Know The Product (KTP)

For the use of a Registered Medical Practitioner or a Hospital or a Laboratory

This information is intended for use by health professionals only

ROCUMIDE

(Rocuronium Bromide Injection)

For Intravenous use

COMPOSITION:
Each ml contains Rocuronium Bromide 10 mg

DESCRIPTION: Rocuronium Bromide is an aminosteroid non-depolarizing neuromuscular blocker or muscle relaxant that facilitates endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

THERAPEUTIC CLASS: Neuromuscular Blockers

CLINICAL PARTICULARS:
Therapeutic indications:
Rocuronium bromide is indicated in adult and paediatric patients (from term neonates to adolescents (0 to < 18 years)) as an adjunct to general anaesthesia to facilitate tracheal intubation during routine sequence induction and to provide skeletal muscle relaxation during surgery. In adults, Rocuronium

bromide is also indicated to facilitate tracheal intubation during rapid sequence induction and as an adjunct in the intensive care unit (ICU) (e.g. to facilitate intubation) for short term use.

POSOLOGY AND METHOD OF ADMINISTRATION:

As with other neuromuscular blocking agents, the dosage of rocuronium bromide 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 medicinal products 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.

Inhalational anaesthetics potentiate the neuromuscular blocking effects of rocuronium bromide. This potentiation becomes clinically relevant during the course of anaesthesia when a certain tissue concentration of the volatile agents is reached. Consequently, adjustments should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of rocuronium bromide during long lasting procedures (longer than 1 hour) under inhalational anaesthesia.

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.

This medicinal product is for single use only.

Surgical Procedures

Tracheal intubation:
The standard intubating dose during routine anaesthesia is 0.6 mg rocuronium bromide per kg body weight, which results in adequate intubation conditions within 60 seconds in nearly all patients. A dose of 1.0 mg rocuronium bromide per kg body weight 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 If a dose of 0.6 mg rocuronium bromide per kg body weight is used for rapid sequence induction of anaesthesia, it is recommended to intubate the patient 90 seconds after administration of rocuronium bromide.

Maintenance dosage:
The recommended maintenance dose is 0.15 mg rocuronium bromide per kg body weight. In case of long-term inhalational anaesthesia, it should be reduced to 0.075 - 0.1 mg of rocuronium bromide per kg body weight.

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 (TOF) are present.

Continuous infusion:
If rocuronium bromide is administered by continuous infusion, it is recommended to give a loading dose of 0.6 mg rocuronium bromide per kg body weight 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 pregnant patients:
In patients undergoing Caesarean section, it is recommended to only use a dose of 0.6 mg rocuronium bromide per kg body weight, since a 1.0 mg/kg dose has not been investigated in this patient group.

Reversal of neuromuscular block induced by neuromuscular blocking agents 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 should be reduced and be titrated to twitch response.

Dosage in paediatric patients:
For neonates (0-28 days), infants (28 days to 3 months), toddlers (>3 months to 2 years), children (2-11 years) and adolescents (12 to 17 years) the recommended intubation dose during routine anaesthesia and maintenance dose are similar to those in adults.
However, the duration of action of the single intubating dose will be longer in neonates and infants than in children.

For continuous infusion in paediatric patients, the infusion rates, with exception of children, are the same as for adults. For children higher infusion rates might be necessary.

Thus, for children the same initial infusion rates as for adults are recommended which should be then 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.

Dosage in 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 rocuronium bromide per kg body weight. A dose of 0.6 mg per kg body weight should be considered for rapid sequence induction of anaesthesia in patients in which a prolonged duration of action is expected however adequate conditions for intubation may not be established for 90 seconds after administration of rocuronium bromide. Regardless of the anaesthetics technique used, the recommended maintenance dose for these patients is 0.075 - 0.1 mg rocuronium bromide per kg body weight, and the recommended infusion rate is 0.3 - 0.4 mg/kg/h (see also 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 a lean body mass.

Intensive care procedures

Tracheal intubation

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

Method of administration

Rocuronium bromide is administered intravenously (i.v.) either as a bolus injection or as a continuous infusion.

CONTRAINDICATIONS:
Hypersensitivity to Rocuronium bromide

UNDESIRABLE EFFECTS: Injection site pain/reaction, anaphylactic reaction e.g. anaphylactic shock, circulatory collapse and shock, tachycardia, bronchospasm

SPECIAL WARNINGS AND PRECAUTIONS FOR USE:
Rocuronium bromide should be administered only by an experienced staff familiar with the use of neuromuscular blocking agents. Adequate facilities and staff for endotracheal intubation and artificial ventilation have to be available for immediate use.

Since rocuronium bromide causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this active substance 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 curarization has been reported for Rocuronium. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block. Other factors which could cause residual curarization 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 should be considered, especially in those cases where residual curarization 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.

Anaphylactic reactions (see above) can occur after the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.

Dose levels higher than 0.9 mg rocuronium bromide per kg body weight may increase the heart rate; this effect could counteract the bradycardia produced by other anaesthetic agents or by vagal stimulation.

In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has

been noted. 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 muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants should be titrated to the effect in the individual patient. This should be done by or under the supervision of experienced clinicians who are familiar with the effects and with appropriate neuromuscular monitoring techniques.

Because rocuronium bromide is always used with other agents and because of the possibility of the occurrence of malignant hyperthermia during anaesthesia, even in the absence of known triggering agents, clinicians should be familiar with the early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anaesthesia. In animal studies it was shown that rocuronium bromide is not a triggering factor for malignant hyperthermia.

Myopathy has been reported after long-term concurrent use of non-depolarisating neuromuscular blockers and corticosteroids. The co-administration period should be reduced to be as short as possible.

Rocuronium should only be administered after full recovery from the neuromuscular blockade caused by suxamethonium.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of rocuronium bromide:

Hepatic and/or biliary tract disease and renal failure

Rocuronium bromide is excreted in urine and bile. 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 the effect has been observed with doses of 0.6 mg rocuronium bromide per kg body weight.

Prolonged circulation time
Conditions associated with prolonged circulation time such as cardiovascular diseases, old age and an oedematous state resulting in an increased volume of distribution, may contribute to a slower onset of the effect.

Neuromuscular disease
Like other neuromuscular blocking agents, rocuronium bromide 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 may have profound effects and rocuronium bromide should be titrated to the response.

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

Obesity

Like other neuromuscular blocking agents, rocuronium bromide 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-depolarizing neuromuscular blocking agents. It is recommended that the dose is titrated to the response.

Conditions which may increase the effects of rocuronium bromide
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.

Paediatric population
The same warnings and precautions as for adults should be taken into consideration.

OVERDOSE:
In the event of overdose and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase inhibiting agent

fails to reverse the neuromuscular effects of rocuronium bromide, artificial ventilation must be continued until spontaneous breathing is restored. Repeated dosages of an acetylcholinesterase inhibitor can be dangerous.

INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORM OF INTERACTION:

The following medicinal products have been shown to influence the magnitude and/or duration of the effect of non-depolarizing neuromuscular blocking agents:

Increased effect:

▪ Halogenated volatile anaesthetics

▪ High doses of: thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate and propofol

▪ Other non-depolarizing neuromuscular blocking agents.

▪ Prior administration of suxamethonium.

▪ Long term concomitant use of corticosteroids and Rocuronium in the ICU may result in prolonged duration of neuromuscular block or myopathy.

Other medicinal products:

- antibiotics: aminoglycosides, lincosamides (e.g. lincomycin and clindamycin), polypeptide antibiotics, acylamino-penicillin antibiotics, tetracyclines, high doses of metronidazole.

- diuretics, thiamine, MAO inhibiting agents, quinidine and its isomer quinine, protamine, adrenergic blocking agents, magnesium salts, calcium channel blocking agents and lithium salts and local anaesthetics (lidocaine i.v., bupivacaine epidural).

Decreased effect:

▪ Neostigmine, edrophonium, pyridostigmine, aminopyridine derivatives

▪ Prior chronic administration of corticosteroids, phenytoin or carbamazepine

▪ Noradrenaline, azathioprine (only transient and limited effect), theophylline, calcium chloride, potassium chloride

▪ Protease inhibitors

Variable effect:

Administration of other non-depolarizing neuromuscular blocking agents in combination with rocuronium bromide 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 may produce potentiation or attenuation of the neuromuscular blocking effect of rocuronium bromide.

Effect of rocuronium on other drugs:

Combined use with lidocaine could result in a more instant effect of lidocaine. Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts.

Paediatric patients:

No formal interaction studies have been performed. The above mentioned interactions for adults should also be taken into account for paediatric patients.

PREGNANACY AND LACTATION:

Rocuronium bromide should only be given to pregnant women when strictly necessary and the attending physician decides that the benefits outweigh the risks. Use of rocuronium bromide during caesarean section at doses of 0.6 mg/kg bodyweight does not affect the Apgar score, the foetal muscle tone or the cardio respiratory adaptation.

It is unknown whether rocuronium bromide/metabolites are excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rocuronium bromide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES:

Rocuronium bromide has a major influence on the ability to drive and use machines**.** It is not recommended to use potentially dangerous machinery or to drive a car during the first 24 hours after the full recovery from the neuromuscular blocking action of rocuronium bromide.

PHARMACOLOGICAL PROPERTIES:

Pharmacodynamic properties:

Rocuronium bromide is an intermediate acting, non-depolarizing neuromuscular blocking agent with a fast onset, possessing all of the characteristic pharmacological actions of this class of medicinal products (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.

Pharmacokinetic properties:

Distribution and elimination: After intravenous administration of a single bolus dose of rocuronium bromide, the time course of the plasma concentration runs in three exponential phases. In normal adults, the mean (95%Cl) 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.

The plasma clearance in geriatric patients and in patients with renal dysfunction is slightly reduced compared to younger patients with normal renal function. In patients with hepatic diseases, the mean elimination half-life is prolonged by 30 minutes and the mean plasma clearance is reduced by 1 ml/kg/min.

When administered as a continuous infusion to facilitate mechanical ventilation for a time period of 20 hours or more, the mean elimination half-life and the mean (apparent) volume of distribution at steady state are increased. A high variability between patients was found in controlled clinical studies, related to the 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, an (apparent) volume of distribution at steady state of 1.5 (±0.8) $l \cdot kg^{-1}$ and a plasma clearance of 2.1 (±0.8) ml/kg/min were found.

Rocuronium bromide is excreted in urine and bile. Excretion in urine approaches 40 % within 12 - 24 hours. After injection of a

radio labeled 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 rocuronium bromide.

Biotransformation: No metabolites are detected in the plasma.

Incompatibilities:
Physical incompatibility has been documented for rocuronium bromide when added to solutions containing the following active substance: 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.

Instructions for use/handing:
Since ROCURONIUM BROMIDE does not contain a preservative, the solution should be used immediately after opening the vial. Any 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.

Compatibility:
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 has been shown to be compatible with: 0.9% NaCl, 5% dextrose, 5% dextrose in saline, sterile water for injections, Lactated Ringers and Haemaccel. Administration should be begun immediately after mixing, and

should be completed within 24 hours. Any unused medicinal product or waste material should be disposed.

Rocuronium Bromide Injection (rocuronium bromide), which has an acidic pH (pH: 3.8 - 4.2), should not be mixed with alkaline solutions (e.g. barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle. If Rocuronium Bromide Injection 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 Injection and drugs for which incompatibility with Rocuronium Bromide Injection has been demonstrated or for which compatibility with Rocuronium Bromide Injection has not been established.

STORAGE: Store in a refrigerator (2°C - 8°C). Do not freeze. Keep out of reach of children.

Storage out of the refrigerator:
Rocuronium may also be stored outside of the refrigerator at a temperature of up to 30°C for a maximum 12 weeks, after which it should be discarded. The product should not be placed back into the refrigerator, once it has been kept outside. The storage period must not exceed the shelf-life.

PRESENTATION:
Each box contains 1 vial of 5 ml.

National
Healthcare
Manufactured by :
National Healthcare Pvt. Ltd.
Chhatapipra, Bara, Nepal.