VECURONIUM HIKMA®

(Vecuronium bromide)

ACTION

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents. Vecuronium is a non-depolarising neuromuscular blocking agent, chemically designated as the aminosteroid 1-(3a, 17bdiacetoxy-2bpiperidino-5a-androstan-16byl)-1 methylpiperidinium bromide. Vecuronium blocks the transmission process between the motor nerve-ending and striated muscle by binding competitively with acetylcholine to the nicotinic receptors located in the motor end-plate region of striated muscle. Unlike depolarising neuromuscular blocking agents, such as suxamethonium, Vecuronium does not cause muscle fasciculations. Within the clinical dosage range, Vecuronium exerts no vagolytic nor ganglion blocking activity.

Tracheal intubation

Within 90 to 120 seconds following intravenous administration of a dose of 0.08 to 0.10 mg vecuronium bromide per kg body weight, good to excellent conditions for tracheal intubation occur and within 3 to 4 minutes following administration of these dosages, general muscle paralysis adequate for any type of surgery is established. The duration of action to 25% recovery of control twitch height (clinical duration) with this dose is 24 to 60 minutes. The time to 95% recovery of control twitch height following this dose is approximately 60 to 80 minutes. With higher dosages of Vecuronium, onset time to maximal block is shortened and duration of action is prolonged.

Continuous intravenous infusion

In case Vecuronium is administered by continuous intravenous infusion, a steady state neuromuscular blockade of 90% can be maintained at a constant rate of delivery and without clinically significant prolongation of the recovery time from neuromuscular block at termination of the infusion. Vecuronium has no cumulative effects if maintenance doses are administered at 25% recovery of control twitch height. Several maintenance doses can therefore be given in succession. The abovementioned properties mean that Vecuronium can be used equally as well in short as in long lasting surgical procedures.

Reversal of neuromuscular block

Administration of acetylcholinesterase inhibitors, such as neostigmine, pyridostigmine or edrophonium, antagonises the action of Vecuronium.

Use in paediatrics

Neonates and infants: In neonates and infants the ED95 dose of vecuronium bromide under nitrous oxide in oxygen anaesthesia was found to be approximately the same (approx. 47µg/kg body weight) as in adults. The onset time of Vecuronium in neonates and infants is considerably shorter as compared to children and adults, probably due to the shorter circulation time and relatively large cardiac output. Also, a greater sensitivity of the neuromuscular junction to the action of neuromuscular blocking agents in these patients may account for a more rapid onset of action. The duration of action and recovery time with Vecuronium is longer in neonates and infants than in adults. Maintenance doses of Vecuronium should therefore be less frequently administered.

Children: In children the ED95 dose of vecuronium bromide under nitrous oxide in oxygen anaesthesia was found to be higher than in adults (0.081 vs 0.043 mg/kg body weight, respectively). In comparison to adults, the duration of action and recovery time with Vecuronium in children are in general approximately 30% and 20-30% shorter respectively. Similar to adults, cumulative effects with repeat maintenance doses of approximately one quarter of the initial dose, and administered at 25% recovery of control twitch height are not observed in paediatric patients.

INDICATIONS

Vecuronium is indicated as an adjunct to general anaesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery.

DOSAGE AND ADMINISTRATION

Dosage

Like other neuromuscular blocking agents, Vecuronium should only be administered by, or under supervision of, experienced clinicians who are familiar with the action and use of these agents. Like with other neuromuscular blocking agents, the dosage of Vecuronium should be individualised in each patient. The anaesthetic method used, the expected duration of surgery, the possible interaction with other medicines that are administered before or during anaesthesia 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 to monitor neuromuscular block and recovery. Inhalational anaesthetics do potentiate the neuromuscular blocking effects of Vecuronium. 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 Vecuronium should be made by administering smaller maintenance doses at less frequent intervals or by using lower infusion rates of Vecuronium during long lasting procedures (longer than 1 hour) under inhalational anaesthesia.

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.

Tracheal intubation

The standard intubating dose during routine anaesthesia is 0.08 to 0.1 mg vecuronium bromide per kg body weight, after which adequate intubation conditions are established within 90 to 120 seconds in nearly all patients.

Dosages of Vecuronium for surgical procedures after intubation with suxamethonium:

Recommended doses: 0.03 to 0.05 mg vecuronium bromide per kg body weight. If suxamethonium is used for intubation, the administration of Vecuronium should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Maintenance dosing: The recommended maintenance dose is 0.02 to 0.03 mg vecuronium bromide per kg body weight. These maintenance doses should best be given when twitch height has recovered to 25% of control twitch height.

Dose requirements for administration of Vecuronium by continuous infusion

If Vecuronium is administered by continuous infusion, it is recommended to give a loading dose first and, when neuromuscular block starts to recover, to start administration of Vecuronium 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, the infusion rate required to maintain neuromuscular block at this level, ranges from 0.8 to 1.4µg vecuronium bromide/kg/min. For neonates and infants, see below. Repeat monitoring of neuromuscular block is recommended since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Dosing in elderly patients

The same intubation and maintenance doses as for younger adults (0.08-0.1 mg/kg and 0.02-0.03 mg/kg, respectively) can be used. However, the duration of action is prolonged in elderly compared to younger subjects due to changes in pharmacokinetic mechanisms. The onset time in elderly is similar to younger adults. In caesarean section and neonatal surgery the dose should not exceed 0.1 mg/kg.

Dosing in paediatric patients

Because of the possible variation of the sensitivity of the neuromuscular junction, especially in neonates (up to 4 weeks) and probably in infants up to 4 months of age, an initial test dose of 0.01 to 0.02 mg vecuronium bromide per kg body weight followed by incremental doses until 90 to 95% depression of twitch response is achieved is recommended. In neonatal surgery the dose should not exceed 0.1 mg/kg. Dose requirements in neonates and infants (1-12 months) are the same as in adults. However, since the onset time of Vecuronium in these patients is considerably shorter than in adults and children, the use of high intubating doses in general is not required for early development of good intubating conditions. Since the duration of action and recovery time with Vecuronium is longer in neonates and infants than in children and adults, maintenance doses are required less frequently. Dose requirements in children (2-10 years) are higher. However, the same intubation and maintenance doses as for adults (0.08-0.1 mg/kg and 0.02-0.03 mg/kg, respectively) are usually sufficient. Since the duration of action is shorter in children, maintenance doses are required more frequently. Although there is very little information on dosage in adolescents, it is advised to use the same dose as in adults, based on the physiological development at this age.

Dosing 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 weight.

Higher doses

Should there be reason for selection of larger doses in individual patients, initial doses ranging from 0.15 mg up to 0.30 mg vecuronium bromide per kg body weight have been administered during surgery both under halothane and neurolept anaesthesia without adverse cardiovascular effects being noted as long as ventilation is properly maintained. The use of these high dosages of Vecuronium pharmacodynamically decreases the onset time and increases the duration of action.

Administration

Vecuronium should be administered following reconstitution. Vecuronium is administered intravenously either as a bolus injection or as a continuous infusion.

RECONSTITUTION

Vecuronium 4 mg:

Addition of 1ml water for injections results in an isotonic solution of pH 4 containing 4 mg vecuronium bromide per ml. (4 mg/ml)

Vecuronium 10 mg:

Addition of 5 ml water for injections results in an isotonic solution of pH 4 containing 2 mg vecuronium bromide per ml. (2 mg/ml) Alternatively, in order to obtain a solution with a lower concentration, Vecuronium 4 mg and Vecuronium 10 mg may be reconstituted with a volume up to 4 ml and 10 ml respectively of the following infusion fluids:

• 5% glucose injection fluid. • 0.9% sodium chloride injection fluid. • Lactated Ringer's solution. • Lactated Ringer's injection and 5% glucose. • Glucose 5% and 0.9% sodium chloride injection.

Following reconstitution, refrigerate. Use within 8 hours. Intended for single use only.

COMPATIBILITY

When Vecuronium is reconstituted with water for injections, the resultant solution can be mixed with the following infusion fluids, packed in PVC or glass, to a dilution up to 40 mg/litre:

• 0.9% NaCl solution. • 5% glucose solution. • Ringer's solution. • Ringer's glucose.

The abovementioned reconstituted solution can also be injected into the line of a running infusion of the following fluids:

• Lactated Ringer's solution. • Lactated Ringer's solution and 5% glucose. • Glucose 5% and 0.9% NaCl solution. • Haemaccel. • Dextran-40 5% in 0.9% NaCl solution

Compatibility studies with other infusion fluids have not been performed.

As is the case for many other agents, incompatibility has been documented for Vecuronium when added to thiopental. Except for those solutions with which Vecuronium has shown to be compatible, it is not recommended to mix Vecuronium with other solutions, or agents in the same syringe or bag. If Vecuronium 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 Vecuronium and medicines for which incompatibility with Vecuronium has been demonstrated or for which compatibility with Vecuronium has not been established.

CONTRAINDICATIONS

Hypersensitivity to vecuronium or the bromide ion or any of the excipients of Vecuronium.

WARNINGS AND PRECAUTIONS

Since Vecuronium causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this medicine until adequate spontaneous respiration is restored. As with other neuromuscular blocking agents, residual curarization has been reported for Vecuronium. 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 medicine 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. Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to muscle relaxants, special precautions should be taken since allergic cross-reactivity to muscle relaxants has been reported.

Since Vecuronium has no cardiovascular effects within the clinical dosage range, it does not attenuate bradycardia that may occur due to the use of some types of anaesthetics and opiates or due to vagal reflexes during surgery. Therefore, reassessment of the use and/or dosage of vagolytic medicines such as atropine for premedication or at induction of anaesthesia, may be of value for surgical procedures during which vagal reactions are more likely to occur (e.g. surgical procedures where anaesthetic medicines with known vagal stimulatory effects are used, ophthalmic, abdominal or anorectal surgery, etc). 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 muscle relaxants. In addition, patients should receive adequate analgesia and sedation. Furthermore, muscle relaxants 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 non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported frequently. 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.

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

Hepatic and/or biliary tract disease: Because vecuronium is excreted in bile and in urine, Vecuronium 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, especially when high doses of vecuronium (0.15-0.2 mg/kg body weight) were administered in patients with hepatic disease.

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

Neuromuscular disease: As with other neuromuscular blocking agents, Vecuronium should be used with extreme caution in cases of neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these patients. The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravis or the myasthenic (Eaton Lambert) syndrome, small doses of Vecuronium may have profound effects and Vecuronium should be titrated to the response.

Hypothermia: In operations under hypothermia, the neuromuscular blocking effect of Vecuronium is increased and the duration is prolonged.

Obesity: Like other neuromuscular blocking agents, Vecuronium 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 agents. It is recommended that the dose is titrated to response.

Conditions which may increase the effects of Vecuronium are: 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.

Use During Pregnancy And Lactation: There are insufficient data on the use of Vecuronium during animal or human pregnancy to assess potential harm to the foetus. Vecuronium should be given to a pregnant woman only when the attending physician decides that the benefits outweigh the risks.

Caesarean section: Studies with Vecuronium, administered in doses up to 0.1 mg/kg, have shown its safety for use in caesarean section. In caesarean section the dose should not exceed 0.1 mg/kg. In several clinical studies Vecuronium did not affect Apgar score, foetal muscle tonus or cardiorespiratory adaptation. From umbilical cord blood sampling it is apparent that only very little placental transfer of Vecuronium occurs which did not lead to the observation of any clinical adverse effect in the newborn.

Note: Reversal of a Vecuronium -induced neuromuscular block may be inhibited or unsatisfactory in patients receiving magnesium sulphate for toxaemia of pregnancy because magnesium salts enhance neuromuscular block.Therefore, in patients receiving magnesium sulphate, the dosage of Vecuronium should be reduced and be carefully titrated to twitch response.

Lactation: There are no human data on the use of Vecuronium during lactation. Vecuronium should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

Preclinical Safety Data: Vecuronium bromide showed no genotoxic, embryotoxic or teratogenic potential. Single and repeated dose toxicity studies in rats, dogs and cats revealed no special hazard for humans.

Effects on ability to drive and use machinery: Since Vecuronium is used as an adjunct to general anaesthesia, the usual precautionary measures after a general anaesthesia should be taken for ambulatory patients.

SIDE EFFECTS

Side effects are rare (<1/1000). The most commonly occurring ADRs include changes in vital signs and prolonged neuromuscular block.

Uncommon/rare (<1/100, >1/10,000) - Very rare: (<1/10,000).

Immune system disorders

Very rare: Hypersensitivity, Anaphylactic reaction, Anaphylactoid reaction, Anaphylactic shock, Anaphylactoid shock.

Nervous system disorders

Very rare: Flaccid paralysis.

Cardiac disorders

Uncommon/rare: Tachycardia.

Vascular disorders

Uncommon/rare: Hypotension.

Very rare: Circulatory collapse and shock, Flushing.

Respiratory, thoracic and mediastinal disorders

Very rare: Bronchospasm.

Skin and subcutaneous tissue disorders

Very rare: Angioneurotic oedema, Urticaria, Rash, Erythematous rash.

Musculoskeletal and connective tissue disorders

Very rare: Muscular weakness- Steroid myopathy.

General disorders and administration site conditions

Uncommon/rare: Drug ineffective, Decreased drug effect/therapeutic response, Increased drug effect/therapeutic response

Very rare: Face oedema, Injection site pain, Injection site reaction.

Injury, poisoning and procedural complications

Uncommon/rare: Prolonged neuromuscular block, Delayed recovery from anaesthesia.

Very rare: Airway complication of anaesthesia.

Prolonged Neuromuscular Block

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the medicine's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnoea. A few cases of myopathy have been reported after Vecuronium was used in the ICU in combination with corticosteroids.

Anaphylactic And Histaminoid Reactions

Anaphylactic Reactions

Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Vecuronium, have been reported. Anaphylactic/anaphylactoid reactions usually comprise of several signs or symptoms, e.g. 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.

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 agents. Experimental studies with intradermal injection of Vecuronium have demonstrated that this medicine has only a weak capacity for inducing local histamine release. Controlled studies in humans failed to demonstrate any significant rise in plasma histamine levels after intravenous administration of Vecuronium. Still, such cases have rarely been reported during large scale use of Vecuronium.

Drug Interactions

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

Effect of other agents on Vecuronium:

Increased Effect

• Halogenated volatile anaesthetics potentiate the neuromuscular block of Vecuronium. The effect only becomes apparent with maintenance dosing. Reversal of the block with anticholinesterase inhibitors could also be inhibited.
• After intubation with suxamethonium
• Long-term concomitant use of corticosteroids and Vecuronium in the ICU may result in prolonged duration of neuromuscular block or myopathy.

Other medicines

• Antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylaminopenicillin antibiotics,
• Diuretics, quinidine, magnesium salts, calcium channel blocking agents, lithium salts, cimetidine, lidocaine and acute administration of phenytoin or ß-blocking agents
• Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino- penicillin antibiotics, quinidine and magnesium salts

Decreased Effect (possible higher dose requirements)

• prior chronic administration of phenytoin or carbamazepine.

Variable Effect

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

Effect of Vecuronium on other agents:

Effect of Vecuronium on lidocaine: Vecuronium combined with lidocaine may result in a quicker onset of action of lidocaine.

OVERDOSAGE

In the event of overdosage 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 Vecuronium, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

STORAGE

Store below 30°C. Protect from light.

PRESENTATIONS

Vials

Vecuronium 4 mg: Vecuronium bromide 4 mg/vial
Vecuronium 10 mg: Vecuronium bromide 10 mg/vial

Excipients: Mannitol, dibasic sodium phosphate.

May include citric acid and/or sodium hydroxide and/ or phosphoric acid for pH adjustment

THIS IS A MEDICAMENT

• A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
• Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
• The doctor and the pharmacist are experts in medicine, its benefits and risks.
• Do not by yourself interrupt the period of treatment prescribed for you.
• Do not repeat the same prescription without consulting your doctor.

Manufactured by Hikma Italy, SpA, Italy
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Keep medicament out of the reach of children

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