MIVACRON

Mivacurium chloride

QUALITATIVE AND QUANTITATIVE COMPOSITION

Injection:

Sterile solution containing 2 mg mivacurium per ml as mivacurium chloride, without an antimicrobial preservative, supplied in ampoules.

PHARMACEUTICAL FORM

Solution for injection or infusion.

CLINICAL PARTICULARS

Indications

MIVACRON is a highly selective, short-acting, non-depolarising neuromuscular blocking agent with a fast recovery profile.

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

The injection formulation contains no antimicrobial preservative and is intended for single patient use.

Dosage and Administration

In common with all neuromuscular blocking agents, monitoring of neuromuscular function is recommended during the use of *MIVACRON* in order to individualise dosage requirements.

With *MIVACRON*, significant train-of-four fade is not seen during onset. It is often possible to intubate the trachea before complete abolition of the train-of-four response of the adductor pollicis muscle has occurred.

Populations

- **Adults**

MIVACRON is administered by intravenous (i.v.) 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 to 0.09) in adults receiving narcotic anaesthesia.

The following dose regimens are recommended for tracheal intubation:

I. A dose of 0.2 mg/kg, administered over 30 seconds, produces good to excellent conditions for tracheal intubation within 2.0 to 2.5 minutes.

II. A dose of 0.25 mg/kg, administered as a divided dose (0.15 mg/kg followed 30 seconds later by 0.1 mg/kg), produces good to excellent conditions for tracheal intubation within 1.5 to 2.0 minutes of completion of administration of the first dose portion.

The recommended bolus dose range for healthy adults is 0.07 to 0.25 mg/kg. The duration of neuromuscular block is related to the dose. Doses of 0.07, 0.15, 0.20 and 0.25 mg/kg produce clinically effective block for approximately 13, 16, 20 and 23 minutes, respectively. Doses of up to 0.15 mg/kg may be administered over 5 to 15 seconds. Higher doses should be administered over 30 seconds in order to minimise the possibility of occurrence of cardiovascular effects.

Full block can be prolonged with maintenance doses of *MIVACRON*. 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* is potentiated by isoflurane or enflurane anaesthesia. If steady-state anaesthesia with isoflurane or enflurane has been established, the recommended initial dose of *MIVACRON* should be reduced by up to 25%.

Halothane appears to have only a minimal potentiating effect on *MIVACRON* and dose reduction is probably not necessary.

Once spontaneous recovery is underway, it is complete in approximately 15 minutes and is independent of the dose administered.

The neuromuscular block produced by *MIVACRON* can be rapidly reversed with standard doses of anticholinesterase agents. However, because spontaneous recovery after *MIVACRON* is rapid, reversal may not be routinely required since it shortens recovery time by only 5 to 6 minutes.

Use by infusion (Injection formulation only):

Continuous infusion of *MIVACRON* may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial *MIVACRON* dose, an infusion rate of 8 to 10 micrograms/kg/min (0.5 to 0.6 mg/kg/h) is recommended.

The initial infusion rate should be adjusted according to the patients response to peripheral nerve stimulation and clinical criteria.

Adjustments of the infusion rate should be made in increments of approximately 1 microgram/kg/min (0.06 mg/kg/h). In general a given rate should be maintained for at least 3 minutes before a rate change is made.

On average, an infusion rate of 6 to 7 micrograms/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. A study has shown that the *MIVACRON* infusion rate requirement should be reduced by up to 50% with sevoflurane. With halothane, smaller reductions in infusion rate may be required.

Spontaneous recovery after infusion of *MIVACRON* is independent of the duration of infusion and comparable to recovery reported for single doses.

Continuous infusion of *MIVACRON* has not been associated with the development of tachyphylaxis or cumulative neuromuscular blockade.

MIVACRON injection (2 mg/ml) may be used undiluted for infusion. It is compatible with the following infusion fluids:

- sodium chloride i.v. infusion (0.9% w/v)
- glucose i.v. infusion (5% w/v)
- sodium chloride (0.18% w/v) and glucose (4% w/v) i.v. infusion
- Lactated Ringers injection, United States Pharmacopoeia (USP).

When diluted with the listed infusion solutions in the proportion of 1 plus 3 (i.e. to give 0.5 mg/ml) *MIVACRON* injection has been shown to be chemically and physically stable for at least 48 hours at 30°C. However, since the product contains no antimicrobial preservative dilution should be carried out immediately prior to use, administration should commence as soon as possible thereafter and any remaining solution should be discarded.

- **Children aged 2 to 12 years**

MIVACRON has a higher ED_{95} (approximately 0.1 mg/kg), faster onset, shorter clinically effective duration of action and more rapid spontaneous recovery in children aged 2 to 12 years, than in adults.

The recommended bolus dose range for children aged 2 to 12 years is 0.1 to 0.2 mg/kg. When administered during stable narcotic or halothane anaesthesia a dose of 0.1 and 0.2 mg/kg produces clinically effective block for an average of 7 minutes and 10 minutes respectively.

A *MIVACRON* dose of 0.2 mg/kg is recommended for tracheal intubation. Maximum block is usually achieved within 2 minutes following administration of this dose and intubation should be possible 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 halothane anaesthesia, the mean infusion rate required to maintain 89 to 99% neuromuscular block averages 10 to 15 mcg/kg/min (0.6 to 1.0 mg/kg/hr).

The neuromuscular blocking action of mivacurium is potentiated by inhalational agents. A study has shown that the mivacurium infusion rate requirement should be reduced by up to 70% with sevoflurane in children aged 2-12 years.

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

- **Children under two years of age**

No dose recommendations for neonates and infants under two years of age can be made until further information becomes available.

- **Elderly**

In elderly patients receiving single bolus doses of *MIVACRON*, 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 by infusion (Injection formulation only):

Elderly patients may also require decreased infusion rates.

- **Patients with cardiovascular disease**

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

MIVACRON has been administered in this way with minimal haemodynamic effects to patients undergoing cardiac surgery.

- **Patients with reduced renal function**

In patients with end-stage renal failure the clinically effective duration of block produced by 0.15 mg/kg *MIVACRON* is approximately 1.5 times longer than in patients with normal renal function.

Subsequently, dosage should be adjusted according to individual clinical response.

Prolonged and intensified neuromuscular blockade may also occur in patients with acute or chronic renal failure as a result of reduced levels of plasma cholinesterase (see Warnings and Precautions).

- **Patients with reduced hepatic function**

In patients with end-stage hepatic failure the clinically effective duration of block produced by 0.15 mg/kg *MIVACRON* is approximately three times longer than in patients with normal hepatic function. This prolongation is related to the markedly reduced plasma cholinesterase activity seen in these patients.

Subsequently, dosage should be adjusted according to individual clinical response.

- **Patients with reduced plasma cholinesterase activity**

MIVACRON 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 (see *Warnings and Precautions*) and by administration of certain drugs (see *Interactions*). The possibility of prolonged neuromuscular block following administration of *MIVACRON* 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 (See *Contraindications and Warnings and Precautions for information about homozygous and heterozygous patients*).

- **Obese patients**

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

Contraindications

– *MIVACRON* is contraindicated in patients known to be homozygous for the atypical plasma cholinesterase gene (see *Warnings and Precautions*).

– *MIVACRON* should not be administered to patients known to have a hypersensitivity to mivacurium or excipients.

Warnings and Precautions

In common with all the other neuromuscular blocking agents *MIVACRON* paralyses the respiratory muscles as well as other skeletal muscles but has no effect on consciousness. *MIVACRON* should be administered only by or under the close supervision of an experienced anaesthetist with adequate facilities for endotracheal intubation and artificial ventilation.

Prolonged and intensified neuromuscular blockade following *MIVACRON* may occur secondary to reduced plasma cholinesterase activity in the following states or pathological conditions:

- physiological variation as in pregnancy and the puerperium (*see Pregnancy and Lactation*).
- genetically determined abnormalities of plasma cholinesterase (*see below and Contraindications*).
- severe generalised tetanus, tuberculosis and other severe or chronic infections.
- chronic debilitating disease, malignancy, chronic anaemia and malnutrition.
- myxoedema and collagen diseases.
- decompensated heart disease.
- peptic ulcer.
- burns (see below).
- end-stage hepatic failure (*see Dosage and Administration*).
- acute, chronic or end-stage renal failure (*see Dosage and Administration*).
- iatrogenic: following plasma exchange, plasmapheresis, cardiopulmonary bypass, and as a result of concomitant drug therapy (*see Interactions*).

In common with suxamethonium/succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of *MIVACRON*. In three such adult patients, a small dose of *MIVACRON* 0.03 mg/kg (approximately the ED_{95-99} in genotypically normal patients), produced complete neuromuscular block for 26 to 128 minutes.

In patients heterozygous for the atypical plasma cholinesterase gene, the clinically effective duration of block of *MIVACRON* 0.15 mg/kg is approximately 10 minutes longer than in control patients.

Once spontaneous recovery had begun, neuromuscular block in these patients was antagonised with conventional doses of neostigmine.

Patients with burns may develop resistance to non-depolarising neuromuscular blocking agents 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 to 0.020 mg/kg *MIVACRON* followed by appropriate dosing guided by monitoring of block with a nerve stimulator.

Caution should be exercised in administering *MIVACRON* to patients with a history suggestive of an increased sensitivity to the effects of histamine, e.g. asthma. If *MIVACRON* is used in this group of patients it should be administered over 60 seconds.

Caution should also be exercised when administering *MIVACRON* to patients who have shown hypersensitivity to other neuromuscular blocking agents since a high rate of cross sensitivity (greater than 50%) between neuromuscular blocking agents has been reported.

MIVACRON 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.

In adults, doses of *MIVACRON* of greater than or equal to 0.2 mg/kg (greater than or equal to 3x ED_{95}) have been associated with histamine release when administered by rapid bolus injection. However, the slower administration of the 0.2 mg/kg *MIVACRON* dose and the divided administration of the 0.25 mg/kg *MIVACRON* dose (see *Dosage and Administration*) minimise the cardiovascular effects of these doses. Cardiovascular safety did not appear to be compromised in children given a rapid bolus dose of 0.2 mg/kg in clinical studies.

MIVACRON does not have significant vagal or ganglion blocking properties in the recommended dosage range. Recommended doses of *MIVACRON* consequently have no clinically significant effects on heart rate and will not counteract the bradycardia produced by many anaesthetic agents or by vagal stimulation during surgery.

In common with other non-depolarising neuromuscular blocking agents, increased sensitivity to *MIVACRON* 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*.

MIVACRON solution 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 solutions). It has been shown to be compatible with some commonly used peri-operative drugs supplied as acidic solutions, e.g. fentanyl, alfentanil, sufentanil, droperidol and midazolam. Where other anaesthetic agents are administered through the same indwelling needle or cannula as used for *MIVACRON*, and compatibility has not been demonstrated, it is recommended that each drug is flushed through with physiological saline.

Studies in malignant hyperthermia-susceptible pigs indicated that *MIVACRON* does not trigger this syndrome. *MIVACRON* has not been studied in malignant hyperthermia-susceptible patients.

Reversal of neuromuscular block: as with other neuromuscular blocking agents, evidence of spontaneous recovery should be observed prior to administration of reversal agent (e.g. neostigmine). The use of a peripheral nerve stimulator to evaluate recovery prior to and following reversal of neuromuscular block is strongly recommended.

No data are available on the long-term use of *MIVACRON* injection in patients undergoing mechanical ventilation in the intensive care unit.

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Interactions

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

MIVACRON has been safely administered following suxamethonium-facilitated tracheal intubation. Evidence of spontaneous recovery from suxamethonium should be observed prior to administration of *MIVACRON*.

In common with all non-depolarising neuromuscular blocking agents the magnitude and/or duration of a non-depolarising 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 drugs: propranolol, calcium channel blockers, lidocaine, procainamide and quinidine
- diuretics: furosemide and possibly thiazides, mannitol and acetazolamide
- magnesium salts
- ketamine
- lithium salts
- ganglion blocking drugs: trimetaphan, hexamethonium.

Drugs that may reduce plasma cholinesterase activity may also prolong the neuromuscular blocking action of *MIVACRON*. These include anti-mitotic drugs, monoamine oxidase inhibitors, ecothiopate iodide, pancuronium, organophosphates, anticholinesterases, certain hormones, bambuterol and selective serotonin uptake inhibitors.

Rarely, certain drugs may aggravate or unmask latent myasthenia gravis or actually induce a myasthenic syndrome; increased sensitivity to *MIVACRON* would be consequent on such a development. Such drugs include various antibiotics, beta-blockers (propranolol, oxprenolol), anti-arrhythmic drugs (procainamide, quinidine), anti-rheumatic drugs (chloroquine, D pencillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

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

A depolarising muscle relaxant such as suxamethonium chloride should not be administered to prolong the neuromuscular blocking effects of non-depolarising agents, as this may result in a prolonged and complex block which can be difficult to reverse with anti-cholinesterase drugs.

Pregnancy and Lactation

Fertility

Fertility studies have not been performed.

Pregnancy

Animal studies have indicated that mivacurium has no adverse effect on foetal development.

There is no information on the use of *MIVACRON* in pregnant women therefore *MIVACRON* should not be used during pregnancy unless the expected clinical benefit to the mother outweighs any potential risk to the foetus.

Plasma cholinesterase levels decrease during pregnancy. *MIVACRON* injection has been used to maintain neuromuscular block during Caesarean section, but due to the reduced levels of plasma cholinesterase, dosage adjustments to the infusion rate were necessary. A further reduction in the infusion rate may also be required during Caesarean section in patients pre-treated with magnesium sulfate, due to the potentiating effects of magnesium. There has been no experience of *MIVACRON* multi-dose vials during Caesarean section.

Lactation

It is not known whether mivacurium is excreted in human milk.

Effects on Ability to Drive and Use Machines

This precaution is not relevant to the use of *MIVACRON*. *MIVACRON* will always be used in combination with a general anaesthetic and therefore the usual precautions relating to performance of tasks following general anaesthesia apply.

Adverse Reactions

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000) including isolated reports, not known (cannot be estimated from the available data).

Immune disorders

Very rare: Severe anaphylactic or anaphylactoid reactions have been reported in patients receiving *MIVACRON* chloride in conjunction with one or more anaesthetic agents.

Cardiac disorders

Uncommon: Transient tachycardia[1]

Vascular disorders

Very common: Flushing[1]

Uncommon: Hypotension[1]

Respiratory, thoracic and mediastinal disorders

Uncommon: Bronchospasm[1]

Skin and subcutaneous tissue disorders

Uncommon: Erythema[1], urticaria[1]

[1]Associated with the use of *MIVACRON* 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* is injected over 30 to 60 seconds or in divided doses over 30 seconds.

Overdose

Symptoms and Signs

Prolonged muscle paralysis and its consequences are the main effects of overdosage with neuromuscular blocking agents. 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 will be required since consciousness is not impaired.

Recovery may be hastened by the administration of anticholinesterase agents 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 agents as required.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

ATC Code

Pharmacotherapeutic group: Peripherally acting muscle relaxants, other quaternary ammonium compounds, ATC code: M03AC10.

Mechanism of Action

Mivacurium is a highly selective, short-acting, non-depolarising neuromuscular blocking agent with a fast recovery profile.

Pharmacodynamic Effects

MIVACRON is a mixture of three mivacurium stereoisomers. The trans-trans and cis-trans stereoisomers comprise 92% to 96% of *MIVACRON* 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.

Pharmacokinetics

Metabolism

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.

The termination of the neuromuscular blocking action of *MIVACRON* is mainly dependent on hydrolysis by plasma pseudocholinesterase, which is present at high levels in human plasma.

Elimination

Multiple degradation/elimination pathways appear to exist for mivacurium (e.g. hydrolysis by liver esterases, elimination in bile and renal excretion).

Pre-Clinical Safety Data

Mutagenicity

Mivacurium has been evaluated in four short-term mutagenicity tests. Mivacurium was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay and the in vivo rat bone marrow cytogenetic assay.

Carcinogenicity

There is no information available on whether mivacurium has carcinogenic potential.

PHARMACEUTICAL PARTICULARS

Incompatibilities

MIVACRON is acidic (approximately pH 4.5) and should not be mixed with highly alkaline solutions, e.g. barbiturates.

Shelf-Life

The expiry date is indicated on the packaging.

Special Precautions for Storage

Injection:

Store between 2°C to 8°C.
Protect from light.
Do not freeze.

Nature and Contents of Container

5ml x 5 glass ampoules, 10ml x 5 glass ampoules

Instructions for Use/Handling

MIVACRON injection has been shown to be compatible with some commonly used peri-operative drugs supplied as acidic solutions.

Where such agents are administered through the same indwelling needle or cannula as used for *MIVACRON* injection, and compatibility has not been demonstrated, it is recommended that each drug is flushed through with physiological saline.

Injection:

Since no antimicrobial preservative is included, *MIVACRON* injection must be used under full aseptic conditions and any dilution carried out immediately before use. Any unused solution in open ampoules should be discarded.

MIVACRON injection is compatible with the following infusion fluids:

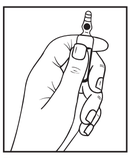
- sodium chloride i.v. infusion (0.9% w/v)
- glucose i.v. infusion (5% w/v)
- sodium chloride (0.18% w/v) and glucose (4% w/v) i.v. infusion
- Lactated Ringers injection, USP.

When diluted with the listed infusion solutions in the proportion of 1 plus 3 (i.e. to give 0.5 mg/ml) *MIVACRON* injection has been shown to be chemically and physically stable for at least 48 hours at 30°C. However, since the product contains no antimicrobial preservative, dilution should be carried out immediately prior to use, administration should commence as soon as possible thereafter and any remaining solution should be discarded.

Instructions to open the ampoule

Ampoules are equipped with the OPC (One Point Cut) opening system and must be opened following the below instructions:

- Hold with the hand the bottom part of the ampoule as indicated in picture n. 1
- Put the other hand on the top of the ampoule positioning the thumb above the coloured point and press as indicated in picture n. 2



Picture 1

Picture 2

Not all presentations are available in every country.

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Version number: GDS12/IPI04SI (S)

Date of issue: December 2020