where previous anaphylactic reactions have occurred following administration of neuromuscular blocking medicines.

Histamine release and histaminoid reactions

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

Rash, exanthema, urticaria, bronchospasm and hypotension have been reported less frequently in patients given ROCURONIUM FRESENIUS.

Residual neuromuscular blockade

Residual neuromuscular blockade has been reported and in order to prevent complications it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block as indicated by a train-of-four (TOF) ratio of 0,9. 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 medicine interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal medicine should be considered, especially in those cases where residual neuromuscular blockade is more likely to occur.

It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia.

Prolonged neuromuscular blockage

The most frequent adverse reaction to non-depolarising blocking medicines (such as ROCURONIUM FRESENIUS) 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 apnoea.

In order to help preclude possible prolongation of neuromuscular blockage and/or overdose, it is strongly recommended that neuromuscular transmission is monitored throughout the use of ROCURONIUM FRESENIUS.

In addition, patients should receive adequate analgesia and sedation. Furthermore, ROCURONIUM FRESENIUS should be titrated to effect in the individual patients by, or under the supervision of, experienced doctors who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Risk of death due to medication errors

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

Malignant hyperthermia

Because ROCURONIUM FRESENIUS is always used with other medicines and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering substances, doctors should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia.

Cardiac effects

ROCURONIUM FRESENIUS may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic medicines or by vagal stimulation.

Myopathy

Myopathy has been reported after long-term use of ROCURONIUM FRESENIUS in the intensive care unit, in combination with corticosteroids. Therefore, for patients receiving both ROCURONIUM FRESENIUS and corticosteroids, the period of use of ROCURONIUM FRESENIUS should be limited as much as possible.
ROCURONIUM FRESENIUS should only be administered after full recovery from the neuromuscular blockade caused by suxamethonium.

Local injection site reactions

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

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of ROCURONIUM FRESENIUS:

Hepatic and/or biliary tract disease and renal failure

ROCURONIUM FRESENIUS is excreted in bile and urine. Therefore, 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 is observed with doses of 0,6 mg/kg ROCURONIUM FRESENIUS.

Prolonged circulation time

Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and oedematous states resulting in an increased volume of distribution, may contribute

to a slower onset of the effect. The duration of action may also be prolonged due to reduced plasma clearance.

Neuromuscular disease

ROCURONIUM FRESENIUS 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 bromide may have profound effects and ROCURONIUM FRESENIUS should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of ROCURONIUM FRESENIUS is increased and the duration prolonged.

Obesity

ROCURONIUM FRESENIUS 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 the response.

Conditions which may increase the effects of ROCURONIUM FRESENIUS:

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

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

ROCURONIUM FRESENIUS contains sodium

ROCURONIUM FRESENIUS contains 3,64 mg sodium per ml, equivalent to 0,18 % of the WHO recommended maximum daily intake of 2 g sodium for an adult.

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 the effect of ROCURONIUM FRESENIUS:

Increased effect

- Halogenated volatile anaesthetics potentiate the neuromuscular block of ROCURONIUM FRESENIUS. The effect only becomes apparent with maintenance dosing (see section 4.2, “Surgical procedures, Maintenance dosing”). Reversal of the block with acetylcholinesterase inhibitors could also be inhibited.
- High doses of: thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate and propofol.
- Other non-depolarising neuromuscular blocking medicines.
- Prior administration of suxamethonium (see section 4.2). Suxamethonium given after the administration of ROCURONIUM FRESENIUS may produce potentiation or attenuation of the neuromuscular blocking effect of ROCURONIUM FRESENIUS (See section 4.4).

- Long-term concomitant use of corticosteroids and ROCURONIUM FRESENIUS in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4).

- *Other medicines:*
  - Antibiotics: aminoglycosides, lincosamides (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, high doses of metronidazole.
  - Diuretics, thiamine, MAO inhibitors, quinidine, quinine, protamine, adrenergic blocking medicines, magnesium salts, calcium channel blocking medicines, lithium salts and local anaesthetics (lidocaine (lignocaine) I.V., bupivacaine epidural) and acute administration of phenytoin or ß-blocking medicines.
  - Recurarisation (return of neuromuscular paralysis) has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4, “Conditions which may increase the effect of ROCURONIUM FRESENIUS”).

Decreased effect

- Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives.
- Prior chronic administration of phenytoin or carbamazepine.
- Norepinephrine (noradrenaline), azathioprine (only transient and limited effect), theophylline, 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 FRESENIUS may produce attenuation or potentiation

of the neuromuscular block, depending on the order of administration and the neuromuscular blocking medicine used.

- Suxamethonium given after the administration of ROCURONIUM FRESENIUS may produce potentiation or attenuation of the neuromuscular blocking effect of ROCURONIUM FRESENIUS.

Effect of ROCURONIUM FRESENIUS on other medicines

Combined use with lidocaine (lignocaine) could result in a quicker onset of action of lidocaine (lignocaine).

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of use of ROCURONIUM FRESENIUS in pregnancy has not been established.

Caesarean section

In patients undergoing Caesarean section, ROCURONIUM FRESENIUS 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 FRESENIUS, 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 FRESENIUS 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 not been investigated 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 FRESENIUS should be reduced and be titrated to twitch response.

Breastfeeding

It is unknown whether rocuronium bromide is excreted in human breast milk. Animal studies have shown insignificant levels of rocuronium bromide in breast milk. After the administration of a single dose, it is recommended to abstain from next breastfeeding for five elimination half-lives of rocuronium, i.e. for about 6 hours.

Fertility

No information available.

4.7 Effects on ability to drive and use machines

Patients should be warned not to handle potentially dangerous machinery or drive a car within 24 hours after full recovery from the neuromuscular blocking action of ROCURONIUM FRESENIUS.

4.8 Undesirable effects

a) Summary of the safety profile

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.

b) Tabulated summary of adverse reactions

System organ class	**Adverse reactions**	**Frequency**
Immune system disorders	Hypersensitivity Anaphylactic reactions, sometimes fatal Anaphylactic shock Anaphylactoid reactions Anaphylactoid shock	Less frequent
Nervous system disorders	Flaccid paralysis	Less frequent
Cardiac disorders	Tachycardia	Less frequent
	Kounis syndrome	Not known*
Vascular disorders	Hypotension Circulatory collapse and shock Flushing	Less frequent
Respiratory, thoracic and mediastinal disorders	Bronchospasm Apnoea Respiratory failure	Less frequent
Skin and subcutaneous tissue disorders	Rash Erythematous rash Itching Exanthema Urticaria Angioneurotic oedema	Less frequent
Musculoskeletal, connective tissue and bone	Skeletal muscle weakness Steroid myopathy	Less frequent

disorders		
General disorders and administration site conditions	Injection site pain Injection site reaction Medicine ineffective Decreased medicine effect/therapeutic response Increased medicine effect/therapeutic response Facial oedema	Less frequent
	Malignant hyperthermia	
Investigations	Increased histamine level	Less frequent
Injury, poisoning and procedural complication	Prolonged neuromuscular block Delayed recovery from anaesthesia Airway complication of anaesthesia	Less frequent

* Frequency cannot be established from the available data.

Reporting of suspected adverse reactions

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of ROCURONIUM FRESENIUS is important. It allows continued monitoring of the benefit/risk balance of ROCURONIUM FRESENIUS. Health care providers are asked to report any suspected adverse reactions via the **Adverse Drug Reaction Reporting Form**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

4.9 Overdose

Symptoms of overdose

See section 4.8. Clinical effects of overdose include apnoea and prolonged paralysis.

Treatment of overdose

Management of ROCURONIUM FRESENIUS overdose is the same as management of overdose of the other neuromuscular medicines.

In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation.

There are two options for the reversal of neuromuscular block:

(1) In adults, sugammadex can be used for reversal of intense (profound) and deep block. The dose of sugammadex to be administered depends on the level of neuromuscular block.

(2) Upon start of spontaneous recovery, sugammadex or 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 FRESENIUS, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase inhibitor can be dangerous.

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.

ATC code: M03AC09.

Mechanism of action:

Rocuronium bromide is an intermediate acting, non-depolarising neuromuscular blocking medicine.

It acts by competing for nicotinic ACh (acetylcholine) receptors at the motor end plate and thereby competitively blocks the binding of ACh. This action is antagonised by acetylcholinesterase inhibitors such as neostigmine and pyridostigmine.

5.2 Pharmacokinetic properties

On intravenous use, the plasma concentration time course follows a three compartment open model. 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 and the plasma clearance is 3,7 (3,5 – 3,9) ml/kg/min.

When administered as a continuous infusion to facilitate mechanical ventilation for 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A large variability amongst patients exists, related to nature and extent of (multiple) organ failure and individual patient characteristics. In patients with multiple organ failure the mean (± SD) elimination half-life is 21,5 (± 3,3) hours, the (apparent) volume of distribution at steady state is 1,5 (± 0,8) l/kg and the plasma clearance rate is 2,1 (± 0,8) ml/kg/min.

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

Elderly patients and patients with renal or hepatic disease

The plasma clearance in elderly patients and in patients with renal dysfunction is reduced, 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.

Infants and children

In infants (3 months to 1 year), the apparent volume of distribution at steady state conditions is increased compared to adults and children (1 to 8 years). In older children (3 to 8 years), a trend is seen towards higher clearance and shorter elimination half-life (approximately 20 minutes) compared to adults, younger children and infants.

5.3 Preclinical safety

Not applicable.

6. PHARMACEUTICALS PARTICULARS

6.1 List of excipients

Sodium acetate trihydrate

Sodium chloride

Glacial acetic acid (for pH-adjustment)

Water for injections.

6.2 Incompatibilities

Physical incompatibility has been documented for ROCURONIUM FRESENIUS when added to solutions containing the following active substances: amphotericin, amoxicillin, azathioprine, cefazolin, cloxacillin, dexamethasone, diazepam, enoximone, erythromycin, famotidine, furosemide, hydrocortisone sodium succinate, insulin, intralipid, methohexital, methylprednisone, prednisolone sodium succinate, thiopental, trimethoprim, and vancomycin.

If ROCURONIUM FRESENIUS 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 FRESENIUS and other medicines, for which incompatibility with ROCURONIUM FRESENIUS has been demonstrated, or for which compatibility with ROCURONIUM FRESENIUS has not been established.

6.3 Shelf life

Unopened vial: 36 months

Opened vial: The product should be used immediately after opening the vial.

After dilution:

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 a 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

Unopened vial: Store in a refrigerator (2 – 8 °C). Protect from light.

Opened vial: The product should be used immediately after opening the vial.

After dilution: See section 6.3.

6.5 Nature and contents of container

ROCURONIUM 25 mg/2,5 ml FRESENIUS: 2,5 ml solution in a clear glass vial with a chlorobutyl rubber stopper and an aluminium cap.

5, 10 or 12 vials are packed into an outer carton.

ROCURONIUM 50 mg/5 ml FRESENIUS: 5 ml solution in a clear glass vial with a chlorobutyl rubber stopper and an aluminium cap.

5, 10 or 12 vials are packed into an outer carton.

ROCURONIUM 100 mg/10 ml FRESENIUS: 10 ml solution in a clear glass vial with a chlorobutyl rubber stopper and an aluminium cap.

5, 10, 12 or 20 vials are packed into an outer carton.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

In nominal concentration of 0,5 mg/ml and 2 mg/ml ROCURONIUM FRESENIUS is compatible with: 0,9 % sodium chloride, 5 % dextrose, 5 % dextrose in 0,9 % sodium chloride, sterile water for injection, lactated Ringer's solution or suitable colloid solution.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi South Africa (Pty) Ltd

Stand 7, Growthpoint Business Park

162 Tonetti Street

Halfway House, Midrand, 1685

South Africa

8. REGISTRATION NUMBERS

ROCURONIUM 25 mg/2,5 ml FRESENIUS: 46/17.1/0060

ROCURONIUM 50 mg/5 ml FRESENIUS: 46/17.1/0061

ROCURONIUM 100 mg/10 ml FRESENIUS:46/17.1/0062

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

26 October 2018

10. DATE OF REVISION OF THE TEXT

15 June 2023