Ranbaxy Pharmaceuticals (Pty) Ltd

MUSCURON 4 mg/vial

INJECTION for IV injection or by IV infusion (Vercuronium bromide)

Professional Information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

MUSCURON 4 mg/vial Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of freeze-dried powder contains 4 mg vecuronium bromide. The reconstituted solution contains 4 mg vecuronium bromide per 2 mL (4 mg/2 mL).

Contains sugar (mannitol 38,80 mg per vial)

'for full list of excipients, see section 6.1'

3. PHARMACEUTICAL FORM

White cake of lyophilized mass

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

The dosage of MUSCURON should be individualised according to individual requirement and response.

Adults

Intubating dose: The usual initial dose is 0,08 to 0,10 mg/kg body mass by IV injection. Under neurolept anaesthesia, conditions for intubation occur within 90 to 120 seconds, and within 3 to 4 minutes following administration of these dosages general muscle paralysis adequate for surgery is established.

Dosages of MUSCURON for surgical procedures after intubation with suxamethonium: 0,03 to 0,05 mg per kg body mass.

If suxamethonium is used for intubation, the administration of MUSCURON should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Maintenance dose: 0,03 to 0,05 mg per kg body mass. These maintenance doses should best be given when twitch height has recovered to 25 % of control twitch height.

Should there be reason for selection of larger doses in individual patients, initial doses ranging from 0,15 mg up to 0,30 mg per kg body mass may be administered as long as ventilation is properly maintained. The use of these high dosages of MUSCURON pharmacodynamically decreases the onset time and increases the duration of action.

Dose requirements for administration by continuous infusion

For prolonged surgical procedures MUSCURON may be given by continuous IV infusion, by further diluting the reconstituted injection to the desired concentration (0,1 to 0,2 mg/mL) in a compatible IV infusion such as 5 % dextrose and 0,9 % sodium chloride. A precise control of the flow rate during continuous infusion is required.

If MUSCURON is administered by continuous infusion, it is recommended to give a bolus dose first (ED_{90} or 2 times ED_{90} dose) and, when neuromuscular block starts to recover, to start administration of MUSCURON by infusion. The infusion rate should be adjusted to maintain twitch response at 10 % of control twitch height. In adults, the infusion rate required to maintain neuromuscular block at this level ranges from 0,8 to 1,4 µg vecuronium bromide/kg/minute. Repeated monitoring of neuromuscular block is essential since infusion rate requirements vary from patient to patient and with the anaesthetic method used.

Caesarean section

In caesarean section the dose should not exceed 0,1 mg/kg body weight.

Paediatric population

Children

The duration of action is, in general, shorter in children older than one year of age than in adults. Since the onset time of MUSCURON in children is considerably shorter, the use of high intubation doses is in general not required for early development of good intubation conditions. Maintenance doses are required more frequently in children, since the duration of action and recovery time with MUSCURON is approximately 30 % shorter in children than in adults.

Children under one year of age

Because of the possible variation of the sensitivity of the neuromuscular junction, it is recommended that an initial test dose of 0,01 to 0,02 mg per kg body mass followed by incremental doses until 90 to 95 % depression of twitch response is achieved, is given.

The duration of muscle paralysis will be prolonged in these children, up to double that seen in children.

Method of administration

MUSCURON is administered by slow IV injection or by IV infusion. MUSCURON should not be administered by IM injection.

The reconstituted solution is clear and colourless.

4.3 Contra-indications

- Hypersensitivity to the vecuronium, to bromide ion or any of the excipients listed in section 6.1.
- Safety in children 3 months or younger has not been established.
- Pregnancy and lactation as safety has not been established.

4.4 Special warnings and precautions for use

Safety and efficacy of MUSCURON in children 3 months or younger have not been established.

Monitoring respiratory function during recovery

The usual precautions of neuromuscular blocking medicine administration should be observed. MUSCURON can cause respiratory paralysis. MUSCURON should be used only by individuals who are experienced in the use of neuromuscular blocking medicines. Ventilatory support is mandatory for patients treated with this medicine until adequate spontaneous respiration is restored.

Vagal reactions

Since MUSCURON exhibits minimal effects on heart rate at the recommended doses, the medicine will not counteract the bradycardia induced when used concomitantly during anaesthesia with medicines that may cause bradycardia. 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.).

Medicine hypersensitivity reactions

Anaphylactic reactions to neuromuscular blocking medicines in general have been reported and precautions for treating such reactions if they would occur should always be taken. Allergic cross-reactivity between neuromuscular blocking medicines has been reported and special caution should be taken in the case of former anaphylactic reactions to neuromuscular-blocking medicines. MUSCURON 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.

Use in the intensive care unit (ICU)

Presently there are insufficient data to give recommendations for the use of MUSCURON in the Intensive Care Unit. As with other muscle relaxants prolonged neuromuscular block following long term use of vecuronium bromide in seriously ill patients in the Intensive Care Unit prolonged paralysis and/or skeletal muscle weakness has been reported. It is essential that during continuous neuromuscular block, patients receive adequate analgesia and sedation and that neuromuscular transmission is monitored throughout. Furthermore, muscle relaxants should be administered in carefully adjusted doses sufficient for the maintenance of less than complete block by or under the supervision of experienced clinicians who are familiar with its actions and with appropriate neuromuscular monitoring techniques.

Myopathy after long term administration of non-depolarising neuromuscular blocking medicines in the ICU in combination with corticosteroid therapy has been reported frequently. Therefore, for patients

receiving both neuromuscular blocking medicines and corticosteroids, the period of use of the neuromuscular blocking medicine should be limited as much as possible.

Residual neuromuscular blockade

As with other neuromuscular blocking medicines, residual neuromuscular blockade has been reported for MUSCURON. 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. 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.

The following disease states may influence the pharmacokinetics

and/or pharmacodynamics action of MUSCURON

Hepatic and/or biliary tract disease

Caution should be exercised when MUSCURON is administered to patients with hepatic dysfunction, since recovery from neuromuscular blockade may be prolonged in these patients. As MUSCURON is excreted mainly via the bile and in urine, moderate changes in the course of neuromuscular block induced by MUSCURON are found in patients with hepatic and /or biliary tract diseases. In these patient groups prolongation of action has been observed, especially when high doses of vecuronium (200 micrograms/kg bodyweight) were administered in patients with hepatic disease.

Renal failure

Since the neuromuscular blockade induced by the medicine may be prolonged in patients with severe renal failure (i.e. creatinine clearance less than 10 mL/minute) a lower than usual initial dose of MUSCURON should be considered in these patients.

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.

Severe obesity or neuromuscular disease

MUSCURON should be administered with caution in severely obese patients since maintenance of an adequate airway and ventilation support prior to, during and following administration of neuromuscular blocking medicines may require particular care in these patients.

As with other neuromuscular blocking medicines, MUSCURON should be used with extreme caution in cases of neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking medicines may be considerably altered in these patients.

The magnitude and direction of this alteration may vary widely. In patients with myasthenia gravisor 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 MUSCURON is increased and the duration is prolonged.

*Other c*onditions which may increase the effects of MUSCURON are:

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

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

Because malignant hyperthermia can occur even in the absence of a recognised precipitating factor, clinicians should be vigilant for its possible development and prepared for its management in any patient undergoing general anaesthesia.

Based on preclinical findings, vecuronium may cause a reduction in the partial thromboplastin time and the prothrombintime, like pancuronium bromide, d-tubocurarine or other non-depolarising neuromuscular blocking medicines.

Burns

Resistance to MUSCURON can develop in burn patients. The degree of resistance depends on the extent of thermal injury and elapsed time since the burn. Therefore, the possible need for substantially increased doses of MUSCURON in burn patients should be considered.

4.5 Interaction with other medicines and other forms of interaction

It has been shown that the following medicines can have an increased effect on the magnitude and/or duration of action of non-depolarising neuromuscular blocking medicines:

Effects of other medicines on vecuronium

- Anaesthetics: ether, isoflurane, methoxyflurane, cyclopropane, halothane and enflurane potentiate the duration and intensity of the effect of MUSCURON. High doses of thiopentone, methohexitone, ketamine, fentanyl, gam mahydroxybutyrate, etomidate.
- Other medicines: other non-depolarising muscle relaxants, prior administration of suxamethonium, aminoglycoside and polypeptide antibiotics, acylamino penicillin antibiotics, lincosamides antibiotics, diuretics, beta-adrenergic blocking medicines, lithium salts, quinidine, lidocaine, calcium-channel blockers, protamine, alpha-adrenergic blocking medicines, imidazole, high doses of metronidazole, thiamine, cimetidine, MAO inhibiting medicines, magnesium salts and acute administration of phenytoin.

A decreased effect on the magnitude and/or duration of action of non-depolarising neuromuscular blocking medicines has been shown with the following medicines:

- Neostigmine, edrophonium, pyridostigmine,aminopyridine derivatives, corticosteroids, prior chronic administration of phenytoin, carbamazepine, noradrenaline, azathioprine, theophylline, KCl, NaCl, $CaCl_2$.

Variable effects have been shown with the following medicines:

- Depolarising muscle relaxants, e.g. suxamethonium given before or after the administration of MUSCURON may produce potentiation or attenuation of the neuromuscular blocking effect of MUSCURON.

Effect of vecuronium on other medicines

Effect of vecuronium on lidocaine

MUSCURON combined with lidocaine may result in a quicker onset of action of lidocaine.

4.6 Fertility,pregnancy and lactation

Pregnancy

There are insufficient data on the use of vecuronium during animal or human pregnancy to assess potential harm to the foetus.

Note

Reversal of MUSCURON-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 MUSCURON should be reduced and be carefully titrated to twitch response.

Breastfeeding

The excretion of vecuronium bromide in milk has not been studied in animals.

Fertility

Animal studies do not indicate an effect on fertility.

4.7 Effects on ability to drive and use machines

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after the full recovery from the neuromuscular blocking action of MUSCURON.

4.8 Undesirable effects

MedDRA System organ class	Frequency	Adverse reactions

Immune system disorders	*Less frequent*	Hypersentivity, anaphylactic reaction, anaphylactoid reaction, anaphylactic shock, anaphylactoid shock
Nervous system disorders	*Less frequent*	*Flaccid paralysis*
Cardiac disorders	*Less frequent*	Tachycardia
Vascular disorders	*Less frequent*	Hypotension, circulatory collapse and shock, flushing
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Respiratory insufficiency or apnoea has been reported, bronchospasm.
Skin and subcutaneous tissue disorders	*Less frequent*	Angioneurotic oedema, urticaria, rash, erythematous rash
Musculoskeletal and connective tissue disorders	*Less frequent*	Skeletal muscle weakness or paralysis has been reported, steroid myopathy.
General disorders and administration site conditions	*Less frequent*	Face oedema, injection site pain, injection site reaction, medicine ineffective, decreased medicine effect/ therapeutic response, increased medicine effect/therapeutic response
Injury, poisoning and procedural complications	*Less frequent*	Prolonged neuromuscular block, delayed recovery from anaesthesia, airway complication of anaesthesia

c. Description of selected adverse reactions

Prolonged Neuromuscular block

The most frequent adverse reaction to non-depolarising blocking medicines 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 (see section 4.4).

Anaphylactic reactions

Although very rare, severe anaphylactic reactions to neuromuscular blocking medicines, 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 medicines are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions (see also under anaphylactic reactions above) should always be taken into consideration when administering these medicines.

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 man failed to demonstrate any significant rise in plasma histamine levels after intravenous administration of vecuronium. Nevertheless, such cases have rarely been reported during large scale use of vecuronium

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care provders are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilator support and sedation. In this situation there are two options for the reversal of neuromuscular block:

(1) 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. The use of sugammadex for the purposes of reversal of vercuronium-induced blockade is recommended for use only in the adult population.

(2) An acetylcholinesterase inhibitor (e.g. neostigmine,edrophonium, pyridostigmine) can be used once spontaneous recovery starts and should be administered in adequate doses.

When administration of a cholinesterase inhibiting medicine fails to reverse the neuromuscular effects of vecuronium, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of a cholinesterase inhibitor can be dangerous.

5 PHARMACOLOGICAL PROPERTIES

A 17.1 Peripherally acting muscle relaxants.

Pharmacotherapeutic group: muscle relaxants, peripherally acting agents, ATC code: MO3A C03.

5.1 Pharmacodynamic properties

Mechanism of action

Vecuronium bromide is a competitive, non-depolarizing neuromuscular blocker, chemically designated as the aminosteroid 1- (3α, 17β-diacetoxy-2β piperidino 5α- androstan-16β-yl)-1 methylpiperidinium bromide. It inhibits neuromuscular transmission by competing with acetylcholine for cholinergic receptors of the motor end-plate of the neuromuscular junction to produce blockade, thereby reducing the response of the end-plate to acetylcholine.

Restoration of normal neuromuscular function can be hastened by increasing the concentration of acetylcholine at the motor end-plate by giving an anticholinesterase such as neostigmine. Vecuronium bromide has little histamine-releasing activity. It also has little vagolytic or ganglion-blocking activity and at usual doses vecuronium bromide produces no significant adverse cardiovascular effects.

Unlike depolarising neuromuscular blocking medicines, such as suxamethonium, vecuronium does not cause muscle fasciculations.

Pharmacodynamic effects

Within the clinical dosage range, vecuronium does not block the sympathetic nicotininic receptors, and thus exerts noganglion blocking activity. In addition, in this dose range vecuronium does not block the parasympathetic muscarinic receptors, and thus exerts no vagolytic activity.

Tracheal intubation

Within 90 to 120 seconds following intravenous administration of a dose of 80 to 100 micrograms vecuronium bromide per kg body weight, good to excellent conditions for endotracheal 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

When vecuronium is administered by continuous intravenous infusion, a steady state neuromuscular block of 90 % can be maintained at a constant rate of medicine 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. These properties allow the use of vecuronium in short, medium and long lasting surgical procedures.

Reversal of neuromuscular block

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

Paediatric population

Children

In children the ED_{95} dose of vecuronium under balanced anaesthesia was found to be higher than in adults (81 vs 43 micrograms/kg bodyweight, 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.

5.2 Pharmacokinetic properties

- **Distribution:** After intravenous administration of 100–150 micrograms/kg vecuronium, the distribution half-life of vecuronium amounts to1,2-1,4 minutes. Vecuronium is mainly distributed in the extracellular fluid compartment. At steady state, the volume of distribution is 0,18-0,51 L.kg-1 in adult patients. The plasma clearance of vecuronium amounts to 3,0-6,4 mL.kg-1.min-1 and its plasma elimination half-life is 36-117 minutes.

- **Biotransformation:** The extent of metabolism of vecuronium is relatively low. In humans, a 3-hydroxy derivative having approximately 50 % less neuromuscular blocking potency than vecuronium is formed in the liver. In patients not suffering from renal or hepatic failure, the plasma concentration of this derivative is below detection limit, and does not contribute to the neuromuscular block occurring after administration of vecuronium.

- **Elimination:** Biliary excretion is the main elimination route. It is estimated that within 24 hours after intravenous administration of vecuronium, 40 to 60 % of the dose administered is excreted into the bile as monoquaternary compounds. Approximately 95 % of these monoquaternary compounds is unchanged vecuronium and less than 5 % is 3-hydroxy vecuronium. Prolonged duration of action has been observed in patients with liver disease and/or biliary tract disease, probably as a result of decreased clearance leading to an increased elimination half-life

  Renal elimination is relatively low. The amount of monoquaternary compounds excreted in the urine collected by intravesical catheter for 24 hours following vecuronium administration is 20-30 % of the dose administered.
  In patients with renal failure, the duration of action may be prolonged. This is probably the result of an increased sensitivity to vecuronium, but it could also be the result of a reduced plasma clearance.

Paediatric population

There are limited pharmacokinetic data for vecuronium in the paediatric population. After intravenous administration, vecuronium plasma clearance is similar across neonates, infants and children (2,8-9,0 mL.kg-1.min-1) and not different from the clearance in adults. Volume of distribution at steady state (Vdss) in infants is similar to the one in adult patients (0,29-0,43 L/kg), whereas it is slightly smaller in children (0,13 – 0,32 L/kg).

5.3 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Mannitol
- Citric acid
- Disodium hydrogen phosphate
- Sodium hydroxide
- Phosphoric acid
- Water for injection

6.2 Incompatibilities

This medicine must not be mixed with other medicines except those mentioned in section 6.6.

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 % sodium chloride) between

administration of vecuronium and medicines for which incompatibility with vecuronium has been demonstrated or for which compatibility with vecuronium has not been established

6.3 Shelf life

24 months

Reconstituted solution containing 2 mg/mL of vecuronium bromide is stable for 24 hours, stored at or below 25 °C.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Do not freeze.

Any unused solution must be discarded.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

2 mL clear Type I glass vial with grey rubber stopper and electric blue flip- top aluminium seal

6.6 Special precautions for disposal and other handling

Reconstitution

For IV injection MUSCURON is reconstituted by the addition of 2 mL water for injection. The reconstituted solution is clear and colourless. Alternatively, in order to obtain a solution with a lower concentration MUSCURON may be reconstituted with a volume up to 4 mL with the following infusion fluids: 5 % glucose injection fluid; 0,9 % sodium chloride injection fluid; Lactated Ringer's solution; 5 % glucose in Lactated Ringer's injection; glucose 5 % in 0,9 % sodium chloride injection; water for Injection.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER (S)

36/17.1/0431

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

23 September 2005

10 DATE OF REVISION OF THE TEXT

03 January 2024