MIVACRON® Injection

NAME OF THE DRUG: Mivacurium chloride

DESCRIPTION:

MIVACRON (mivacurium chloride), has the chemical name (E)-(1R,1'R)-2,2'-[4-octenediylbis (oxytrimethylene)] bis [1, 2, 3, 4-tetrahydro-6, 7-dimethoxy-2methyl-1-(3, 4, 5 trimethoxybenzyl) isoquinolinium] dichloride. The molecular formula is C_{58}H_{80}Cl_{2}N_{2}O_{14} and the molecular weight is 1100.18. The structural formula is given below.

![Structural formula of mivacurium chloride]

The partition coefficient of the compound is 0.015 in a 1-octanol/distilled water system at 25°C.

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. 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.

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 6.5) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in water for injections. Hydrochloric acid may have been added to adjust pH.

Actions

MIVACRON (mivacurium chloride) is a non-depolarising skeletal muscular relaxant for intravenous administration with a short duration of action. This drug should be administered only by adequately trained individuals familiar with its actions, characteristics and hazards.

PHARMACOLOGY:

Pharmacodynamics

The mechanism by which mivacurium chloride exerts its action is most likely by binding competitively to cholinergic receptors on the motor end-plate to antagonise the action of acetylcholine, resulting in a block of neuromuscular transmission. The action is antagonised by acetylcholinesterase inhibitors, such as neostigmine.
The time to maximum neuromuscular block is similar for recommended doses of MIVACRON and intermediate-acting agents (eg, atracurium), but longer than for the ultra-short-acting agent, suxamethonium. The clinically effective duration of action of MIVACRON (a mixture of three stereoisomers) is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of suxamethonium.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle twitch response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.06 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anaesthesia. The pharmacodynamics of doses of MIVACRON ≥ED_{95} administered over 5 to 15 seconds during opioid/nitrous oxide/oxygen anaesthesia are summarised in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n=32) following an initial dose of 0.15 mg/kg MIVACRON and 7 to 8 minutes (range: 4 to 24, n=85) following initial doses of 0.20 or 0.25 mg/kg MIVACRON.

In children (2 to 12 years), MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, and shorter duration of action than in adults. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 5 minutes (n=4) following an initial dose of 0.20 mg/kg MIVACRON. Recovery following reversal is faster in children than in adults (Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
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<tbody>
<tr>
<td><strong>Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anaesthesia</strong></td>
</tr>
<tr>
<td><strong>Initial MIVACRON Dose (mg/kg)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Adults</td>
</tr>
<tr>
<td>0.07 to 0.10 (\text{n=47})</td>
</tr>
<tr>
<td>0.15 (\text{n=50})</td>
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<tr>
<td></td>
</tr>
<tr>
<td>0.20 (^4) (\text{n=50})</td>
</tr>
<tr>
<td>0.25 (^4) (\text{n=48})</td>
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<tr>
<td></td>
</tr>
<tr>
<td>Children 2 to 12 Years</td>
</tr>
<tr>
<td>0.11 to 0.12 (\text{n=17})</td>
</tr>
<tr>
<td>0.20 (\text{n=18})</td>
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</table>

\(^1\) Values shown are medians of means from individual studies (range of individual patient values).

\(^2\) Clinically effective duration of neuromuscular block.
3 Data available for as few as 40% of adults in specific dose groups and for 22% of children in the 0.20 mg/kg dose group due to administration of reversal agents or additional doses of MIVACRON prior to 95% recovery or T4/T1 ratio recovery to ≥75%.

4 Rapid administration not recommended due to possibility of decreased blood pressure. Administer 0.20 mg/kg over 30 seconds; administer 0.25 mg/kg as divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg) see DOSAGE AND ADMINISTRATION.

Repeated administration of maintenance doses or continuous infusion of MIVACRON for up to 2.5 hours is not associated with development of tachyphylaxis or cumulative neuromuscular blocking effects in ASA Physical Status I-II patients. Limited data are available from patients receiving infusions for longer than 2.5 hours. Spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).

Administration of MIVACRON over 60 seconds does not alter the time to maximum neuromuscular block or the duration of action.

The duration of action of MIVACRON, including its stereoisomers, may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity and is markedly prolonged in patients homozygous for the atypical plasma cholinesterase gene (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

The neuromuscular block produced by the stereoisomers in MIVACRON is readily antagonised by anticholinesterase agents. As seen with other nondepolarising neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

Volatile anaesthetics may decrease the dosing requirement for MIVACRON and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enfurane may decrease the effective dose of MIVACRON by as much as 25%, and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. Halothane has little or no effect on the ED50 of MIVACRON, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see DOSAGE AND ADMINISTRATION and Interactions with Other Drugs).

Haemodynamics:
Administration of MIVACRON in doses up to and including 0.15 mg/kg (2 x ED95) over 5 to 15 seconds to ASA Physical Status I-II patients during narcotic/nitrous oxide/oxygen anaesthesia is associated with minimal changes in mean arterial blood pressure (MAP) or heart rate (HR).

Higher doses of ≥0.20 mg/kg (≥3 x ED95) may be associated with transient decreases in MAP and increases in HR in some patients. These decreases in MAP are usually maximal within 1 to 3 minutes following the dose, typically resolve without treatment in an additional 1 to 3 minutes, and are usually associated with increases in plasma histamine concentration. Decreases in MAP can be minimised by administering MIVACRON over 30 to 60 seconds.

Pharmacokinetics:
Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for the inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite. 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. Renal and biliary excretion of unchanged mivacurium are minor elimination pathways. Limited tissue distribution and high metabolic clearance results in a short half-life (see **DOSAGE AND ADMINISTRATION**).

In young healthy subjects, exposure increased with dose following single doses of 0.10, 0.15 and 0.25 mg/kg, and the plasma clearance was 60.4, 70.4 and 40.2 mL/min/kg respectively. The corresponding volumes of distribution were 0.052, 0.178 and 0.153 L/kg. The plasma terminal elimination half-life varied between 1.74 and 2.63 minutes.

In liver transplant patients, the plasma half-life of mivacurium was increased to 4.4 minutes compared to 1.75 minutes in subjects with normal liver function; the duration of paralysis was prolonged also. This difference is most likely due to the reduced plasma cholinesterase in these subjects, an enzyme normally synthesised by the liver. No significant alteration in pharmacokinetic parameters was found in subjects undergoing kidney transplantation.

No significant toxicity attributable to mivacurium or its isomers or degradation products has been identified.

Cardiovascular effects as a consequence of histamine release are likely to be minimal at recommended doses and can be reduced still further by reducing the speed at which mivacurium is administered.

**INDICATIONS:**

MIVACRON is a highly selective, non-depolarising neuromuscular blocking agent with a fast recovery profile, and a short duration of action. MIVACRON is used as an adjunct to general anaesthesia to relax skeletal muscles and to facilitate tracheal intubation and mechanical ventilation.

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

**CONTRAINDICATIONS:**

MIVACRON Injection should not be administered to patients known to have an allergic hypersensitivity to mivacurium.

MIVACRON is contra-indicated in patients known to be homozygous for atypical plasma cholinesterase gene (see **PRECAUTIONS**).

**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 mivacurium 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, patients homozygous for the atypical plasma cholinesterase gene (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of mivacurium. In three such adult patients, a small dose of MIVACRON 0.03 mg/kg (less than half the ED95 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 mivacurium 0.15 mg/kg is approximately 10 min longer than in control patients.

Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. (see DOSAGE AND ADMINISTRATION: Use in patients with reduced plasma cholinesterase activity).

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.

Caution should also be exercised when administering mivacurium 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.

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

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 (eg, barbiturate solutions). It has been shown to be compatible with some commonly used peri-operative drugs supplied as acidic solutions, eg, Sublimaze, Droleptan, and Hypnovel. 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.

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 0.015-0.020 mg/kg MIVACRON followed by appropriate dosing guided by monitoring of block with a nerve stimulator.

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

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

The Potential for Histamine Release:
MIVACRON, like other drugs used during anaesthesia, has the potential to cause histamine release and therefore there is a potential for anaphylactoid reactions in some individuals. For this reason it is essential that appropriate resuscitative equipment be immediately available.

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

MIVACRON should be administered over a period of 60 seconds to patients who may be unusually sensitive or susceptible to falls in arterial blood pressure.

In adults, doses of MIVACRON of ≥0.2 mg/kg (≥3 x ED₉₅) 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.

The Administration of MIVACRON following Suxamethonium:
MIVACRON has been safely administered following suxamethonium to facilitate tracheal intubation, however there are no pharmacokinetic data to determine the duration of action under these circumstances. Evidence of the onset of spontaneous recovery from suxamethonium should be observed prior to administration of MIVACRON.

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.

**Use in Pregnancy:**

**Category B2**
There is no information on the use of MIVACRON in pregnant women. MIVACRON should not be used during pregnancy unless the expected clinical benefit to the mother outweighs any potential risk to the foetus.

Subcutaneous doses of up to 0.8 mg/kg in rats and 0.5 mg/kg in mice on days 6 to 15 of gestation have not been found to cause fetotoxic or teratogenic effects.

There has been no experience with the use of MIVACRON during Caesarean section.

**Use in Lactation:**
It is not known whether mivacurium is excreted in human milk.

MIVACRON should not be given to lactating women unless the expected benefit to the mother outweighs the possible risk to the infant.

**Mutagenic Potential:**
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.

**Carcinogenic Potential:**
There is no information available on whether mivacurium has carcinogenic potential.

**Fertility:**
Fertility studies have not been performed.

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

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.

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 infusion requirements may be reduced as a result of interaction with:

- Antibiotics, including the aminoglycosides, polymyxins, spectinomycin, tetracyclines, lincomycin, clindamycin, bacitracin, colistin sulfate, and colistin sulfomethate sodium.
Anti-arrhythmic drugs: propranolol, calcium channel blockers, lignocaine, 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, ecotiothiophate iodoiide, pANCuronium, organophosphates, anticholinesterases, certain hormones such as oral contraceptives and glucocorticoids, and bambuterol.

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, oxprenalol), antiarrhythmic drugs (procainamide, quinidine), antirheumatic drugs (chloroquine, D-penicillamine), trimetaphan, chlorpromazine, steroids, phenytoin and lithium.

In common with other non-depolarising neuromuscular blocking agents, the onset of block is likely to be lengthened and the duration of block shortened in patients receiving chronic phenytoin or carbamazepine therapy.

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.

**ADVERSE REACTIONS:**

Associated with the use of MIVACRON there have been reports of skin flushing, erythema, urticaria, mild transient hypotension, transient tachycardia or bronchospasm which have been attributed to histamine release. These effects are dose related and are more common if initial doses of 0.2 mg/kg or more are given rapidly. The risk of histamine-related side effects is reduced if MIVACRON is injected over 30 to 60 seconds or as divided doses over 30 seconds, when higher doses are employed. Very, rarely, severe anaphylactic or anaphylactoid reactions have been reported in patients receiving MIVACRON in conjunction with one or more anaesthetic agents.

The following adverse experiences were reported in patients administered MIVACRON (all events judged by investigators during the clinical trials to have a possible causal relationship):

**Incidence Greater Than 1%:**
Cardiovascular: Flushing (15%)

**Incidence Less Than 1%:**
Cardiovascular: Hypotension, Tachycardia, Bradycardia, Cardiac Arrhythmia, Phlebitis
Respiratory: Bronchospasm, Wheezing, Hypoxemia
Dermatological: Rash, Urticaria, Erythema, Injection Site Reaction
Nonspecific: Prolonged Drug Effect
Neurologic: Dizziness
Musculoskeletal: Muscle Spasms

**DOSAGE AND ADMINISTRATION:**

To avoid distress to the patient, MIVACRON should not be administered before unconsciousness has been induced.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualised (see **PHARMACOLOGY**). Factors that may warrant dosage adjustment include but may not be limited to: The presence of significant kidney, liver, or cardiovascular disease, obesity (patients weighing ≥ 30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anaesthetic agents.

The onset of conditions suitable for tracheal intubation occurs earlier after a conventional intubation dose of suxamethonium than after recommended doses of MIVACRON.

**Use by injection in adults:**

MIVACRON is administered by intravenous injection. The mean dose required to produce 95% suppression of the adductor pollicis single twitch response to ulnar nerve stimulation (ED₉₅) 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 (see Table 2):

I. A dose of 0.2 mg/kg, administered over 30 seconds, generally produced good to excellent conditions for tracheal intubation within 2 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) in one trial, produced good to excellent conditions for tracheal intubation within 1.5 to 2.0 minutes of completion of administration of the first dose portion.

<table>
<thead>
<tr>
<th>Dosing Paradigma</th>
<th>Anesthetic Induction Technique Studied</th>
<th>Time to Generally Good-to-Excellent Intubating Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.20 mg/kg iv (over 30 sec)</td>
<td>Thiopental/opioid/ N₂O/O₂ or propofol/opioid</td>
<td>2 to 2.5 min after completion of dose</td>
</tr>
<tr>
<td>0.25 mg/kg iv (0.15 mg/kg followed in 30 sec by 0.10 mg/kg)</td>
<td>Propofol/opioid</td>
<td>1.5 to 2 min after completion of 0.15 mg/kg dose</td>
</tr>
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</table>

*a Dosing instituted after induction of adequate general anesthesia*
The recommended bolus dose range for healthy adults is 0.07 to 0.25 mg/kg, the highest dose being divided. The duration of neuromuscular blockade is related to the dose. Doses of 0.07, 0.15, 0.20 and 0.25 mg/kg produced clinically effective block for approximately 13, 16, 20 and 23 minutes respectively.

Initial doses of 0.15 mg/kg may be administered over 5 to 15 seconds. Higher doses should be administered over 30 seconds or 60 seconds, or as divided doses in order to minimise the possibility of occurrence of cardiovascular effects including the transient decreases in blood pressure observed in some patients given these doses over 5 to 15 seconds. The quality of intubation conditions does not significantly differ for the doses of MIVACRON recommended in Table 2, but the onset of suitable intubation conditions may be reached earlier with the higher dose of 0.25 mg/kg. The choice of a particular dose and regimen should be based on individual circumstances and patient requirements (see PHARMACOLOGY, PRECAUTIONS, and ADVERSE REACTIONS).

In patients with clinically significant cardiovascular disease and in patients with any history suggesting a greater sensitivity to the release of histamine or other mediators (eg, asthma), the dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS). No data are available on the use of doses of MIVACRON above 0.15 mg/kg in patients with clinically significant kidney or liver disease or with asthma.

Clinically effective neuromuscular block may be expected to last for 15 to 20 minutes (range: 9 to 38) and spontaneous recovery may be expected to be 95% complete in 25 to 30 minutes (range: 16 to 41) following 0.15 mg/kg MIVACRON administered to patients receiving opioid/nitrous oxide/oxygen anaesthesia. The expected duration of clinically effective block and time to 95% spontaneous recovery following 0.20 mg/kg MIVACRON are approximately 20 and 30 minutes, respectively, and following 0.25 mg/kg MIVACRON are approximately 25 and 35 minutes. Initiation of maintenance dosing during opioid/nitrous oxide/oxygen anaesthesia is generally required approximately 15, 20 and 25 minutes following initial doses of 0.15, 0.20 and 0.25 mg/kg MIVACRON, respectively. Maintenance doses of 0.10 mg/kg each provide approximately 15 minutes of additional clinically effective block. For shorter or longer durations of action, smaller or larger maintenance doses may be administered. Successive supplementary doses do not give rise to accumulation of neuromuscular blocking effects.

The neuromuscular block action of mivacurium is potentiated by isoflurane or enflurane anaesthesia. Recommended initial doses of MIVACRON may be used to facilitate tracheal intubation prior to the administration of these agents; however, if MIVACRON is first administered after steady-state anaesthesia with isoflurane or enflurane has been established (administered with nitrous oxide-oxygen to achieve 1.25 MAC), the initial MIVACRON dose may be reduced by as much as 25%. Greater reductions in the MIVACRON dose may be required with higher concentrations of enflurane or isoflurane. With halothane, which has only a minimal potentiating effect on MIVACRON, a smaller dosage reduction may be considered.

**Reversal:**

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

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

**Continuous infusion in adults:**
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 µg/kg/min (0.5 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 3 minutes before a rate change is made. On average, an infusion rate of 6 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 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.

MIVACRON Injection is compatible with the following infusion fluids:

- Sodium Chloride Intravenous Infusion (0.9% w/v)
- Glucose Intravenous Infusion (5% w/v)
- Lactated Ringer's Injection, USP
- Sodium Chloride (0.18% w/v) and Glucose (4% w/v) Intravenous Infusion.

When diluted with the listed infusion solutions in the ratio of 1 to 3 (ie 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 MIVACRON 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.

**Use in children aged 2 to 12 years:**
MIVACRON 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 children aged 2 to 12 years is 0.1 to 0.2 mg/kg. Higher doses are not recommended. When administered during stable narcotic anaesthesia doses of 0.1 and 0.2 mg/kg produce 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. Although intubation has not been specifically studied in this age group, maximum block is achieved approximately 2 minutes following administration of this dose (0.5-1.0 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 to 15 μg/kg/min (0.6 to 1.0 mg/kg/hr).

The neuromuscular blocking action of mivacurium is potentiated by inhalational agents. Once spontaneous recovery is underway, it is complete in approximately 10 minutes.

**Use in children under 2 years of age:**
No dose recommendations for children under 2 years of age can be made until further information becomes available.

**Use in the 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 decreased infusion rates or 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 (0.15 mg/kg or less) should be administered over 60 seconds. MIVACRON has been administered in this way with minimal haemodynamic effects to patients undergoing cardiac surgery.

**Use in 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.

Doses in excess of 0.15 mg/kg have not been studied in these patients.

**Use in 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.

Doses in excess of 0.15 mg/kg have not been studied in these patients.

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 Precautions).

**Use in patients with reduced plasma cholinesterase activity:**
Mivacurium is metabolized by plasma cholinesterase. Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (eg patients heterozygous or homozygous for the atypical plasma cholinesterase gene), and in various pathologic conditions (see Precautions) and by administration of certain drugs (see Interactions with Other Drugs). The possibility of prolonged neuromuscular block
following administration of MIVACRON must be considered in patients with reduced plasma cholinesterase activity. Mild reductions (ie within 20% of the lower limit of the normal range) are not associated with clinically significant effects on duration. (See Contraindications and Precautions for information about homozygous and heterozygous patients)

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

**Monitoring:**
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 possible to intubate the trachea before complete abolition of the train-of-four response of the adductor pollicis muscle has occurred.

**OVERDOSAGE:**

**Signs:**
Prolonged muscle paralysis and its consequences are the main signs 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.

**PRESENTATION:**
MIVACRON is a clear, pale yellow, sterile, aqueous solution in a glass ampoule, containing 2 mg/mL mivacurium as mivacurium chloride. The 10 mL ampoules are presented in packs of 5 ampoules.

**Storage:**
Store below 25°C. Protect from light. DO NOT FREEZE

**Pharmaceutical Precautions:**
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 acidic (approximately pH 4.5) and should not be mixed with highly alkaline solutions, eg, barbiturates. 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 (see PRECAUTIONS).

NAME AND ADDRESS OF THE SPONSOR:

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Approved by the Therapeutic Goods Administration: 1 June 1995
Date of Safety-Related Notification: 12 November 2008

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Issue No. 6