SOUTH AFRICAN PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

MIVACRON 5 (intravenous injection)

COMPOSITION

Each 1 ml of MIVACRON 5 contains 2 mg of mivacurium as mivacurium chloride.

Excipient:

Water for injection

Sugar free

CATEGORY AND CLASS

A 17.1 Peripherally acting muscle relaxants

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mivacurium is a short-acting, non-depolarising, neuromuscular blocking medicine. The termination of the neuromuscular blocking action of mivacurium is mainly dependent on hydrolysis by plasma pseudocholinesterase, which is present at high levels in human plasma. Multiple degradation/elimination pathways appear to exist for mivacurium (e.g. hydrolysis by liver esterases, elimination in bile and renal excretion).

Pharmacokinetic properties

Mivacurium chloride is a mixture of three stereoisomers. The trans-trans and cis-trans stereoisomers comprise 92 % to 96 % of mivacurium chloride and when studied in cats their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The cis-cis isomer has been estimated from studies in cats to have one-tenth of the neuromuscular blocking potency of the other two stereoisomers. Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite. Pharmacological studies in cats and dogs have shown that the metabolites possess insignificant neuromuscular, autonomic or cardiovascular activity at concentrations higher than seen in man.

INDICATIONS

MIVACRON 5 is used as an adjunct to general anaesthesia to relax skeletal muscles and to facilitate tracheal intubation and mechanical ventilation.

CONTRAINDICATIONS

- Use in children under the age of 2 years since safety and efficacy has not been established.
- MIVACRON 5 should not be administered to patients known to have a hypersensitivity to mivacurium chloride or other benzyl isoquinolinium derivatives (or to benzyl alcohol).
- Patients known to be homozygous for the atypical plasma cholinesterase gene.

WARNINGS AND SPECIAL PRECAUTIONS

MIVACRON 5 PARALYSES THE RESPIRATORY MUSCLES AS WELL AS OTHER SKELETAL MUSCLES BUT HAS NO EFFECT ON CONSCIOUSNESS. MIVACRON 5 SHOULD BE ADMINISTERED ONLY BY OR UNDER THE CLOSE SUPERVISION OF AN

EXPERIENCED ANAESTHETIST WITH ADEQUATE FACILITIES FOR TRACHEAL INTUBATION AND ARTIFICIAL VENTILATION.

MONITORING OF NEUROMUSCULAR FUNCTION IS RECOMMENDED DURING THE USE OF MIVACRON 5 IN ORDER TO INDIVIDUALISE DOSAGE REQUIREMENTS.

Caution should also be exercised when administering MIVACRON 5 to patients who have shown hypersensitivity to other neuromuscular blocking medicines since cross-sensitivity between neuromuscular blocking medicines has been reported.

MIVACRON 5 is metabolised by plasma cholinesterase. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g. patients heterozygous or homozygous for the atypical plasma cholinesterase gene) and in various pathologic conditions and by administration of certain medicines.

Mild reductions (i.e. within 20 % of the lower limit of the normal range) are not associated with clinically significant effects on duration. The potential for histamine release exists in susceptible patients during MIVACRON 5 administration. Caution should be exercised in administering MIVACRON 5 to patients with a history suggestive of an increased sensitivity to the effects of histamine.

MIVACRON 5 should be administered over a period of 60 seconds to patients who may be unusually sensitive to falls in arterial blood pressure, for example those who are hypovolaemic. MIVACRON 5 does not have significant vagal or ganglion blocking properties in the recommended dosage range. Recommended doses of MIVACRON 5 consequently have no clinically significant effects on heart rate and will not counteract the bradycardia produced by many anaesthetic medicines or by vagal stimulation during surgery. Increased

sensitivity to MIVACRON 5 can be expected in patients with myasthenia gravis, other forms of neuromuscular disease and cachectic patients. Severe acid-base or electrolyte abnormalities may increase or reduce sensitivity to MIVACRON 5. Patients with burns may develop resistance to non-depolarising neuromuscular blocking medicines and require increased doses. However, such patients may also have reduced plasma cholinesterase activity, requiring dose reduction.

Consequently, burn patients should be given a test dose of 0,015 mg/kg to 0,020 mg/kg MIVACRON 5 followed by appropriate dosing guided by monitoring of block with a nerve stimulator. MIVACRON 5 has not been studied in malignant hyperthermia-susceptible patients. No data is available on the long-term use of MIVACRON 5 in patients undergoing mechanical ventilation in the intensive care unit.

Reversal of neuromuscular block: Evidence of spontaneous recovery should be observed prior to the administration of reversal medicines (e.g. neostigmine). The use of a peripheral nerve stimulator to evaluate recovery prior to and following reversal of neuromuscular block is strongly recommended.

INTERACTIONS

The neuromuscular block produced by MIVACRON 5 may be potentiated by the concomitant use of inhalational anaesthetics such as enflurane, isoflurane, sevoflurane and halothane.

MIVACRON 5 has been safely administered following succinylcholine-facilitated tracheal intubation. Evidence of spontaneous recovery from succinylcholine should be observed prior to administration of MIVACRON 5. A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising medicines, as this may result in a prolonged and complex block which can be

difficult to reverse with anticholinesterase medicines. The magnitude and/or duration of neuromuscular block may be increased and maintenance requirements may be reduced as a result of interaction with:

- Antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin and clindamycin;
- anti-arrhythmic medicines: propranolol, calcium channel blockers, lignocaine, procainamide and quinidine;
- diuretics: furosemide and possibly thiazides, mannitol and acetazolamide;
- magnesium salts;
- ketamine;
- lithium salts;
- ganglion blocking medicine: trimethaphan, hexamethonium.

Medicine that may reduce plasma cholinesterase activity may also prolong the neuromuscular blocking action of MIVACRON 5. These include antimitotic medicine, monoamine oxidase inhibitors, ecothiopate iodide, pancuronium, organophosphates, anticholinesterases, certain hormones, bambuterol. Rarely, certain medicines may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to MIVACRON 5 would be consequent on such a development. Such medicines include various antibiotics, beta-blockers (propranolol, oxprenolol), anti-arrhythmic medicine (procainamide, quinidine), antirheumatic medicine (chloroquine, D-penicillamine), trimethaphan, chlorpromazine, steroids, phenytoin and lithium.

The onset of block may be lengthened and the duration of block shortened in patients receiving chronic phenytoin or carbamazepine therapy.

The administration of combinations of non-depolarising neuromuscular blocking medicines in conjunction with MIVACRON 5 may produce a degree of neuromuscular blockade in excess of that which might be expected from an equipotent total dose of MIVACRON 5. Any synergistic effect may vary between different medicine combinations.

HUMAN REPRODUCTION

The use of MIVACRON 5 in pregnancy and lactation has not been established.

Plasma cholinesterase levels decrease during pregnancy. The effect on the MIVACRON 5 dosage has not been established. During caesarean section in patients pre-treated with magnesium sulphate ($MgSO_4$), due to the potentiating effects of Mg^{2+}, an infusion rate of MIVACRON 5 of 1,6 µg/kg/min was used and recovery time was 13 minutes.

DOSAGE AND DIRECTIONS FOR USE

This formulation contains no antimicrobial preservative and is intended for single patient use. MIVACRON 5 must be used under full aseptic conditions and any dilution carried out immediately before use. Any unused solution in open ampoules or in infusion solutions should be discarded.

Use by injection in adults

MIVACRON 5 is administered over 5 to 15 seconds by intravenous injection. The mean dose required to produce 95 % suppression of the adductor pollicis single twitch response to ulnar nerve stimulation (ED_{95}) is 0,07 mg/kg (range 0,06 mg/kg to 0,09 mg/kg) in adults receiving narcotic anaesthesia. The recommended initial bolus dose range for adults is 0,07 mg/kg to 0,15 mg/kg. The duration of neuromuscular blockade is related to the dosage. Doses of 0,07 mg/kg and 0,15 mg/kg produce clinically effective block for approximately 10 to 15 minutes and 15 to 20 minutes respectively. A MIVACRON 5 dose of 0,15 mg/kg produces

good-to-excellent conditions for tracheal intubation within 2,5 minutes in the majority of patients. Full block can be prolonged with maintenance doses of MIVACRON 5. Doses of 0,1 mg/kg administered during narcotic anaesthesia each provide approximately 15 minutes of additional clinically effective block.

Successive supplementary doses do not give rise to accumulation of neuromuscular blocking effect. The neuromuscular blocking action of MIVACRON 5 is potentiated by inhalational anaesthesia. If stable-state anaesthesia with isoflurane or enflurane has been established, the recommended initial dose of MIVACRON 5 should be reduced by up to 25 %. Halothane appears to have only a minimal potentiating effect on MIVACRON 5 and dose reduction is not necessary. Once spontaneous recovery is underway, it is usually complete in approximately 15 minutes and is independent of the size of the MIVACRON 5 dose administered. The neuromuscular block produced by MIVACRON 5 can be rapidly reversed with standard doses of anticholinesterase medicines. However, because spontaneous recovery after MIVACRON 5 is rapid, reversal may not be routinely required since it shortens recovery time by only 5 to 6 minutes.

Use as infusion in adults

Continuous infusion of MIVACRON 5 may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial MIVACRON 5 dose, an infusion rate of 8 µg/kg/min to 10 µg/kg/min (0,5 mg/kg/hr to 0,6 mg/kg/hr) is recommended. The initial infusion rate should be adjusted according to the patient's response to peripheral nerve stimulation and clinical criteria. Adjustments of the infusion rate should be made in increments of approximately 1 µg/kg/min (0,06 mg/kg/hr). In general a given rate should be maintained for at least three minutes before a rate change is made. On average an infusion rate of 6 µg/kg/min to 7 µg/kg/min will maintain neuromuscular block within the range of 89 % to 99 % for extended periods in adults receiving narcotic anaesthesia.

During steady-state isoflurane or enflurane anaesthesia, reduction in the infusion rate by up to 40 % should be considered. With sevoflurane, the mivacurium infusion rate may be reduced by up to 50 %.

With halothane smaller reductions in infusion rate may be required. Spontaneous recovery after infusion of MIVACRON 5 is independent of the duration of infusion and comparable to recovery reported for single doses. Continuous infusion of MIVACRON 5 has not been associated with the development of tachyphylaxis or cumulative neuromuscular blockade. MIVACRON 5 (2 mg/ml) may be used undiluted for infusion. MIVACRON 5 is compatible with the following infusion fluids:

- Sodium chloride intravenous infusion (0,9 % *m/v*);
- glucose intravenous infusion (5 % *m/v*);
- sodium chloride (0,9 % *m/v*) and glucose (5 % *m/v*) intravenous infusion;
- lactated Ringer's injection, USP.

When diluted with the listed infusion solutions in the ratio of 1 plus 3 (i.e. to give 0,5 mg/ml) MIVACRON 5 has been shown to be chemically and physically stable for at least 24 hours at 30 °C.

MIVACRON 5 is acidic (approximately pH 4,5) and should not be mixed in the same syringe or administered simultaneously through the same needle with highly alkaline solutions (e.g. barbiturate salts). Where other anaesthetic medicines are administered through the same indwelling needle or cannula as MIVACRON 5 and compatibility has not been demonstrated, each medicine must be flushed through with physiological saline. It has been shown to be compatible with some commonly used peri-operative medicines supplied as acidic solutions e.g. fentanyl, alfentanil, sufentanil, droperidol and midazolam.

Use in children aged 2 to 12 years

MIVACRON 5 has a higher ED_{95} (0,1 mg/kg), faster onset, shorter clinically effective duration of action and more rapid spontaneous recovery in 2 to 12 year old children than in adults. The recommended initial bolus dose range for MIVACRON 5 is 0,1 mg/kg to 0,2 mg/kg. When administered during stable narcotic anaesthesia doses of 0,1 mg/kg and 0,2 mg/kg produce clinically effective block for an average of 7 minutes and 10 minutes respectively. A MIVACRON 5 dose of 0,2 mg/kg is recommended for tracheal intubation. Maximum block is achieved approximately 2 minutes following administration of this dose (0,5 to 1,0 minute faster than in adults) and good-to-excellent intubation conditions should be obtained within this time. Maintenance doses are generally required more frequently in children than in adults.

Available data suggest that a maintenance dose of 0,1 mg/kg will give approximately 6 to 7 minutes of additional clinically effective block. Children generally require higher infusion rates than adults. During narcotic anaesthesia the infusion rate required to maintain 89 % to 99 % neuromuscular block averages 10 µg/kg/min to 15 µg/kg/min (0,6 mg/kg/hr to 1,0 mg/kg/hr).

The neuromuscular blocking action of MIVACRON 5 is potentiated by inhalational medicines. The mivacurium infusion rate requirement should be reduced by up to 70 % with sevoflurane in children aged 2 to 12 years.

Once spontaneous recovery is underway, it is usually complete in approximately 10 minutes.

Use in the elderly

In elderly patients receiving single bolus doses of MIVACRON 5, the onset time, duration of action and recovery rate may be extended relative to younger patients by 20 % to 30 %.

Elderly patients may also require smaller or less frequent maintenance bolus doses.

Use in patients with cardiovascular disease

In patients with clinically significant cardiovascular disease, the initial dose of MIVACRON 5 should be administered over 60 seconds.

Use in patients with reduced renal function

In patients with end-stage renal failure the clinically effective duration of block of 0,15 mg/kg MIVACRON 5 is approximately 1,5 times that in control patients.

Use in patients with reduced hepatic function

In patients with end-stage liver failure the clinically effective duration of block of 0,15 mg/kg MIVACRON 5 is approximately three times that in control patients. This prolongation is related to the markedly reduced plasma cholinesterase activity seen in these patients.

Use in patients with reduced plasma cholinesterase activity (e.g. organophosphate exposure)

The possibility of prolonged neuromuscular block following administration of MIVACRON 5 must be considered in patients with reduced plasma cholinesterase activity. Mild reductions (i.e. within 20 % of the lower limit of the normal range) are not associated with clinically significant effects on duration. In patients heterozygous for the atypical plasma cholinesterase gene, the clinically effective duration of block of 0,15 mg/kg MIVACRON 5 is approximately 10 minutes longer than in control patients.

MIVACRON 5 is not recommended in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS AND SPECIAL PRECAUTIONS).

Use in obese patients

In obese patients (those weighing 30 % or more above their ideal body mass for height), the initial dose of MIVACRON 5 should be based upon ideal body mass and not actual body mass.

SIDE EFFECTS

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1 000, < 1/100), rare (≥ 1/10 000, < 1/1 000) and very rare (< 1/10 000) including isolated reports.

Immune disorders

Very rare: severe anaphylactic or anaphylactoid reactions have been reported in patients receiving MIVACRON 5 in conjunction with one or more anaesthetic medicines

Cardiac disorders

Uncommon: transient tachycardia*

Vascular disorders

Very common: flushing*

Uncommon: hypotension*

Respiratory, thoracic and mediastinal disorders

Uncommon: bronchospasm*

Skin and subcutaneous tissue disorders

Uncommon: erythema*, urticaria*

* Associated with the use of MIVACRON 5 there have been reports of skin flushing, erythema, urticaria, hypotension, transient tachycardia or bronchospasm which have been attributed to histamine release. These effects are dose-related and more common following initial doses of 0,2 mg/kg or more when given rapidly and are reduced if MIVACRON 5 is injected over 30 to 60 seconds or in divided doses over 30 seconds.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENTS

Symptoms

Prolonged muscle paralysis and its consequences are the main effects of overdosage with neuromuscular blocking medicines. However, the risk of haemodynamic side effects, especially decreases in blood pressure may be increased.

Treatment

It is essential to maintain a patent airway together with assisted positive pressure ventilation until spontaneous respiration is adequate. Full sedation may be required since consciousness is not impaired. Recovery will be hastened by the administration of anticholinesterase medicines accompanied by atropine or glycopyrrolate once evidence of spontaneous recovery is present.

Cardiovascular support may be provided by proper positioning of the patient and administration of fluids or vasopressor medicines as required.

IDENTIFICATION

A clear solution practically free from particles.

PRESENTATION

1 x 5 ml clear, colourless glass ampoule. 5 ampoules are packed into an expanded plastic nest and placed into a unit cardboard carton.

STORAGE INSTRUCTIONS

Store between 2 °C to 8 °C.

Protect from light.

Do not freeze.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

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