1. NAME OF THE MEDICINAL PRODUCT

Rocuronium bromide Kalceks 10 mg/ml solution for injection/infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml Rocuronium bromide Kalceks contains 10 mg rocuronium bromide.
Each vial with 5 ml of solution contains 50 mg rocuronium bromide.

Excipients with known effect: 1 ml contains 1.64 mg sodium.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection/infusion.
Clear, colourless or yellowish solution , free from visible particles.
Solution pH is 3.8-4.2.
Approximate osmolality is 280 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rocuronium bromide Kalceks 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 Kalceks is also indicated as an adjunct in the intensive care unit (ICU) to facilitate intubation and mechanical ventilation.

4.2 Posology and method of administration

Posology
Like other neuromuscular blocking agents, Rocuronium bromide Kalceks should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these drugs.

As with other neuromuscular blocking agents, the dosage of Rocuronium bromide Kalceks 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 drugs 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 neuromuscular block and recovery.

Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Rocuronium bromide Kalceks . This 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 bromide Kalceks should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Rocuronium bromide Kalceks during long lasting procedures (longer than 1 hour) under inhalational anaesthesia (see section 4.5).

In adult patients the following dosage recommendations may 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, after

which adequate intubation conditions are established within 60 seconds in nearly all patients. A dose of 1.0 mg/kg rocuronium bromide is recommended for facilitating tracheal intubation conditions during rapid sequence induction of anaesthesia, after which adequate intubation conditions are established within 60 seconds in nearly all patients. If a dose of 0.6 mg/kg rocuronium bromide is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

For use of rocuronium bromide during rapid sequence induction of anaesthesia in patients undergoing Caesarean section reference is made to section 4.6.

Higher doses
Should there be reason for selection of larger doses in individual patients, there is no indication from clinical studies that the use of initial doses up to 2 mg/kg rocuronium bromide is associated with an increased frequency or severity of cardiovascular effects. The use of these high dosages of rocuronium bromide 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; in the case of long-term inhalational anaesthesia, this should be reduced to 0.075-0.1 mg/kg rocuronium bromide. The maintenance doses should best be given when twitch height has recovered to 25% of control twitch height, or when 2 to 3 responses to train of four stimulation are present.

Continuous infusion
If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg/kg rocuronium bromide and, when neuromuscular block starts to recover, to start administration by infusion. The infusion rate should be adjusted to maintain twitch response at 10% of control twitch height or to maintain 1 to 2 responses to train of four stimulation. In adults under intravenous anaesthesia, the infusion rate required to maintain neuromuscular block at this level ranges from 0.3-0.6 mg/kg/h (300-600 micrograms/kg/h) and under inhalational anaesthesia the infusion rate ranges from 0.3-0.4 mg/kg/h. Continuous monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Paediatric population
For infants (28 days-2 months), toddlers (3-23 months), children (2-11 years) and adolescents (12-17 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 the exception of children (2-11 years), are the same as for adults. For children aged 2-11 years higher infusion rates might be necessary.

Thus, for children (2-11 years) the same initial infusion rates as for adults are recommended and then 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 in rapid sequence induction in paediatric patients is limited.
Rocuronium bromide is therefore not recommended for facilitating tracheal intubation conditions during rapid sequence induction in paediatric patients.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The standard intubation dose for geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure during routine anaesthesia is 0.6 mg/kg rocuronium bromide. A dose of 0.6 mg/kg should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected. Regardless of the anaesthetic technique used, the recommended maintenance dose for these patients is 0.075-0.1 mg/kg rocuronium bromide, and the recommended infusion rate is 0.3-0.4 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 weight of 30% or more above ideal body weight) doses should be reduced taking into account 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 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 80-90% (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 the individual response. Thereafter, individual dose requirements remain relatively constant.

A large between patient variability in hourly infusion rates has been found in controlled clinical studies, with mean hourly infusion rates ranging from 0.2-0.5 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. Administration up to 7 days has been investigated.

Special populations
Rocuronium bromide Kalceks is not recommended for the facilitation of mechanical ventilation in the intensive care in paediatric and geriatric patients due to a lack of data on safety and efficacy.

Method of administration
Rocuronium bromide Kalceks is administered intravenously either as a bolus injection or as a continuous infusion (see section 6.6).

4.3 Contraindications

Hypersensitivity to rocuronium or to the bromide ion or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Since Rocuronium bromide Kalceks causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug 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 . In order to prevent complications resulting from residual neuromuscular blockade, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Geriatric 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 acetylcholinesterase 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 Kalceks , hypersensitivity to other neuromuscular blocking agents should be excluded. Rocuronium bromide Kalceks 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 Kalceks should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Because rocuronium bromide is always used with other drugs 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 Kalceks 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 Kalceks :

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 Kalceks 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 Kalceks may have profound effects and Rocuronium bromide Kalceks should be titrated to the response.

Hypothermia

In surgery under hypothermic conditions, the neuromuscular blocking effect of Rocuronium bromide Kalceks is increased and the duration prolonged.

Obesity

Like other neuromuscular blocking agents, Rocuronium bromide Kalceks 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 Kalceks

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.

Sodium

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

4.5 Interactions with other medicinal products and other forms of interaction

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

Effect of other drugs on Rocuronium bromide Kalceks

Increased effect:
- Halogenated volatile anaesthetics potentiate the neuromuscular block of Rocuronium bromide Kalceks . 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 Kalceks in the ICU may result in prolonged duration of neuromuscular block or myopathy (see section 4.4 and 4.8).

Other drugs:
- 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 i.v, bupivacaine epidural) and acute administration of phenytoin or β-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 Kalceks 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 Kalceks may produce potentiation or attenuation of the neuromuscular blocking effect of Rocuronium bromide Kalceks .

Effect of Rocuronium bromide Kalceks on other drugs

Rocuronium bromide Kalceks combined with lidocaine may result in a quicker onset of action of lidocaine.

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 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. Caution should be exercised when prescribing Rocuronium bromide Kalceks to pregnant women.

Caesarean section
In patients undergoing Caesarean section, Rocuronium bromide Kalceks 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 Kalceks , 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 parturients undergoing Caesarean section. Rocuronium bromide Kalceks 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 Kalceks 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 Kalceks during lactation. Rocuronium bromide Kalceks should be given to lactating women only when the attending physician decides that the benefits outweigh the risks. 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.

4.7 Effects on ability to drive and use machines

Since Rocuronium bromide Kalceks 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

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. See also the explanations below the table.

Tabulated list of adverse reactions

MedDRA SOC	Preferred term[1]		
	Uncommon / Rare[2] (<1/100,>1/10000)	Very rare (<1/10000)	Not Known
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock	
Nervous system disorders		Flaccid paralysis	
Eye disorders			Mydriasis[2,3] Fixed pupils[2,3]
Cardiac disorders	Tachycardia		Kounis syndrome
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing	
Respiratory, thoracic and mediastinal disorders		Bronchospasm	
Skin and subcutaneous tissue disorders		Angioneurotic oedema Urticaria Rash Erythematous rash	
Musculoskeletal and connective tissue disorders		Muscular weakness[4] Steroid myopathy[4]	

General disorders and administration site conditions	Drug ineffective Drug effect/therapeutic response decreased Drug effect/therapeutic response increased Injection site pain Injection site reaction	Face oedema	
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anaesthesia	Airway complication of anaesthesia	

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[1] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.

[2] Post- marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over three rather than five categories.

[3] In the context of a potential increase of permeability or compromise of the integrity of the Blood-Brain Barrier (BBB)

[4] After long- term use in the ICU.

Anaphylaxis

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including rocuronium bromide , 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 drugs.

In clinical studies only a slight increase in mean plasma histamine levels has been observed following rapid bolus administration of 0.3-0.9 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 drug'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 clinical 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 clinical 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%.

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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose

In the event of overdosage 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)

An acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) or sugammadex can be used once spontaneous recovery starts and should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent fails to reverse the neuromuscular effects of Rocuronium bromide Kalceks , 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action
Rocuronium bromide Kalceks (rocuronium bromide) is a fast onset, intermediate acting non-depolarising neuromuscular blocking agent, possessing all of the characteristic pharmacological actions of this class of drugs (curariform). 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.

Pharmacodynamic effects
The ED_{90} (dose required to produce 90% depression of the twitch response of the thumb to stimulation of the ulnar nerve) during intravenous anaesthesia is approximately 0.3 mg/kg rocuronium bromide. The ED_{95} in infants is lower than in adults and children (0.25, 0.35 and 0.40 mg/kg respectively).

The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with 0.6 mg/kg rocuronium bromide is 30-40 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 50 minutes. The mean time of spontaneous recovery of twitch response from 25 to 75% (recovery index) after a bolus dose of 0.6 mg/kg rocuronium

bromide is 14 minutes. With lower dosages of 0.3-0.45 mg/kg rocuronium bromide (1-1$^1/_2$ x ED_{90}), onset of action is slower and duration of action is shorter. With high doses of 2 mg/kg, clinical duration is 110 minutes.

Intubation during routine anaesthesia
Within 60 seconds following intravenous administration of a dose of 0.6 mg/kg rocuronium bromide (2 x ED_{90} under intravenous anaesthesia), adequate intubation conditions can be achieved in nearly all patients of which in 80% intubation conditions are rated excellent. General muscle paralysis adequate for any type of procedure is established within 2 minutes.
After administration of 0.45 mg/kg rocuronium bromide, acceptable intubation conditions are present after 90 seconds.

Rapid Sequence Induction
During rapid sequence induction of anaesthesia under propofol or fentanyl/thiopental anaesthesia, adequate intubation conditions are achieved within 60 seconds in 93% and 96% of the patients respectively, following a dose of 1.0 mg/kg rocuronium bromide. Of these, 70% are rated excellent. The clinical duration with this dose approaches 1 hour, at which time the neuromuscular block can be safely reversed. Following a dose of 0.6 mg/kg rocuronium bromide, adequate intubation conditions are achieved within 60 seconds in 81% and 75% of the patients during a rapid sequence induction technique with propofol or fentanyl/thiopental, respectively.

Paediatric population
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.

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
The duration of action of maintenance doses of 0.15 mg/kg rocuronium bromide, might be somewhat longer under enflurane and isoflurane anaesthesia in geriatric patients and in patients with hepatic and/or renal disease (approximately 20 minutes) than in patients without impairment of excretory organ functions under intravenous anaesthesia (approximately 13 minutes) (see section 4.2). No accumulation of effect (progressive increase in duration of action) with repetitive maintenance dosing at the recommended level has been observed.

Intensive Care Unit
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 (1-5) hours in patients without multiple organ failure and 4 (1-25) hours in patients with multiple organ failure.

Cardiovascular surgery
In patients scheduled for cardiovascular surgery the most common cardiovascular changes during the onset of maximum block following 0.6-0.9 mg/kg rocuronium bromide are a slight and clinically insignificant 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 Kalceks .

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 (66-80) minutes, the (apparent) volume of distribution at steady state conditions is 203 (193 - 214) ml/kg and plasma clearance is 3.7 (3.5 - 3.9) ml/kg/min.

Rocuronium is excreted in urine and bile. Excretion in urine approaches 40% within 12-24 hours. After injection of a radiolabeled 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. No metabolites are detected in plasma.

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

Geriatric patients and patients with hepatic and/or biliary tract disease and/or renal failure
In controlled studies the plasma clearance in geriatric 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 (see section 4.2).

Intensive Care unit
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 (see section 4.2).

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

There is no proper animal model to mimic the usually extremely complex clinical situation of the ICU patient. Therefore the safety of Rocuronium bromide Kalceks when used to facilitate mechanical ventilation in the Intensive Care Unit is mainly based on results obtained in clinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Sodium acetate trihydrate Acetic acid glacial
(for pH adjustment)
Water for injection
No preservative has been added.

6.2 Incompatibilities

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

Rocuronium bromide Kalceks must not be mixed with other medicinal products except those mentioned in section 6.6.

If Rocuronium bromide Kalceks is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Rocuronium bromide Kalceks and drugs for which incompatibility with rocuronium bromide has been demonstrated or for which compatibility with Rocuronium bromide Kalceks has not been established.

6.3 Shelf life

Unopened vial:
The expiry date of the product is indicated on the packaging materials (see also section 6.4 “Special precautions for storage”). Since Rocuronium bromide Kalceks does not contain a preservative, the solution should be used immediately after opening the vial.

Diluted solution:

The chemical and physical in-use stability of the diluted product (see section 6.6) has been demonstrated for 72 hours at 30°C.
From a microbiological point of view, the diluted product should be used immediately after dilution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user/administrator and would normally not be longer than 24 hours at 2 to 8°C unless the dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Storage in the Refrigerator
Store in the refrigerator (2 -8°C). Do not freeze.

Storage out of the refrigerator

The product may also be stored outside the refrigerator at a temperature of up to 25°C for a maximum of 12 weeks, after which it should be discarded. The product should not be placed back into the refrigerator once it has been kept outside. After first removal from the refrigerator, the 12 week shelf life applies and must not exceed the expiry date given on the pack.

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

6.5 Nature and contents of container

5 ml of solution is filled in a colourless (type I) glass vial closed with a bromobutyl rubber stopper and flip-off aluminium cap.
Package size: 10 vials.

6.6 Special precautions for disposal and other handling

For single use.

Compatibility studies with the following infusion fluids have been performed: In nominal concentrations of 0.5 mg/ml and 2.0 mg/ml Rocuronium bromide Kalceks has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections and Lactated Ringers solution.

Administration should be begun immediately after dilution, and should be completed within 24 hours. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

FAMAR HEALTHCARE SERVICES MADRID, S.A.U, SPAIN AVDA. DE LEGANES, 62, 28923, ALCORCON,MADRID, SPAIN

8. MARKETING AUTHORIZATION HOLDER

A.L. MEDI-MARKET LTD.
3 , HAKATIF STREET , EMEK HEFER INDUSTRIAL PARK , 3877701

9. MARKETING AUTHORIZATION NUMBER

165-82-35870-00

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