PRODUCT MONOGRAPH

^{Pr}MIVACRON®

(Mivacurium Chloride)

2 mg/mL Injection

Nondepolarising Skeletal Neuromuscular Blocking Agent

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PRODUCT MONOGRAPH

NAME OF DRUG

PrMIVACRON®

Mivacurium Chloride Injection

THERAPEUTIC CLASSIFICATION

Nondepolarising Skeletal Neuromuscular Blocking Agent

THIS DRUG SHOULD BE ADMINISTERED BY, OR UNDER THE SUPERVISION OF, EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, OR HAZARDS.

ACTION AND CLINICAL PHARMACOLOGY

MIVACRON (mivacurium chloride) is a short-acting, nondepolarising skeletal neuromuscular blocking agent which is hydrolyzed by plasma cholinesterase. Mivacurium chloride results in a blockade of neuromuscular transmission by binding competitively with cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine.

Pharmacodynamics

The time to maximum neuromuscular block is similar for mivacurium and intermediate-acting agents (e.g., atracurium), but longer than for the ultra-short-acting agent, succinylcholine. The clinically effective duration of action of mivacurium is one-third to one-half that of intermediate-acting agents and 2 to 2.5 times that of succinylcholine.

The average ED_{95} (dose required to produce 95% suppression of the adductor pollicis muscle response to ulnar nerve stimulation) of MIVACRON is 0.07 mg/kg (range: 0.06 to 0.09 mg/kg) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of various doses of $\geq ED_{95}$ administered over 5 to 15 seconds during stable-state opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. Administration of MIVACRON over 60 seconds does not alter the time to maximum neuromuscular block or the duration of action.

Table 1
The Pharmacodynamic Dose-Response of MIVACRON (≥ ED_{95})
During Stable-State Opioid/Nitrous Oxide/Oxygen Anesthesia
in ASA Physical Status I–II Patients

Initial MIVACRON Dose (mg/kg)	Maximum Twitch Suppression[1] %	Time to Maximum Block[1] (min)	Time to Spontaneous Recovery[1]				
			5% Recovery (min)	25% Recovery[2] (min)	95% Recovery[3] (min)	T_4/T_1 Ratio ≥75%[3] (min)	25%–75% Recovery Index (min)
Adults: Dose Administered Over 5–15 sec							
0.07–0.08	91.2	4.9	8	12	21	21	6
(n=18)	(68–100)	(3.5–7.3)	(7–9)	(10–16)	(10–32)	(10–28)	(4.5–9.0)
0.10	97.3	3.9	12	14	25	24	6
(n=18)	(80–100)	(2.0–6.7)	(8–19)	(8–24)	(14–36)	(16–36)	(2.8–9.0)
0.15	99.6	3.3	13	16	26	26	6
(n=50)	(53–100)	(1.5–8.8)	(6–31)	(9–38)	(16–41)	(15–45)	(3.3–9.2)
0.20[4]	99.9	2.5	16	20	31	34	7
(n=50)	(93–100)	(1.2–6.0)	(10–29)	(10–36)	(15–51)	(19–56)	(3.6–15.5)
0.25[4]	100	2.3	19	23	34	43	8
(n=48)	(97–100)	(1.0–4.8)	(11–29)	(14–38)	(22–64)	(26–75)	(3.5–24.3)
Adults: Dose Administered Over 30 sec (0.20 mg/kg) and 60 sec (0.25 mg/kg)							
0.20	100	2.9	16	19	31	35	7
(n=27)	(95–100)	(1.5–4.3)	(10–25)	(8–29)	(15–43)	(29–46)	(4.0–10.0)
0.25	100	1.8	17	21	30	33	6
(n=18)	(100–100)	(1.1–2.5)	(10–26)	(12–31)	(18–47)	(28–38)	(3.4–10.8)
Children 2 to 12 years: Dose Administered Over 5–15 sec							
0.11–0.12	98.3	2.8	5	7	–	–	–
(n=17)	(89–100)	(1.2–4.6)	(3–9)	(4–10)			
0.20	99.5	1.9	7	10	19	16	5
(n=18)	(95–100)	(1.3–3.3)	(3–12)	(6–15)	(14–26)	(12–23)	(3.8–5.4)
0.25	100	1.6	7	9	–	–	–
(n=9)	(100–100)	(1.0–2.2)	(4–9)	(5–12)			

[1] Values shown are medians of means from individual studies (range of individual patient values)
[2] Duration of clinically effective 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 T_4/T_1 ratio recovery to ≥75%
[4] Rapid administration not recommended due to possibility of decreased blood pressure. Administer 0.20 mg/kg over 30 sec; administer 0.25 mg/kg as divided dose (0.15 mg/kg followed 30 sec later by 0.10 mg/kg). **see DOSAGE AND ADMINISTRATION**. When MIVACRON was administered as a divided dose of 0.15 mg/kg followed 30 sec later by 0.1 mg/kg, the maximum reduction in train-of-four count was observed at 4.6 minutes after the initial MIVACRON dose.

When administered during the induction of adequate anesthesia using thiopental or propofol, nitrous oxide/oxygen, and co-induction agents such as fentanyl and/or midazolam, doses of 0.15 mg/kg (2 x ED_{95}) MIVACRON administered over 5 to 15 seconds or 0.20 mg/kg MIVACRON administered over 30 seconds produced generally good-to-excellent tracheal intubation conditions in 2.5 to 3 and 2 to 2.5 minutes, respectively. A dose of 0.25 mg/kg MIVACRON administered as a divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg) produced generally good-to-excellent intubation conditions in 1.5 to 2 minutes after initiating the dosing regimen. Rapid bolus administration of MIVACRON at doses of 0.20 and 0.25 mg/kg should be avoided, as these doses may be associated with transient decreases in mean arterial blood pressure (MAP) and increases in heart rate (HR) in some patients (see **Hemodynamics** and **DOSAGE AND ADMINISTRATION**).

Tachyphylaxis or cumulative neuromuscular blocking effects are not observed when MIVACRON is administered as repeated maintenance doses or as a continuous infusion for up to 2.5 hours in ASA Physical Status I-II patients. Spontaneous recovery after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1). Limited data are available from patients receiving infusions of MIVACRON for longer than 2.5 hrs.

MIVACRON has a higher ED_{95} (0.10 mg/kg), faster onset, shorter duration of action, and more rapid recovery time in 2 to 12 year-old children than in adults (Table 1). Under conditions of opioid/nitrous oxide/oxygen anesthesia, the time to maximum neuromuscular block for 0.20 mg/kg MIVACRON in children is approximately 80 seconds faster than the time for an equipotent dose (0.15 mg/kg) in adults. Recovery following reversal is faster in children than in adults. In children, 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.

Antagonism

The neuromuscular block produced by MIVACRON is readily antagonized by anticholinesterase agents. The deeper the level of neuromuscular block at reversal, the longer the time required for recovery of neuromuscular function and the greater the dose of anticholinesterase agent required. Because spontaneous recovery after MIVACRON is rapid, routine reversal may not always result in a clinical benefit.

Histamine Release

Like certain other benzylisoquinoline compounds, MIVACRON has a tendency to release histamine, particularly at higher doses. Plasma histamine levels generally peak within the first few minutes following the initial MIVACRON bolus injection and return toward baseline by 5 minutes post-injection. In clinical trials, the histamine release response was reduced when 0.20 and 0.25 mg/kg doses were administered slowly over 30 or 60 seconds. Administration of the 0.15 mg/kg dose at injection rates slower than 5 to 15 seconds has not been studied for effects on histamine release, but may be expected to result in a diminished occurrence of this reaction.

Table 2
Histamine Release Responses Following the Administration of MIVACRON at Various Doses and Delivery Rates

Parameters			Plasma Histamine Concentration (pg/mL)			
Dose (mg/kg)	Delivery Rate (sec)	Post-Injection Sample Time (min)	n	Mean	Range	% Pts ≥ 2-fold increase
0.15	5–15	0	11	549	109–2138	
		2	11	877	101–2902	27
		5	11	429	93–1484	18
0.20	5–15	0	30	466	113–2279	
		2	30	2270	103–14999	63
		5	30	950	63–3419	53
0.20	30	0	18	757	153–2524	
		2	18	1209	231–8548	39
		5	18	657	211–3239	22
0.25	5–15	0	30	534	137–2121	
		2	30	6341	321–57257	77
		5	30	1710	91–18103	37
0.25	30	0	9	667	252–2039	
		2	9	1453	178–4275	44
		5	9	911	126–2521	11
0.25	60	0	18	560	79–5076	
		2	18	518	128–2507	33
		5	18	372	88–1020	17

Hemodynamics

MIVACRON-induced histamine release is sometimes associated with decreases in mean arterial blood pressure (MAP) and increases in heart rate (HR). For patients receiving bolus doses of 0.15 mg/kg MIVACRON over 5 to 15 seconds during clinical trials, average mean arterial blood pressure values at the time of maximal change during the first 5 minutes post-injection were in the range of 88 to 102% of pre-injection values. At higher doses of 0.20 to 0.30 mg/kg delivered over 5 to 15 seconds, transient decreases in mean arterial blood pressure of 20% or more were reported in 45 to 86% of patients (see Table 5 in **ADVERSE REACTIONS**). These decreases in mean arterial pressure were usually maximal within 1 to 3 minutes following the dose and typically resolved without treatment in an additional 1 to 3 minutes, although pharmacological intervention was occasionally necessary. Owing to the increased incidence of decreases in mean arterial blood pressure at doses of 0.20 to 0.30 mg/kg, rapid bolus administration of these doses in routine clinical practice should be avoided. Decreases in mean arterial pressure are diminished by administering MIVACRON slowly over 30 to 60 seconds (see **DOSAGE AND ADMINISTRATION**).

Children experience minimal changes in MAP or HR after administration of ≤0.20 mg/kg MIVACRON over 5 to 15 seconds. Higher doses (≥ 0.25 mg/kg) may be associated with transient decreases in MAP in some children (Table 5).

In patients with cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures, MIVACRON was associated with few changes in MAP or HR when administered as a 0.15 mg/kg dose over 60 seconds. Higher doses (0.20–0.25 mg/kg) administered over 60 seconds were associated with transient decreases in MAP in some patients. More rapid administrations of MIVACRON have not been studied in this patient population.

Pharmacokinetics

The mean elimination half-life of MIVACRON ranges from 1.7 to 2.6 minutes in healthy, young adults administered 0.10 to 0.25 mg/kg MIVACRON. Mean plasma clearance rates range from 40 to 70 mL/min/kg and mean steady-state volume of distribution values range from 0.08 to 0.11 L/kg. The short elimination half-life and high clearance are consistent with the short duration of action of MIVACRON.

Elderly

Pharmacokinetic parameters in 9 healthy elderly patients (68 to 77 years) administered 0.10 mg/kg MIVACRON were not significantly different from those of 9 healthy young adults (21 to 47 years). However, the onset of maximum twitch suppression was delayed by approximately 1 to 2 minutes (n=8). The clinically effective duration of action of 0.10 mg/kg MIVACRON averaged 3 to 4 minutes longer in elderly patients than in young adults (see Table 3).

Renal Impairment

Pharmacokinetic parameters were not significantly different in 9 patients with end-stage kidney disease undergoing kidney transplant surgery and 8 control patients with normal renal function. However, average times from injection of 0.15 mg/kg MIVACRON to 25% and 95% recovery were longer in patients with end-stage kidney disease than in patients with normal renal function (see Table 3).

Hepatic Impairment

In 9 patients with end-stage liver disease undergoing liver transplant surgery, plasma clearance was approximately 50% lower than that in 8 control patients with normal hepatic function, while the elimination half-life increased to 4.4 minutes from the 1.8 minute control value. Average times from injection of 0.15 mg/kg MIVACRON to 25% and 95% recovery were longer in patients with end-stage liver disease (n=8) than in patients with normal hepatic function (see Table 3). The longer duration of action in patients with end-stage liver disease is likely related to the markedly decreased plasma cholinesterase activity (30% of healthy patient values).

Table 3
Pharmacodynamic Parameters[1] of MIVACRON in Different Patient Groups During Isoflurane/Nitrous Oxide/Oxygen Anesthesia

ASA Physical Status I–II					
Parameter	**Young Adult Patients (21–47 years) (n=9)**	**Young Adult Patients (20–36 years) (n=8)**	**Elderly Patients (68–77 years) (n=8)**	**Kidney Transplant Patients (27–41 years) (n=9)**	**Liver Transplant Patients[4] (22–59 years) (n=8)**
Initial Dose[2]	0.10 mg/kg	0.15 mg/kg	0.10 mg/kg	0.15 mg/kg	0.15 mg/kg
Maximum Block (%)	98 (83–100)	99.8 (98–100)	99 (95–100)	100 (100–100)	100 (100–100)
Time to Maximum Block (min)	3.2 (2.0–6.0)	1.9 (0.8–3.5)	4.8 (3.0–7.0)	2.6 (1.0–4.5)	2.1 (1.0–4.0)
Clinically Effective Duration of Block[3] (min)	17 (9–29)	19 (12–30)	20 (14–28)	30 (19–58)	57 (29–80)

[1] Values shown are mean (range)
[2] Doses administered over 5 to 15 seconds
[3] Time from injection to 25% recovery of the control twitch height
[4] Liver transplant patients received isoflurane without nitrous oxide

Stereochemistry

MIVACRON is a mixture of three stereoisomers: the *trans-trans* diester, the *cis-trans* diester, and the *cis-cis* diester. These isomers do not interconvert *in vivo*. The two more potent isomers, *cis-trans* (36% of the mixture) and *trans-trans* (57% of the mixture), have very high clearance rates that exceed cardiac output, reflecting the extensive metabolism by plasma cholinesterase. The volume of distribution is relatively small, reflecting limited tissue distribution secondary to the polarity and large molecular weight of mivacurium. The combination of high metabolic clearance and low distribution volume results in a short elimination half-life of approximately 2 minutes for the two active isomers. These findings are consistent with the short duration of action of MIVACRON. Table 4 presents the results from a study in which 9 ASA physical status I-II patients received a 5 µg/kg/min MIVACRON infusion for a 60-minute period followed by a 10 µg/kg/min infusion for an additional 60 minutes. The pharmacokinetics of these isomers appeared to be dose-proportional as the steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled when the infusion rate was increased from 5 to 10 µg/kg/min.

Table 4
Stereoisomer Pharmacokinetic Parameters[1] of MIVACRON
in ASA Physical Status I–II Adult Patients[2] [n=9]
During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* isomer	*cis-trans* isomer	*cis-cis* isomer
$t_{1/2}$ (min)	2.3 (1.4–3.6)	2.1 (0.8–4.8)	55[3] (32–102)
Volume of Distribution (L/kg)	0.15 (0.06–0.24)	0.27 (0.08–0.56)	0.31 (0.18–0.46)
Plasma Clearance (mL/min/kg)	53 (32–105)	99 (52–230)	4.2 (2.4–5.4)

[1] Values shown are mean (range)
[2] Ages 31 to 48 years
[3] n=8

In cats, the *cis-cis* isomer (6% of the mixture) has approximately one-tenth the neuromuscular blocking potency of the *trans-trans* and *cis-trans* isomers. The neuromuscular blocking potency of the *cis-cis* isomer in humans has not been established; however, modeling of clinical pharmacokinetic/pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a two-hour infusion. In studies in which infusions of up to 2.5 hours were administered to ASA Physical Status I-II patients, the 25%–75% recovery times were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not contribute significant neuromuscular block during use for up to 2.5 hours. Limited data are available from infusions of longer duration or from patients with compromised elimination capacities (hepatic or renal failure).

Metabolism and Excretion

Hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary monoester, a quaternary alcohol and a dicarboxylic acid. Tests in which these metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce significant neuromuscular, autonomic, or cardiovascular effects following administration of MIVACRON. Little MIVACRON is excreted unchanged in urine and bile, but urine and bile are important elimination pathways for the metabolites. In young adults, approximately 40 to 50% of an administered dose is excreted in the urine within 5 to 6 hours, while in the elderly approximately 30% of the total dose is excreted within this time span. High metabolite concentrations (412 to 1832 times the simultaneously determined plasma concentration) were found in samples of bile approximately 70 to 90 minutes after an initial dose of MIVACRON in patients undergoing cholecystectomy.

INDICATIONS AND CLINICAL USE

MIVACRON (mivacurium chloride) is indicated as an adjunct to general anesthesia, to facilitate non-emergency tracheal intubation and to provide skeletal muscle relaxation during surgery.

CONTRAINDICATIONS

MIVACRON (mivacurium chloride) is contraindicated in patients with a known hypersensitivity to this or other benzylisoquinolinium compounds or with a history (e.g., severe anaphylactoid reactions or asthma) suggesting the risk of serious adverse reactions in response to histamine release. Multiple-dose vials of MIVACRON contain benzyl alcohol, while single-dose vials do not. Use of MIVACRON from multiple-dose vials is contraindicated in patients with a known hypersensitivity to benzyl alcohol.

In newborn infants (children less than 1 month in age), benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. Intravenous preparations containing benzyl alcohol should not be used in newborns.

WARNINGS

MIVACRON (MIVACURIUM CHLORIDE) SHOULD BE USED ONLY BY THOSE TRAINED IN AIRWAY MANAGEMENT AND RESPIRATORY SUPPORT. EQUIPMENT AND PERSONNEL MUST BE IMMEDIATELY AVAILABLE FOR TRACHEAL INTUBATION AND SUPPORT OF VENTILATION, INCLUDING ADMINISTRATION OF POSITIVE PRESSURE OXYGEN. ADEQUACY OF RESPIRATION MUST BE ASSURED THROUGH ASSISTED OR CONTROLLED VENTILATION. REVERSAL AGENTS SHOULD BE IMMEDIATELY AVAILABLE. A PERIPHERAL NERVE STIMULATOR SHOULD BE EMPLOYED TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTICHOLINESTERASE ANTAGONISM.

General

MIVACRON has no known effect on consciousness, pain threshold, or cerebration. To avoid distress to the patient, neuromuscular block should not be induced before unconsciousness.

Histamine Release

The possibility of substantial histamine release with consequent bronchospasm or anaphylaxis in sensitive individuals must be considered. Particular caution should be observed when considering the use of MIVACRON in patients for whom substantial histamine release would be especially hazardous (e.g., patients with clinically significant cardiovascular disease) or in patients with any history suggesting a greater than normal sensitivity to histamine release. Release of histamine is related to the dose and speed of injection. If MIVACRON is to be administered to these patients, an initial dose not exceeding 0.15 mg/kg should be administered slowly over 1 minute. Hemodynamic status should be monitored and adequate hydration assured.

Homozygotes for Atypical Plasma Cholinesterase

MIVACRON is not recommended for patients who are known or suspected to be homozygotes for the atypical plasma cholinesterase gene.

Other Diseases and Disorders

In patients who have neuromuscular diseases such as myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of neuromuscular blocking agents may have profound effects. For patients having conditions in which prolonged neuromuscular blockade is a possibility (e.g., neuromuscular disease, carcinomatosis, severe cachexia or debilitation), a peripheral nerve stimulator and use of a small test dose (0.015-0.02 mg/kg) may be of particular value in monitoring the response to the administration of muscle relaxants.

MIVACRON has not been studied in patients with bronchial asthma or burns or during vaginal delivery or cesarean section. The use of MIVACRON in these situations is, therefore, not recommended.

Long-Term Use in the Intensive Care Unit (ICU)

To reduce the possibility of prolonged neuromuscular blockade and other complications that might occur following long-term use in the ICU, MIVACRON or any other neuromuscular blocking agent should be administered in carefully adjusted doses by or under the supervision of experienced clinicians who are familiar with its actions and with appropriate peripheral nerve stimulator muscle monitoring techniques.

Reversal of Neuromuscular Blockade

Evidence of spontaneous recovery from neuromuscular blockade should be observed prior to administration of reversal agents (e.g. neostigmine). The use of a peripheral nerve stimulator to evaluate recovery prior to and during reversal of neuromuscular blockade is strongly recommended.

Compatibility

MIVACRON Injection is acidic (pH 3.5–5.5) and should not be mixed in the same syringe with highly alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions) or administered simultaneously through the same needle during intravenous infusion. In the presence of an alkaline solution, there is a risk that MIVACRON may be inactivated and a free acid precipitated.

PRECAUTIONS

Cardiovascular Disease

Caution should be exercised in administering MIVACRON (mivacurium chloride) to patients with clinically significant cardiovascular disease for whom transient decreases in blood pressure would be especially hazardous. In clinical trials, MIVACRON has been administered to 106 ASA III and IV patients undergoing coronary artery bypass graft (CABG) and valve replacement procedures during narcotic anesthesia. When administered as a 0.15 mg/kg bolus dose, delivered over 60 seconds, MIVACRON did not result in major fluctuations in mean arterial pressure in these patients (mean values 98–101% of baseline at 2 minutes post-injection, range 84–110%). However, when MIVACRON was administered at 0.20 or 0.25 mg/kg doses over 60 seconds, individual patients experienced transient episodes of marked hypotension (see Table 5 under **ADVERSE REACTIONS**). More rapid rates of bolus delivery have not been tested in patients with cardiovascular disease.

In clinical trials in ASA I and II patients, a 0.15 mg/kg dose of MIVACRON delivered over 5 to 15 seconds was associated with transient decreases in mean arterial pressure of 20% or more in 21% of patients.

MIVACRON has no clinically significant effect on heart rate at recommended doses and will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Long-Term Use in the ICU

No information is available concerning the efficacy and safety of long-term (days to weeks) intravenous MIVACRON infusion to facilitate mechanical ventilation in the ICU.

In rare cases, long-term use of other neuromuscular blocking drugs to facilitate mechanical ventilation in ICU settings has been associated with prolonged paralysis and/or skeletal muscle weakness that is first noted during attempts to wean patients from the ventilator. In such patients, neuromuscular blockade may have been enhanced by acid-base or electrolyte imbalances, hypoxic episodes of varying duration, extreme debilitation, and/or concurrent treatment with broad spectrum antibiotics, narcotics and/or steroids. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial muscles and small muscles of the extremities then to the remaining muscles. In rare cases recovery may require an extended period of time or even rehabilitation. Therefore, when long-term mechanical ventilation is indicated, the risk-benefit ratio of neuromuscular blockade must be considered.

WHENEVER THE USE OF MIVACRON OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO CONTINUOUSLY MONITOR NEUROMUSCULAR TRANSMISSION DURING ADMINISTRATION AND RECOVERY. ADDITIONAL DOSES OF MIVACRON OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, THE INFUSION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Burns

Resistance to nondepolarising neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn. Patients with burns may have reduced pseudocholinesterase activity which may offset this resistance. MIVACRON has not been studied in patients with burns, but use of a test dose (0.015–0.02 mg/kg) is recommended.

Acid-Base or Electrolyte Abnormalities

Acid-base and/or electrolyte abnormalities may antagonize or potentiate the action of neuromuscular blocking agents. For example, hyperkalemia has been reported to antagonize nondepolarising agents while hypokalemia has been associated with an enhancement of their activity.

Histamine Release

In 11 patients administered a 0.15 mg/kg bolus dose of MIVACRON over 5 to 15 seconds, mean plasma histamine levels were increased 1.6-fold (range: 0.5 – 4-fold) at 2 minutes post-injection

and returned to near baseline levels at 5 minutes post-injection. At a dose of 0.20 mg/kg delivered over 5 to 15 seconds, mean histamine levels were typically increased 3- to 6-fold at 2 minutes post-injection. When administration of the drug was slowed to 30 seconds, the 0.20 mg/kg dose typically resulted in a 2-fold increase in histamine levels. Slow bolus injections should be considered whenever the risk of histamine release is to be minimized.

Intramuscular Use

No data are available to support the use of MIVACRON by intramuscular injection.

Renal and Hepatic Disease

The effects of renal and hepatic dysfunction on the action of MIVACRON have been studied in a small number of patients with end-stage kidney (n=9) or liver disease (n=8) undergoing transplantation surgery. For kidney transplant patients, the mean 25% and 95% recovery times were increased by 1.6 and 1.9 times, respectively, over the values obtained in elective surgery patients (n=8). For liver transplant patients, both of these recovery times were tripled. The possibility of prolonged neuromuscular block must be considered when MIVACRON is used in patients with renal or hepatic disease. Chronic hepatic diseases such as hepatitis, liver abscess, and cirrhosis of the liver are commonly associated with pronounced reductions in plasma cholinesterase activity. Acute or chronic renal disease may also be associated with reduced plasma cholinesterase activity.

Plasma Cholinesterase Deficiency

The possibility of prolonged neuromuscular block following the administration of MIVACRON must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase: PsChE) activity.

PsChE activity may be diminished in the presence of genetic abnormalities of PsChE (e.g., patients heterozygous or homozygous for atypical PsChE), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. PsChE activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of PsChE (e.g., organophosphate insecticides, echothiophate, and certain antineoplastic drugs). Consideration should be given to administration of a test dose of MIVACRON in patients suspected of having a clinically significant reduction of PsChE activity.

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. In patients with the heterozygous genotype (1 in 40 patients), the mean clinically effective duration of action of 0.1 and 0.2 mg/kg doses is increased by approximately 50%.

As with succinylcholine, patients homozygous for atypical PsChE (1 in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In four of these patients, a small dose of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block produced by MIVACRON in patients homozygous for atypical PsChE could be antagonized with conventional doses of neostigmine. In one adult patient who was homozygous for the atypical plasma cholinesterase gene, a 0.18 mg/kg dose of MIVACRON produced complete neuromuscular blockade for about 4 hours. Recovery of all four responses to train-of-four stimulation occurred after 6 hours and extubation was performed after 8 hours.

Malignant Hyperthermia

Multiple factors in anesthesia practice are suspected of triggering malignant hyperthermia (MH), a potentially fatal hypermetabolic state of skeletal muscle. Halogenated anesthetic agents and succinylcholine are recognized as the principal pharmacologic triggering agents in MH-susceptible patients; however, since MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient scheduled for general anesthesia. In a study of 8 MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients.

Drug Interactions

MIVACRON has been administered safely following succinylcholine- facilitated tracheal intubation. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarising agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

No information is available on the administration of MIVACRON, prior to succinylcholine, to attenuate some of the side effects of succinylcholine (e.g. muscle pain and fasciculations). The administration of MIVACRON in conjunction with other non-depolarising neuromuscular blocking agents, simultaneously or consecutively, has been reported to produce neuromuscular blockade of a degree and duration exceeding 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 succinylcholine 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.

Based on data from two studies of adult patients receiving isoflurane (n=34) or enflurane (n=32) anesthesia, these agents may decrease the ED_{50} doses of MIVACRON by as much as 25%. MIVACRON bolus doses in the recommended therapeutic range are not potentiated by halogenated anesthetics in a consistent or clinically significant manner. In some clinical studies, infusion requirements were approximately 30% lower during steady-state anesthesia with enflurane or isoflurane than during opioid/ nitrous oxide/oxygen anesthesia. Halothane has little or no effect on the ED_{50} of MIVACRON, but may prolong its duration of action and decrease the average infusion requirement in adult patients.

Drugs which may enhance the neuromuscular blocking action of nondepolarising agents such as MIVACRON include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium salts, local anesthetics, procainamide, and quinidine. The neuromuscular blocking effects of MIVACRON may also be enhanced by drugs that reduce plasma cholinesterase activity (e.g., chronically administered oral contraceptives, glucocorticoids, pancuronium or certain monoamine oxidase inhibitors) or by drugs that irreversibly inhibit plasma cholinesterase (e.g. organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

Pregnancy (Teratogenic Effects)

Teratology testing in nonventilated pregnant rats and mice revealed no maternal or fetal toxicity or teratogenic effects. However, as mivacurium was administered by the subcutaneous route at sub-paralysing doses, the relevance of these studies to the clinical use of the drug cannot be assessed. Because animal reproduction studies have not been performed under conditions that would approximate those of clinical use, MIVACRON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. There are no studies of MIVACRON in pregnant women.

Labor and Delivery

The use of MIVACRON during labor, vaginal delivery or cesarean section has not been studied in humans. Doses of 0.08 and 0.20 mg/kg MIVACRON given to 3 female beagles undergoing cesarean section resulted in negligible levels of mivacurium in umbilical vessel blood of neonates and no deleterious effects on the puppies. In humans, it is not known whether MIVACRON administered to the mother has effects on the fetus. The possibility that a forceps delivery will be necessary may increase. The possibility of respiratory depression in the neonate should be considered following deliveries during which a neuromuscular blocking agent has been administered. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nursing Mothers

It is not known whether MIVACRON is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when MIVACRON is administered to a nursing woman.

Pediatric Use

For children 2 to 12 years of age, see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**. The safety and efficacy of MIVACRON in children below the age of 2 years have not been established.

Geriatric Use

MIVACRON has been administered to elderly patients ≥65 years of age (n=64), including patients with significant cardiovascular disease (n=31) (see **Cardiovascular Disease**). The duration of neuromuscular block may be slightly longer in elderly patients (see **CLINICAL PHARMACOLOGY**).

Obesity

Ideal body weight should be considered in dosage calculations for obese patients with appropriate attention to the attendant risk of underdosing. Severe obesity may pose airway or ventilatory problems before, during, or after the use of nondepolarising neuromuscular blockers.

Increased Volume of Distribution

The onset of action of neuromuscular blocking agents may be delayed in patients in whom the volume of distribution is increased as a result of old age, edematous states, or cardiovascular disease. In these patients, more time should be permitted for the drug to achieve its maximal effect.

Hypothermia

Hypothermia (25–28°C) has been associated with a decreased requirement for nondepolarising neuromuscular blocking agents.

ADVERSE REACTIONS

MIVACRON (mivacurium chloride) was well tolerated during extensive clinical trials. Prolonged neuromuscular block, which is an important adverse experience associated with neuromuscular blocking agents as a class, was reported as an adverse experience in 3 of 2074 patients administered MIVACRON. In 2074 patients administered MIVACRON in clinical trials, the following adverse experiences were reported (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
Neurologic:	Dizziness
Musculoskeletal:	Muscle Spasms
Nonspecific:	Prolonged Drug Effect

Skin flushing, erythema, urticaria, hypotension, tachycardia, wheezing, or bronchospasm associated with the use of MIVACRON have been attributed to histamine release. Histamine release is dose related and more common following the rapid administration of initial doses of 0.2 mg/kg or more and can be reduced by injecting MIVACRON slowly over 30 to 60 seconds or in divided doses over 30 seconds.

The most commonly reported adverse experience was transient, dose-related cutaneous flushing about the face, neck and/or chest. In clinical trials, flushing was reported in approximately 25% of adult patients who received 0.15 mg/kg over 5 to 15 seconds. Flushing reactions typically had an onset time of 1 to 2 minutes and a duration of 3 to 5 minutes.

Hypotension was infrequently reported as an adverse experience in the clinical trials of MIVACRON. One of 332 (0.3%) healthy adults who received 0.15 mg/kg MIVACRON over 5 to 15 seconds and none of 37 cardiac surgery patients who received 0.15 mg/kg MIVACRON over 60 seconds were treated for a decrease in blood pressure in association with the administration of MIVACRON. Treatment for a decrease in blood pressure was reported in 1% to 2% of healthy adults given $\geq$ 0.20 mg/kg MIVACRON over 5 to 15 seconds, 2% to 3% of healthy adults given 0.20 mg/kg over 30 seconds, none of 100 healthy adults given 0.25 mg/kg as a divided dose (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg), and 2% to 4% of cardiac surgery patients given $\geq$ 0.20 mg/kg over 60 seconds. None of 63 children who received the recommended dose of 0.20 mg/kg MIVACRON was treated for a decrease in blood pressure in association with the administration of MIVACRON.

Table 5
Frequency of Maximum Changes in Mean Arterial Pressure (MAP) and Heart Rate (HR) Following Doses of MIVACRON Administered Over 5 to 15 seconds to Healthy Adult and Pediatric Patients and Over 60 seconds to Adult Patients with Cardiovascular Disease During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial MIVACRON Dose (mg/kg)		Maximum Change[1]		Patients with 20–29% Dec or Inc				Patients with 30–39% Dec or Inc				Patients with ≥40% Dec or Inc			
				MAP		HR		MAP		HR		MAP		HR	
		MAP (mm Hg)	HR (beats/min)	Dec %	Inc %	Dec %	Inc %	Dec %	Inc %	Dec %	Inc %	Dec %	Inc %	Dec %	Inc %
Adults (ASA Physical Status I–II)															
0.07	(n=14)	0.7 (–18 to 23)	–2.4 (–14 to 23)	7	14	0	0	0	0	0	0	0	0	0	0
0.10	(n=16)	0 (–14 to 4.1)	–5.8 (–25 to 8)	0	0	0	0	0	6	0	0	0	1	0	0
0.15	(n=53)	–4.1 (–42 to 32)	–2.6 (–43 to 19)	19	2	3	8	4	4	4	2	1	1	0	1
0.20[2]	(n=53)	–14.1 (–41 to 16)	4.1 (–33 to 33)	14	4	5	7	30	0	0	8	13	0	0	7
0.25[2]	(n=44)	–14.2 (–48 to 59)	5.6 (–36 to 61)	14	3	2	18	39	2	0	14	14	2	0	8
Children 2–12 years (ASA Physical Status I–II)															
0.11–0.12	(n=17)	0.8 (–14 to 17)	–0.7 (–18 to 17)	0	9	0	0	0	6	0	0	0	0	0	0
0.20	(n=17)	–0.2 (–17 to 17)	–2.4 (–32 to 17)	6	21	3	0	0	0	0	0	0	0	0	0
0.25	(n=8)	–10.4 (–24 to 9)	–6.1 (–18 to 5)	19	0	0	0	13	0	0	0	0	0	0	0
Adults (ASA Physical Status III–IV)[3]															
0.15	(n=36)	–1.3 (–3.8 to 0.7)	–3.4 (–4.7 to –2.7)	0	3	0	0	0	0	0	0	0	0	0	0
0.20	(n=43)	0.9 (0.0 to 3.6)	–2.7 (–3.2 to 0)	0	2	0	2	2	7	0	0	0	2	0	0
0.25	(n=23)	0.7 (–0.9 to 2.6)	–3.7 (–5.5 to –1.9)	4	4	4	4	4	4	0	0	4	0	0	0

[1] Values shown are medians of means from individual studies (range of individual patient values)
[2] Rapid administration not recommended due to possibility of decreased blood pressure. Administer 0.20 mg/kg over 30 sec; administer 0.25 mg/kg as divided dose (0.15 mg/kg followed 30 sec later by 0.10 mg/kg). See **DOSAGE AND ADMINISTRATION**.
[3] For recommended dosage in patients with cardiovascular disease, see **DOSAGE AND ADMINISTRATION**.

Observed During Clinical Practice

General: allergic reactions, anaphylactoid reactions (very rarely,severe anaphylactic or anaphylactoid reactions) have been reported.

Musculoskeletal: diminished drug effect, prolonged drug effect, re-paralysis following initial cholinesterase-induced reversal

Cardiovascular: hypotension, flushing, edema, angioedema, tachycardia, bradycardia, cardiovascular collapse, cardiac arrest, arrhythmias

Respiratory: bronchospasm, laryngospasm, wheezing

Integumentary: rash, erythema, urticaria

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The possibility of iatrogenic overdosage can be minimized by carefully monitoring the muscle twitch response to peripheral nerve stimulation. Overdosage with neuromuscular blocking agents may result in neuromuscular block beyond the time needed for surgery and anesthesia. The primary treatment is maintenance of a patent airway and controlled ventilation until recovery of normal respiration is assured. Once evidence of spontaneous recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine or edrophonium) in conjunction with an appropriate anticholinergic agent. Overdosage may increase the risk of histamine release and hemodynamic side effects, especially decreases in blood pressure. If needed, cardiovascular support may be provided by proper positioning of the patient, fluid administration, and/or vasopressor agent administration. A peripheral nerve stimulator should be used to monitor recovery.

Antagonism of Neuromuscular Blockade

Anticholinesterase agents should be used to antagonize neuromuscular blockade only after spontaneous recovery of the muscle twitch response has begun. Antagonists should not be administered if complete neuromuscular blockade is evident or suspected. Owing to the rapid spontaneous recovery from mivacurium-induced neuromuscular blockade, the use of anticholinesterase reversal agents may not always represent a clinically significant advantage in terms of recovery time. However, mivacurium-induced neuromuscular blockade can be antagonized by anticholinesterase agents once spontaneous recovery has begun. As with other nondepolarising neuromuscular blocking agents, the time required for anticholinesterase- mediated recovery is longer for reversals attempted at deeper levels of blockade.

Administration of 0.030 to 0.064 mg/kg neostigmine or 0.5 mg/kg edrophonium to adults at approximately 10% recovery from neuromuscular block (range: 1–15%) produced 95% recovery of the muscle twitch response and a T_4/T_1 ratio of $\geq$75% in about 10 minutes. The time from 25% recovery of the muscle twitch response to T_4/T_1 ratios of $\geq$75% under these conditions of antagonism averaged about 7 to 9 minutes. In comparison, average times for spontaneous recovery from 25% to a T_4/T_1 ratio of $\geq$75% were 12 to 13 minutes.

Patients should be evaluated for adequate clinical evidence of antagonism, e.g. 5-second head lift and grip strength. Ventilation must be supported until no longer required.

Conditions which may be associated with delayed antagonism include debilitation, carcinomatosis, concomitant use of certain broad spectrum antibiotics, or use of anesthetic agents or other drugs that enhance neuromuscular blockade or depress respiration.

DOSAGE AND ADMINISTRATION

To avoid distress to the patient, MIVACRON (mivacurium chloride) should not be administered before unconsciousness has been induced. It should not be mixed in the same syringe, or administered simultaneously through the same needle, with alkaline solutions (e.g., barbiturate solutions).

MIVACRON should be administered intravenously only. **Do not administer MIVACRON by the intramuscular route**. The dosage information provided below is intended as a guide only. The use of a peripheral nerve stimulator will permit the most advantageous use of MIVACRON, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery. Dosage requirements may vary and dosage should be individualized. The duration of action of MIVACRON may be increased in elderly patients or in patients with renal or hepatic disease. In patients known or suspected of having a significant reduction in plasma cholinesterase activity, consideration should be given to the administration of a small test dose of MIVACRON (see **PRECAUTIONS**).

When using MIVACRON or other neuromuscular blocking agents to facilitate tracheal intubation, it is important to recognize that the most important factors affecting intubation are the depth of general anesthesia and the level of neuromuscular block. Satisfactory intubating conditions can usually be achieved before complete neuromuscular block is attained if there is adequate anesthesia.

When using a stimulator to monitor onset of neuromuscular block, clinical studies have shown that all four twitches of the train-of-four response may be present, with little or no fade, at the times recommended for intubation. Therefore, as with other neuromuscular blocking agents, it is important to use other criteria, such as clinical evaluation of the status of relaxation of jaw muscles and vocal cords, in conjunction with peripheral muscle twitch monitoring, to guide the appropriate time of intubation.

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

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

Adults

Initial Bolus Doses

Doses of 0.15 mg/kg administered over 5 to 15 seconds, 0.20 mg/kg administered over 30 seconds, or 0.25 mg/kg administered in divided doses (0.15 mg/kg followed 30 seconds later by 0.10 mg/kg) are recommended for facilitation of non-emergency tracheal intubation for most patients (see Table 6).

Table 6
Recommended Initial Dosing Regimens for Adults

Dosing Paradigm[1]	Anesthetic Induction Technique Studied	Time to Generally Good-to-Excellent Intubating Conditions
0.15 mg/kg, i.v. (over 5 to 15 sec)	Thiopental/opioid/N_2O/O_2 or propofol/opioid	2.5–3 min after completion of dose
0.20 mg/kg, i.v. (over 30 sec)	Thiopental/opioid/N_2O/O_2 or propofol/opioid	2–2.5 min after completion of dose
0.25 mg/kg, i.v. (0.15 mg/kg followed 30 sec later by 0.10 mg/kg)	Propofol/opioid	1.5–2 min after completion of 0.15 mg/kg dose

[1] Dosing instituted after induction of adequate general anesthesia

The purpose of slowed or divided dosing of MIVACRON at doses above 0.15 mg/kg is to minimize the transient decreases in blood pressure, and other symptoms of histamine release, observed in some patients given these doses over 5 to 15 seconds (see **CLINICAL PHARMACOLOGY**, **PRECAUTIONS**, and **ADVERSE REACTIONS**). The quality of intubation conditions does not significantly differ for the times and doses of MIVACRON recommended in Table 6, but the onset of suitable intubation conditions may be reached earlier with higher doses. The choice of a particular dose and regimen should be based on individual circumstances and patient requirements (see **PRECAUTIONS**).

In patients for whom a sudden decrease in blood pressure may prove hazardous (e.g., patients with significant cardiovascular disease) or with any history suggesting a greater sensitivity to histamine release, the dose of MIVACRON should be $\leq$0.15 mg/kg 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.

In patients receiving opioid/nitrous oxide/oxygen anesthesia, 0.15 mg/kg MIVACRON typically produces 96% to 100% maximal twitch suppression (range: 53–100%) in 3 to 7 minutes (range: 2–11 min). Clinically effective neuromuscular block generally lasts 15 to 20 minutes (range: 8–38 min) and spontaneous recovery may be expected to be 95% complete in 25 to 30 minutes (range: 14–74 min).

A dose of 0.10 mg/kg produces a mean 96% to 100% maximal twitch suppression in about 4 minutes during balanced anesthesia with a mean clinically effective duration of action of approximately 15 minutes (range: 8–24 min).

The expected duration of clinically effective block and the 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 anesthesia is generally required approximately 15, 20, and 25 minutes following initial MIVACRON doses of 0.15, 0.20, and 0.25 mg/kg, respectively (see Table 1). Maintenance doses of 0.10 mg/kg, administered to patients at approximately 10% twitch recovery, each provide approximately 13 minutes (range: 10–19 min) of $\geq$95% twitch suppression. For a shorter or longer duration of action, smaller or larger maintenance doses may be administered. 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 (see **CLINICAL PHARMACOLOGY**).

Continuous Infusion

Continuous infusion of MIVACRON may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from the initial dose, an infusion rate of 9 to 10 µg/kg/min counteracts the rapid spontaneous recovery of neuromuscular function in most patients (Tables 7 and 8). If continuous infusion is initiated simultaneously with the administration of an initial bolus dose, a lower initial infusion rate should be used (e.g., 4 µg/kg/min). In either case, the initial infusion rate should be adjusted according to the response to peripheral nerve stimulation and to clinical criteria. On average, an infusion rate of 6 to 7 µg/kg/min (range: 1–15 µg/kg/min) may be expected to maintain neuromuscular block within the range of 89% to 99% for extended periods in adults receiving opioid/nitrous oxide/oxygen anesthesia. Upon cessation of infusions delivered at these rates, 25% recovery can generally be expected in about 6 to 9 minutes (range: 2–45 min) and 95% recovery in 16 to 24 minutes (range: 8–34 min).

Children

MIVACRON has not been studied in children under 2 years of age.

Initial Bolus Doses

Dosage requirements for MIVACRON on a mg/kg basis are higher in children than in adults. Onset and recovery of neuromuscular block occur more rapidly in children than in adults (see **CLINICAL PHARMACOLOGY**).

The recommended initial dose of MIVACRON in children 2 to 12 years of age is 0.20 mg/kg. The use of MIVACRON to facilitate endotracheal intubation in children has not been studied. In 18 pediatric patients, an initial dose of 0.20 mg/kg produced maximum block of 95% to 100% in an average of 1.9 minutes (range: 1–3 min) and clinically effective block for 10 minutes (range: 6–15 min) during stable opioid/nitrous oxide/ oxygen anesthesia. Under the same anesthetic conditions, doses of 0.11 to 0.12 mg/kg produced maximum neuromuscular block of 89% to 100% in an average of 2.8 minutes (range: 1–5 min) and clinically effective block for an average of 7 minutes (range: 4–10 min) in 17 pediatric patients. Maintenance doses may be required more frequently in children than in adults. Administration of MIVACRON doses above the recommended range (>0.20 mg/kg) is associated with transient decreases in MAP in some children.

Continuous Infusion

Children require higher MIVACRON infusion rates than adults. During opioid/nitrous oxide/oxygen anesthesia the infusion rate required to maintain 89% to 99% neuromuscular block averages 14 µg/kg/min (range: 5–31 µg/kg/min). Following cessation of infusion, 25% recovery can typically be expected in 3 to 4 minutes (range: 2–11 min) and 95% recovery in 11 to 12 minutes (range: 6–17 min). The principles for infusion of MIVACRON in adults (see above) are also applicable to children.

Infusion Rate Tables

For adults and children the amount of infusion solution required per hour depends upon the clinical requirements of the patient, the concentration of MIVACRON in the infusion solution, and the patient's weight. The contribution of the infusion solution to the fluid requirements of the patient must be considered. Table 7 provides guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops = 1 mL) of MIVACRON Injection (2 mg/mL). Table 8 gives similar guidelines when admixtures of MIVACRON are to be used (see **PHARMACEUTICAL INFORMATION**, **Parenteral Products**).

Table 7
Infusion Rates for Maintenance of Neuromuscular Blockade
During Opioid/Nitrous Oxide/Oxygen Anesthesia
Using MIVACRON Injection (2 mg/mL) - mL/h

Patient Weight (kg)	MIVACRON Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	1.2	1.5	1.8	2.1	2.4	3.0	4.2	4.8	5.4	6.0
15	1.8	2.3	2.7	3.2	3.6	4.5	6.3	7.2	8.1	9.0
20	2.4	3.0	3.6	4.2	4.8	6.0	8.4	9.6	10.8	12.0
25	3.0	3.8	4.5	5.3	6.0	7.5	10.5	12.0	13.5	15.0
35	4.2	5.3	6.3	7.4	8.4	10.5	14.7	16.8	18.9	21.0
50	6.0	7.5	9.0	10.5	12.0	15.0	21.0	24.0	27.0	30.0
60	7.2	9.0	10.8	12.6	14.4	18.0	25.2	28.8	32.4	36.0
70	8.4	10.5	12.6	14.7	16.8	21.0	29.4	33.6	37.8	42.0
80	9.6	12.0	14.4	16.8	19.2	24.0	33.6	38.4	43.2	48.0
90	10.8	13.5	16.2	18.9	21.6	27.0	37.8	43.2	48.6	54.0
100	12.0	15.0	18.0	21.0	24.0	30.0	42.0	48.0	54.0	60.0

Table 8
Infusion Rates for Maintenance of Neuromuscular Block
During Opioid/Nitrous Oxide/Oxygen Anesthesia
Using MIVACRON Admixture (0.5 mg/mL) - mL/hr

Patient Weight (kg)	MIVACRON Delivery Rate (µg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
	Infusion Delivery Rate (mL/hr)									
10	5	6	7	8	10	12	17	19	22	24
15	7	9	11	13	14	18	25	29	32	36
20	10	12	15	17	19	24	34	38	43	48
25	12	15	18	21	24	30	42	48	54	60
35	17	21	26	29	34	42	59	67	76	84
50	24	30	36	42	48	60	84	96	108	120
60	29	36	43	50	58	72	101	115	130	144
70	34	42	50	59	67	84	118	134	151	168
80	39	48	58	67	77	96	134	154	173	192
90	44	54	65	76	86	108	151	173	194	216
100	48	60	72	84	96	120	168	192	216	240

PHARMACEUTICAL INFORMATION

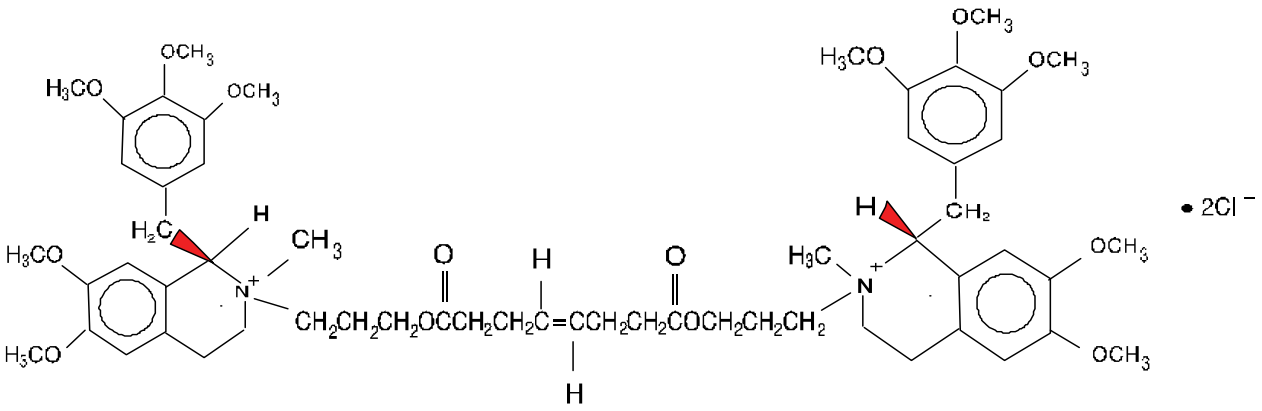
Drug Substance

Brand Name: MIVACRON

Common Name: Mivacurium Chloride

Chemical Name: [*R*-[*R**,*R**-(*E*)]]-2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]isoquinolinium] dichloride

Chemical Name: Isoquinolinium, 2,2'-[(1,8-dioxo-4-octene-1,8-diyl)bis(oxy-3,1-propanediyl)]bis[1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)methyl]-,dichloride,[*R*-[*R**,*R**-(*E*)]]



Molecular Formula: $C_{58}H_{80}Cl_2N_2O_{14}$

Molecular Weight: 1 100.18

Description: Mivacurium chloride, an off-white to yellow amorphous solid, is a mixture of three stereoisomers: the *trans-trans* diester (1R, 1'R, 2S, 2'S), the *cis-trans* diester (1R, 1'R, 2R, 2'S), and the *cis-cis* diester (1R, 1'R, 2R, 2'R), with an approximate ratio of 60:35:6, respectively.

Solubility: It is soluble in water, ethanol and 1-octanol.

pKa: A quaternary ammonium salt, it is completely ionizable at all concentrations measured. No pKa values can be assigned.

Partition Coefficient: 0.015 in a 1-octanol/distilled water system at 25°C.

Melting Point: Decomposes at approximately 125°C.

Composition

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5–5.5) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust pH. Multiple dose vials contain 0.9% w/v benzyl alcohol.

Storage Recommendations

Store MIVACRON Injection at room temperature of 15° to 25°C. DO NOT FREEZE.

Parenteral Products

MIVACRON Injection should not be mixed with highly alkaline solutions (e.g., barbiturate solutions).

MIVACRON Injection is compatible with:

- 5% Dextrose Injection USP
- 0.9% Sodium Chloride Injection USP
- 5% Dextrose and 0.9% Sodium Chloride Injection USP
- Lactated Ringer's Injection USP
- 5% Dextrose in Lactated Ringer's Injection

These solutions may be administered simultaneously with MIVACRON Injection or used to prepare admixtures of MIVACRON Injection (e.g., 0.5 mg/mL). Compatibility studies with other parenteral products have not been done.

Dilution stability

MIVACRON Injection diluted to 0.5 mg mivacurium per mL in the above mentioned diluents is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at room temperature for up to 24 hours. All solutions should be visually inspected for particulate matter and discoloration prior to intravenous administration whenever solution and container permit. Solutions which are not clear and colorless should not be used. Aseptic techniques should be used to avoid microbial contamination of the admixture. Admixtures of MIVACRON Injection should be prepared for single-patient use only and used within 24 hours of preparation. The unused portion of the admixture should be discarded.

AVAILABILITY OF DOSAGE FORMS

MIVACRON Injection, 2 mg mivacurium per mL is available in the following sizes:

- 10 mL Single Dose Vials in trays of 10
- 20 mL Multiple Dose Vials containing 0.9% w/v benzyl alcohol as a preservative in trays of 10
- 50 mL Multiple Dose Vials containing 0.9% w/v benzyl alcohol as a preservative in a box of 1

PHARMACOLOGY

The relative neuromuscular blocking potencies of mivacurium, succinylcholine, and atracurium were studied in cats, dogs, and monkeys:

	Cat		Dog		Rhesus Monkey	
Drug (i.v.)	**ED_{95} (mg/kg)**	**Duration (min)**	**ED_{95} (mg/kg)**	**Duration (min)**	**ED_{95} (mg/kg)**	**Duration (min)**
Mivacurium	0.055	12-15	0.02	18-22	0.03-0.04	9-12
Succinylcholine	0.05	5-6	0.075	7-12	2.0	4-6
Atracurium	0.16	15	0.13	35	0.15	25

Note: *ED_{95}* is defined as the dose necessary to cause 95 percent inhibition of the tibialis anterior twitch contraction. *Duration* is the time from drug injection to the point of recovery of the twitch to 95 percent of control values. Data obtained in n $\geq$5 for each species.

Mivacurium, administered as a single dose or by continuous infusion in amounts that produced clinically useful levels of neuromuscular blockade, had no sympatholytic or vagolytic effects in anesthetized dogs or monkeys.

Intravenous doses of mivacurium in Rhesus monkeys (20 x ED_{95}), dogs (15-30 x ED_{95}) and cats (16-30 x ED_{95}) produced variable and transient effects on mean arterial pressure and heart rate. The predominant effect was hypotension which was dose-dependent and of a shorter duration than the neuromuscular blockade.

Studies conducted in cats in the presence or absence of bilateral renal artery ligation suggested that pathways other than renal clearance contributed to the dissipation of neuromuscular blockade. The ED_{95} of mivacurium was significantly higher following portal vein administration than following femoral vein administration suggesting that the liver plays a role in the clearance and/or metabolism of mivacurium in cats.

Pharmacokinetics

The pharmacokinetics of mivacurium was studied in dogs (0.020 mg/kg i.v.) and cats (0.065 mg/kg i.v.). The following data were obtained:

Parameter	**Dog (n = 4)**	**Cat (n = 5)**
Volume of Distribution (Vdss)	0.192 L/kg	0.068 L/kg
Half-Life $t_{1/2\beta}$	15 minutes	5.9 minutes
25% to 75% Recovery	6.3 minutes	3.0 minutes
Plasma Concentration During Initial (5%) Recovery	38 ng/mL	108 ng/mL

In dogs, mivacurium was excreted predominantly in urine and bile as unchanged drug; while in cats, mivacurium was excreted principally in bile and urine as metabolites formed by hydrolysis.

TOXICOLOGY

Acute

The LD_{50} values for intravenous and subcutaneous injections of mivacurium chloride determined in the rat were 0.27 mg/kg and 5.45 mg/kg, respectively.

Subacute

Mivacurium dichloride was administered to anesthetized, ventilated dogs (n=6) and monkeys (n=6) twice weekly for three weeks under conditions simulating clinical usage. The doses used represented up to 15 x ED_{50} in dogs and 50 x ED_{50} in monkeys. Observations and measurements in these studies included behaviour (dogs), appetite (dogs), clinical observations, body weights, electrocardiography, ophthalmology, clinical pathology, hematology (dogs), serum chemistry (dogs), urinalyses (dogs), gross pathology and histopathology. There were no deaths or drug-induced toxicity noted in either study.

In a second monkey study, the animals were dosed as above, but were administered either label strength mivacurium or drug that had been heat degraded to 80% of label strength. There were no changes that could be attributed to either form of mivacurium compared to control animals.

Mutagenicity

Mivacurium dichloride was not found to be mutagenic in the Ames *Salmonella* assay nor in the L5178Y/$TK^{+/-}$ mouse lymphoma assay. No structural or numerical chromosome observations were noted in cultured human lymphocytes exposed to mivacurium dichloride in the presence or absence of metabolic activation.

An *in vivo* cytogenicity study in rats revealed no significant increase in the incidence of structural or numerical chromosome abnormalities, compared to vehicle controls, due to mivacurium dichloride.

Teratology

Teratology studies were conducted in pregnant mice and rats. Mivacurium was administered subcutaneously at 2 dose levels (0.4 and 0.8 mg/kg/day in rats and 0.25 and 0.5 mg/kg/day in mice). Mivacurium was given on days 6 through 15 of the gestational period of major organogenesis. Mivacurium was not maternally toxic, embryotoxic or teratogenic. However, as mivacurium was administered by the subcutaneous route at sub-paralysing doses, the relevance of these studies to the clinical use of the drug cannot be assessed.

Special Studies

Mivacurium was tested for its potential to excite malignant hyperthermia in 8 susceptible Pietrain pigs. No evidence of malignant hyperthermia was seen at mivacurium doses of 1 and 4 x ED_{95} given as an intravenous bolus.

Mivacurium was shown to be non-irritating when injected perivenously or intramuscularly in dogs as a 1 mL solution of 2 mg/mL mivacurium.

A 2 mg/mL solution of mivacurium dichloride did not flocculate plasma protein nor excessively hemolyze a 50% suspension of red blood cells when tested at 1:1 or 1:4 ratios with human type O positive plasma or red blood cell suspension. The hemolysis seen was no different from that caused by sterile water for injection and was greater than that caused by isotonic saline.

REFERENCES

1. Alifimoff JK, Goudsouzian NG. Continuous infusion of mivacurium in children. Br J Anaesth 1989; 63:520-524.

2. Brandom BW, Woelfel SK, Cook DR, et al. Comparison of mivacurium and suxamethonium administered by bolus and infusion. Br J Anaesth 1989; 62:488-493.

3. Caldwell JE, Kitts JB, Heier T, et al. The dose-response relationship of mivacurium chloride in humans during nitrous oxide-fentanyl or nitrous oxide-enflurane anesthesia. Anesthesiology 1989; 70:31-35.

4. Coghlan SFE, McDonald PF, Csepregi G. Use of alfentanil with propofol for nasotracheal intubation without neuromuscular block. Br J Anaesth 1993; 70:89-91.

5. From RP, Pearson KS, Choi WW, et al. Neuromuscular and cardiovascular effects of mivacurium chloride (BW B1090U) during nitrous oxide-fentanyl-thiopentone and nitrous oxide-halothane anaesthesia. Br J Anaesth 1990; 64:193-198.

6. Goldberg ME, Larijani GE, Azad SS, et al. Comparison of tracheal intubating conditions and neuromuscular blocking profiles after intubating doses of mivacurium chloride or succinylcholine in surgical outpatients. Anesth Analg 1989; 69:93-99.

7. Goldhill DR, Whitehead JP, Emmott RS, et al. Neuromuscular and clinical effects of mivacurium chloride in healthy adult patients during nitrous oxide-enflurane anaesthesia. Br J Anaesth 1991; 67:289-295.

8. Goudsouzian NG, Alifimoff JK, Eberly C, et al. Neuromuscular and cardiovascular effects of mivacurium in children. Anesthesiology 1989; 70:237-242.

9. Jensen FS, Viby-Mogensen J, Ostergaard D. Significance of plasma cholinesterase for the anaesthetist. Current Anaesthesia and Critical Care, 1991; 2: 232-237.

10. Ramsey FM, Geffin B, Heslop MJ, et al. Safety and efficacy of mivacurium for endotracheal intubation. Anesth Analg 1989; 68:S321.

11. Sarner JB, Brandom BW, Woelfel SK, et al. Clinical pharmacology of mivacurium chloride (BW B1090U) in children during nitrous oxide-halothane and nitrous oxide-narcotic anesthesia. Anesth Analg 1989; 68:116-121.

12. Savarese JJ, Ali HH, Basta SJ, et al. The clinical neuromuscular pharmacology of mivacurium chloride (BW B1090U). Anesthesiology 1988; 68:723-732.

13. Savarese JJ, Ali HH, Basta SJ, et al. The cardiovascular effects of mivacurium chloride (BW B1090U) in patients receiving nitrous oxide-opiate-barbiturate anesthesia. Anesthesiology 1989; 70:386-394.

14. Shanks CA, Fragen RJ, Pemberton D, et al. Mivacurium-induced neuromuscular blockade following single bolus doses and with continuous infusion during either balanced or enflurane anesthesia. Anesthesiology 1989; 71:362-366.

15. Stoops CM, Curtis CA, Kovach DA, et al. Hemodynamic effects of mivacurium chloride administered to patients during oxygen-sufentanil anesthesia for coronary artery bypass grafting or valve replacement. Anesth Analg 1989; 68:333-339.

16. Weber S, Brandom BW, Powers DM, et al. Mivacurium chloride (BW B1090U)-induced neuromuscular blockade during nitrous oxide-isoflurane and nitrous oxide-narcotic anesthesia in adult surgical patients. Anesth Analg 1988; 67:495-499.