CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION:NDA 20098/S009

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CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: NDA 20098/S009

Trade Name: MIVACRON Injection and MIVACRON Injection Premixed Infusion

Generic Name: (mivacurium chloride)

Sponsor: Glaxo-Wellcome Incorporated

Approval Date: May 19, 1998

Indication: Provides for labeling changes for MIVACRON based on your commitment to Phase 4 studies made at the time of approval

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number:NDA 20098/S009

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-098/S-009

MAY 19 1998

Glaxo-Wellcome Incorporated
Five Moore Drive
Research Triangle Park, North Carolina 27709

Attention: Robert Bohinski
Manager
Regulatory Affairs

Dear Mr. Bohinski:

Please refer to your supplemental new drug application dated May 12, 1997, received May 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for MIVACRON® Injection and MIVACRON® Injection Premixed Infusion (mivacurium chloride).

We acknowledge receipt of your submission dated May 20, 1997. The User Fee goal date for this application is May 20, 1998.

This supplemental application provides for labeling changes for MIVACRON based on your commitment to Phase 4 studies made at the time of approval.

We have completed the review of this supplemental application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed draft labeling. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDA 20-098/S-009. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, Maryland 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Ken Nolan, Project Manager, at 301-443-3741.

Sincerely,

Cynthia G. McCormick, M.D.
Director
Division of Anesthetic, Critical Care, and
Addiction Drug Products, HFD-170
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20098/S009

FINAL PRINTED LABELING

PRODUCT INFORMATION

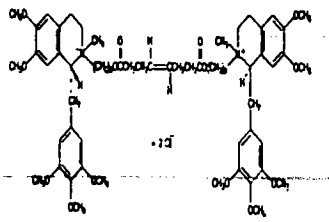
MIVACRON® Injection

MIVACRON® Premixed Infusion

(mivacurium chloride)

This drug should be administered only by adequately trained individuals familiar with its actions, characteristics, and hazards.

DESCRIPTION: MIVACRON (mivacurium chloride) is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous administration. Mivacurium chloride is [*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. The molecular formula is $C_{58}H_{80}Cl_2N_2O_{14}$ and the molecular weight is 1100.18. The structural formula is:



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: (1*R*, 1′*R*, 2*S*, 2′*S*), the *trans-trans* diester; (1*R*, 1′*R*, 2*R*, 2′*S*), the *cis-trans* diester; and (1*R*, 1′*R*, 2*R*, 2′*R*), the *cis-cis* diester. The *trans-trans* and *cis-trans* stereoisomers comprise 92% to 96% of mivacurium chloride and their neuromuscular blocking potencies are not significantly different from each other or from mivacurium chloride. The *cis-cis* diester has been estimated from studies in cats to have one-tenth the neuromuscular blocking potency of the other two stereoisomers.

MIVACRON Injection is a sterile, non-pyrogenic solution (pH 3.5 to 5.0) containing mivacurium chloride equivalent to 2 mg/mL mivacurium in Water for Injection. Hydrochloric acid may have been added to adjust

Table 1: Pharmacodynamic Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial Dose of MIVACRON®* (mg/kg)	Time to Maximum Block (min)	Time to Spontaneous Recovery†			
		5% Recovery (min)	25% Recovery‡ (min)	95% Recovery§ (min)	T_4/T_1 Ratio ≥75% (min)
Adults					
0.07 to 0.10 [n = 47]	4.9 (2.0 - 7.6)	11 (7 - 19)	13 (8 - 24)	21 (10 - 36)	21 (10 - 36)
0.15 [n = 50]	3.3 (1.5 - 8.8)	13 (6 - 31)	16 (9 - 38)	26 (16 - 41)	26 (15 - 45)
0.20‖ [n = 50]	2.5 (1.2 - 6.0)	16 (10 - 29)	20 (10 - 36)	31 (15 - 51)	34 (19 - 56)
0.25‖ [n = 48]	2.3 (1.0 - 4.8)	19 (11 - 29)	23 (14 - 38)	34 (22 - 64)	43 (26 - 75)
Children 2 to 12 Years					
0.11 to 0.12 [n = 17]	2.8 (1.2 - 4.6)	5 (3 - 9)	7 (4 - 10)	–	–
0.20 [n = 18]	1.9 (1.3 - 3.3)	7 (3 - 12)	10 (6 - 15)	19 (14 - 26)	16 (12 - 23)
0.25 [n = 9]	1.6 (1.0 - 2.2)	7 (4 - 9)	9 (5 - 12)	–	–

* Doses administered over 5 to 15 seconds.

† Values shown are medians of means from individual studies (range of individual patient values).

‡ Clinically effective duration of neuromuscular block.

§ 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%.

‖ 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.

Administration of MIVACRON over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of MIVACRON may be prolonged in patients with reduced plasma cholinesterase (pseudocholinesterase) activity (see PRECAUTIONS: **Reduced Plasma Cholinesterase Activity** and CLINICAL PHARMACOLOGY: **Individualization of Dosages** subsection).

Interpatient variability in duration of action occurs with MIVACRON as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of MIVACRON during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery

at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

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).

Hemodynamics: Administration of MIVACRON in doses up to and including 0.15 mg/kg (2 x ED_{95}) over 5 to 15 seconds to ASA Physical Status I-II patients during opioid/nitrous oxide/oxygen anesthesia is associated with minimal changes in mean arterial blood pressure (MAP) or heart rate (HR) (Table 2).

Table 2: Cardiovascular Dose Response During Opioid/Nitrous Oxide/Oxygen Anesthesia

Initial Dose of MIVACRON* (mg/kg)		% of Patients With ≥30% Change			
		MAP		HR	
		Dec	Inc	Dec	Inc
Adults					
0.07 to 0.10	[n = 49]	0%	2%	0%	0%
0.15	[n = 53]	4%	4%	4%	2%
0.20†	[n = 53]	30%	0%	0%	8%
0.25†	[n = 44]	39%	2%	0%	14%
Children 2 to 12 years					
0.11 to 0.12	[n = 17]	0%	6%	0%	0%
0.20	[n = 17]	0%	0%	0%	0%
0.25	[n = 8]	13%	0%	0%	0%

* Doses administered over 5 to 15 seconds.

† 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.

Higher doses of ≥0.20 mg/kg (≥3 x ED_{95}) 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 minimized by administering MIVACRON over 30 to 60 seconds (see CLINICAL PHARMACOLOGY: **Individualization of Dosages** subsection and PRECAUTIONS: **General**).

Table 3: Stereoisomer Pharmacokinetic Parameters* of Mivacurium in ASA Physical Status I-II Adult Patients† [n = 18] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	*trans-trans* isomer	*cis-trans* isomer
Elimination Half-life ($t_{½}$, min)	2.0 (1.0 - 3.6)	1.8 (0.8 - 4.8)
Volume of Distribution‡ (mL/kg)	147 (67 - 254)	276 (79 - 772)
Plasma Clearance (mL/min/kg)	53 (26 - 98)	99 (44 - 199)

* Values shown are mean (range).
† Ages 31 to 48 years.
‡ Volume of distribution during the terminal elimination phase.

The *cis-cis* isomer (6% of the mixture) has approximately one-tenth the neuromuscular blocking potency of the *trans-trans* and *cis-trans* isomers in cats. Neuromuscular blocking effects due to the *cis-cis* isomer cannot be ruled out in humans; however, modeling of clinical pharmacokinetic-pharmacodynamic data suggests that the *cis-cis* isomer produces minimal (<5%) neuromuscular block during a 2-hour infusion. In studies of ASA Physical Status I-II patients receiving infusions of MIVACRON lasting as long as 4 to 6 hours, the 5% to 25% and the 25% to 75% recovery indices were independent of the duration of infusion, suggesting that the *cis-cis* isomer does not affect the rate of post-infusion recovery.

Distribution: The volume of distribution of *cis-trans* and *trans-trans* isomers in healthy surgical patients is relatively small reflecting limited tissue distribution (Table 3). The volume of distribution of *cis-cis* isomer is also small and averaged 335 mL/kg (range:192-523) in the 18 healthy surgical patients whose data are displayed in Table 3. The protein binding of mivacurium has not been determined due to its rapid hydrolysis by plasma cholinesterase.

Metabolism: Enzymatic hydrolysis by plasma cholinesterase is the primary mechanism for inactivation of mivacurium and yields a quaternary alcohol and a quaternary monoester metabolite. Tests in which these two

Table 4: Stereoisomer Pharmacokinetic Parameters* of Mivacurium in ASA Physical Status I-II Adult Patients [18-58 Years] and Elderly Patients [60-81 Years] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	Isomer	Adult Patients (n = 12)	Elderly Patients (n = 8)
Plasma Clearance (mL/min/kg)	*trans-trans* isomer	54 (34 - 129)	32 (18 - 55)
	cis-trans isomer	91 (27 - 825)	47 (24 - 93)

* Values shown are median (range).

The second study showed no clinically important differences in the pharmacokinetics of the individual isomers nor the ED_{95} determined for 36 young adult patients (18 to 40 years) and 35 elderly patients (≥65 years) during opioid/nitrous oxide/oxygen anesthesia. Following infusions for up to 3.5 hours in these patients, the rate of spontaneous recovery was slightly (~2 to 4 minutes, on average) slower in the elderly patients than in young adult patients.

In an earlier study of the pharmacodynamics of 0.1 mg/kg MIVACRON administered to eight elderly patients (68 to 77 years) and nine adult patients (18 to 49 years) during N_2O/O_2/isoflurane anesthesia, the time to onset was approximately 1.5 minutes slower in elderly patients than in adult patients. In addition, the clinical duration was slightly (~3 minutes, on average) longer in elderly patients than in adult patients; these differences are not considered clinically important.

Although these studies showed conflicting findings, in general, the clearances of the more potent isomers are most likely lower in elderly patients. This difference does not lead to clinically important differences in the ED_{95} of MIVACRON or the infusion rate of MIVACRON required to produce 95% T_1 suppression in elderly patients. However, the time to onset may be slower, the duration may be slightly longer, and the rate of recovery may be slightly slower.

Patients with Renal Disease: An early clinical trial showed that the clinically effective duration of action of 0.15 mg/kg MIVACRON was about 1.5 times longer in kidney transplant patients than in healthy patients, presumably due to reduced clearance of one or more isomers. A second study was conducted in seven patients with mild to

Table 5: Stereoisomer Pharmacokinetic Parameters* of Mivacurium in ASA Physical Status I-II Adult Patients with Normal Renal Function [Serum Creatinine ≤1.0 mg/dL], Patients with Mild to Moderate Renal Dysfunction [Serum Creatinine 1.3 to 2.7 mg/dL] and Patients with Severe Renal Dysfunction [Serum Creatinine >6.2 mg/dL] During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	Isomer	Normal Renal Function (n = 10)	Mild to Moderate Renal Dysfunction (n = 8)	Severe Renal Dysfunction (n = 7)
Plasma Clearance (mL/min/kg)	*trans-trans* isomer	54 (19 - 91)	49 (43 - 59)	53 (17 - 82)
	cis-trans isomer	97‡ (28 - 215)	93 (72 - 115)	110 (23 - 199)
	cis-cis isomer	4.0 (2.9 - 5.4)	2.5 (1.9 - 3.8)	2.8 (2.1 - 4.7)
Volume of Distribution† (mL/kg)	*trans-trans* isomer	179 (67 - 492)	243 (119 - 707)	238 (93 - 397)
	cis-trans isomer	303§ (97 - 776)	474 (284 - 908)	416‖ (64 - 802)
	cis-cis isomer	287 (169 - 424)	323 (254 - 473)	276 (213 - 351)
Half-life (min)	*trans-trans* isomer	2.6 (1.0-6.8)	3.6 (1.7-10.7)	3.2 (1.6-4.1)
	cis-trans isomer	2.3§ (0.7 - 5.2)	3.7 (2.2 - 6.9)	2.6‖ (1.2 - 5.1)
	cis-cis isomer	52 (28 - 80)	90 (66 - 103)	73 (34 - 111)
25% to 75% Recovery Index (min)		10.8¶ (7.3 - 19.9)	9.2 (5.2 - 13.8)	10.3§ (4.1 - 14.2)

* Values shown are mean (range).
† Volume of distribution during the terminal elimination phase.
‡ n = 9
§ n = 8;
‖ n = 6;
¶ n = 11.

Table 6: Pharmacokinetic and Pharmacodynamic Parameters* of Mivacurium In ASA Physical Status I-II Patients and In Patients with Mild or Moderate Cirrhosis During Opioid/Nitrous Oxide/Oxygen Anesthesia

Parameter	Isomer	Normal Hepatic Function (n = 10)	Degree of Hepatic Failure	
			Mild Cirrhosis (n = 5)	Moderate Cirrhosis (n = 6)
Plasma Clearance (mL/min/kg)	trans-trans isomer	66 (34 - 99)	43 (22 - 64)	31 (11 - 66)
	cis-trans isomer	124‡ (57 - 218)	73 (34 - 111)	52 (18 - 128)
	cis-cis isomer	8.6 (4.5 -13.3)	8.6 (4.5-16.7)	5.6 (3.5 - 9.7)
Volume of Distribution† (mL/kg)	trans-trans isomer	204‡ (94 - 269)	221 (118-457)	191 (74 - 273)
	cis-trans isomer	201‡ (89 - 411)	152 (102 - 256)	111 (56 - 164)
	cis-cis isomer	159 (106 - 219)	147 (91 - 232)	164 (135 - 185)
Half-life (min)	trans-trans isomer	2.4‡ (1.3 - 3.9)	3.7 (1.7 - 5.1)	5.3 (1.7 - 8.5)
	cis-trans isomer	1.2‡ (0.6 - 2.1)	1.6 (1.0 - 2.1)	1.9 (0.9 - 3.0)
	cis-cis isomer§	-	-	-
25% to 75% Recovery Index (min)		7.3 (4.7 - 9.6)	9.5 (5.7 - 12.3)	16.4 (6.3 - 26.2)

* Values shown are mean (range).

† Volume of distribution during the terminal elimination phase.

‡ n = 9.

§ not available.

Individualization of Dosages: DOSES OF MIVACRON SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING ADMINISTRATION OF MIVACRON IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

The neuromuscular blocking action of MIVACRON is potentiated by isoflurane or enflurane anesthesia. Recommended initial doses of MIVACRON (see DOSAGE AND ADMINISTRATION) may be used for intubation prior to the administration of these agents. If MIVACRON is first administered after establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial dose of MIVACRON should be reduced by as much as 25%, and the infusion rate reduced by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking action of MIVACRON may be expected with higher concentrations of enflurane or isoflurane. The use of halothane requires no adjustment of the initial dose of MIVACRON, but may prolong the duration of action and decrease the average infusion rate by as much as 20% (see PRECAUTIONS: **Drug Interactions**).

When MIVACRON is administered to patients receiving certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide, and quinidine, longer durations of neuromuscular block may be expected and infusion requirements may be lower (see PRECAUTIONS: **Drug Interactions**).

When MIVACRON is administered to patients chronically receiving phenytoin or carbamazepine, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher (see PRECAUTIONS: **Drug Interactions**).

Severe acid-base and/or electrolyte abnormalities may potentiate or cause resistance to the neuromuscular blocking action of MIVACRON. No data are available in such patients and no dosing recommendations can be made (see PRECAUTIONS: **General**).

Burns: While patients with burns are known to develop resistance to nondepolarizing neuromuscular blocking agents, they may also have reduced plasma cholinesterase activity. Consequently, in these patients, a test dose of not more than 0.015 to 0.020 mg/kg MIVACRON is recommended, followed by additional appropriate dosing guided by the use of a neuromuscular block monitor (see PRECAUTIONS: **General**).

Cardiovascular Disease: In patients with clinically significant cardiovascular disease, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds (see CLINICAL PHARMACOLOGY: **Hemodynamics** subsection and PRECAUTIONS: **General**).

Obesity: Obese patients (patients weighing ≥30% more than their ideal body weight) dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight, had a greater probability of experiencing a decrease of ≥30% in MAP (see CLINICAL PHARMACOLOGY:

MIVACRON IS METABOLIZED BY PLASMA CHOLINESTERASE AND SHOULD BE USED WITH GREAT CAUTION, IF AT ALL, IN PATIENTS KNOWN TO BE OR SUSPECTED OF BEING HOMOZYGOUS FOR THE ATYPICAL PLASMA CHOLINESTERASE GENE.

MIVACRON Injection and MIVACRON Premixed Infusion are acidic (pH 3.5 to 5.0) and may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions).

Multiple-dose vials of MIVACRON contain benzyl alcohol. In newborn infants, benzyl alcohol has been associated with an increased incidence of neurological and other complications which are sometimes fatal. Single-use vials and MIVACRON Premixed Infusion do not contain benzyl alcohol (see PRECAUTIONS: **Pediatric Use**).

PRECAUTIONS:

General: Although MIVACRON (a mixture of three stereoisomers) is not a potent histamine releaser, the possibility of substantial histamine release must be considered. Release of histamine is related to the dose and speed of injection.

Caution should be exercised in administering MIVACRON to patients with clinically significant cardiovascular disease and patients with any history suggesting a greater sensitivity to the release of histamine or related mediators (e.g., asthma). In such patients, the initial dose of MIVACRON should be 0.15 mg/kg or less, administered over 60 seconds; assurance of adequate hydration and careful monitoring of hemodynamic status are important (see CLINICAL PHARMACOLOGY: **Hemodynamics** and **Individualization of Dosages**).

Obese patients may be more likely to experience clinically significant transient decreases in MAP than non-obese patients when the dose of MIVACRON is based on actual rather than ideal body weight. Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (see CLINICAL PHARMACOLOGY: **Hemodynamics** and **Individualization of Dosages**).

Recommended doses of MIVACRON have no clinically significant effects on heart rate; therefore, MIVACRON will not counteract the bradycardia produced by many anesthetic agents or by vagal stimulation.

Neuromuscular blocking agents may have a profound effect in patients with neuromuscular diseases (e.g., myasthenia gravis and the myasthenic syndrome). In these and other conditions in which prolonged neuromuscular block is a possibility (e.g., carcinomatosis), the use of a peripheral nerve stimulator and a dose

MIVACRON has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg MIVACRON, the clinically effective duration of action was 8 to 11 minutes longer in patients heterozygous for the atypical gene than in genotypically normal patients.

As with succinylcholine, patients homozygous for the atypical plasma cholinesterase gene (1 in 2,500 patients) are extremely sensitive to the neuromuscular blocking effect of MIVACRON. In three such adult patients, a small dose of 0.03 mg/kg (approximately the ED_{10-20} in genotypically normal patients) produced complete neuromuscular block for 26 to 128 minutes. Once spontaneous recovery had begun, neuromuscular block in these patients was antagonized with conventional doses of neostigmine. One adult patient, who was homozygous for the atypical plasma cholinesterase gene, received a dose of 0.18 mg/kg MIVACRON and exhibited complete neuromuscular block for about 4 hours. Response to post-tetanic stimulation was present after 4 hours, all four responses to train-of-four stimulation were present after 6 hours, and the patient was extubated after 8 hours. Reversal was not attempted in this patient.

Malignant Hyperthermia (MH): In a study of MH-susceptible pigs, MIVACRON did not trigger MH. MIVACRON has not been studied in MH-susceptible patients. Because MH can develop in the absence of established triggering agents, the clinician should be prepared to recognize and treat MH in any patient undergoing general anesthesia.

Long-Term Use in the Intensive Care Unit (ICU): No data are available on the long-term use of MIVACRON in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although MIVACRON (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between MIVACRON and succinylcholine has not been systematically studied. Prior administration of succinylcholine can potentiate the neuromuscular blocking effects of nondepolarizing agents. Evidence of spontaneous recovery from succinylcholine should be observed before the administration of MIVACRON.

The use of MIVACRON before succinylcholine to attenuate some of the side effects of succinylcholine has not been studied.

There are no clinical data on the use of MIVACRON with other nondepolarizing neuromuscular blocking agents.

Labor and Delivery: The use of MIVACRON during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether MIVACRON administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg MIVACRON given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in MIVACRON in umbilical vessel blood of neonates and no deleterious effects on the puppies.

Nursing Mothers: It is not known whether any of the stereoisomers of mivacurium are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised following administration of MIVACRON to a nursing woman.

Pediatric Use: MIVACRON has not been studied in pediatric patients below the age of 2 years (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in children 2 to 12 years of age).

Geriatric Use: MIVACRON was safely administered during clinical trials to 64 elderly (≥65 years) patients, including 31 patients with significant cardiovascular disease (see PRECAUTIONS: **General** subsection). The time to onset may be slower, the duration may be slightly longer, and the rate of recovery may be slightly slower in elderly patients (see CLINICAL PHARMACOLOGY).

ADVERSE REACTIONS:

Observed in Clinical Trials: MIVACRON (a mixture of three stereoisomers) was well tolerated during extensive clinical trials in inpatients and outpatients. 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 2,074 patients administered MIVACRON. The most commonly reported adverse experience following the administration of MIVACRON was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of MIVACRON and was reported in about 25% of adult patients who received 0.15 mg/kg MIVACRON over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of MIVACRON and lasted for 3 to 5 minutes. Of 105 patients who experienced flushing after 0.15 mg/kg MIVACRON, two patients also experienced mild hypotension that was not treated, and one patient experienced moderate wheezing that was successfully treated.

Overall, 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

agent (see **Antagonism of Neuromuscular Block** subsection below). Overdosage may increase the risk of 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.

Antagonism of Neuromuscular Block: ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED WHEN COMPLETE NEUROMUSCULAR BLOCK IS EVIDENT OR SUSPECTED. THE USE OF A PERIPHERAL NERVE STIMULATOR TO EVALUATE RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCK IS RECOMMENDED.

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

Patients administered antagonists 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.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and the concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular block or separately cause respiratory depression (see PRECAUTIONS: **Drug Interactions**). Under such circumstances the management is the same as that of prolonged neuromuscular block (see OVERDOSAGE).

DOSAGE AND ADMINISTRATION: MIVACRON SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of MIVACRON should be individualized (see CLINICAL PHARMACOLOGY: **Individualization of Dosages**). 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 $\geq$30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents.

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

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 CLINICAL PHARMACOLOGY: **Individualization of Dosages**).

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 (e.g., 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.

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 anesthesia. 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 anesthesia is generally required approximately 15, 20, and 25 minutes following initial doses of 0.15, 0.20, and 0.25 mg/kg MIVACRON, respectively (see Table 1). 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.

The neuromuscular blocking action of MIVACRON is potentiated by isoflurane or enflurane anesthesia. 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 establishment of stable-state isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC), the initial dose of MIVACRON may be reduced by as much as 25%. Greater reductions in the dose of MIVACRON 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.

Continuous Infusion: Continuous infusion of MIVACRON may be used to maintain neuromuscular block. Upon early evidence of spontaneous recovery from an initial dose, an initial infusion rate of 9 to 10 mcg/kg/min is recommended. If continuous infusion is initiated simultaneously with the administration of an initial dose, a lower initial infusion rate should be used (e.g., 4 mcg/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 5 to 7 mcg/kg/min (range: 1 to 15) may be expected to maintain neuromuscular block within the

Table 8: Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON® Premixed Infusion (0.5 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (mcg/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

Table 9: Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using MIVACRON® Injection (2 mg/mL)

Patient Weight (kg)	Drug Delivery Rate (mcg/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

MIVACRON Premixed Infusion in Flexible Plastic Containers: The flexible plastic container is fabricated from a specially formulated, nonplasticized, thermoplastic co-polyester (CR3). Water can permeate from inside the container into the overwrap but not in amounts sufficient to affect the solution significantly. Solutions inside the plastic container also can leach out certain of the chemical components in very small amounts

MIVACRON® Injection and MIVACRON® Premixed Infusion (mivacurium chloride)

INAPSINE® (droperidol) Injection, diluted as directed

Compatibility studies with other parenteral products have not been conducted.

Dilution Stability: MIVACRON Injection diluted to 0.5 mg mivacurium per mL in 5% Dextrose Injection USP, 5% Dextrose and 0.9% Sodium Chloride Injection USP, 0.9% Sodium Chloride Injection USP, Lactated Ringer's Injection USP, or 5% Dextrose in Lactated Ringer's Injection is physically and chemically stable when stored in PVC (polyvinyl chloride) bags at 5° to 25°C (41° to 77°F) for up to 24 hours. Aseptic techniques should be used to prepare the diluted product. Admixtures of MIVACRON should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted MIVACRON should be discarded after each case.

NOTE: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. Solutions which are not clear and colorless should not be used.

HOW SUPPLIED: MIVACRON Injection, 2 mg mivacurium in each mL.
5-mL Single-Use Vials. Tray of 10 (NDC 0173-0705-44).
10-mL Single-Use Vials. Tray of 10 (NDC 0173-0705-95).
20-mL Multiple-Dose Vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants). Tray of 10 (NDC 0173-0542-00).
50-mL Multiple-Dose Vials containing 0.9% w/v benzyl alcohol as a preservative (see WARNINGS concerning newborn infants). Tray of 3 (NDC 0173-0538-00).

MIVACRON Premixed Infusion in 5% Dextrose Injection USP, 0.5 mg mivacurium in each mL.

50-mL (in a 100-mL unit) Flexible Plastic Containers (NDC 0173-0709-01).
100-mL (in a 100-mL unit) Flexible Plastic Containers (NDC 0173-0709-02).

STORAGE: Store MIVACRON Injection at room temperature of 15° to 25°C (59° to 77°F). Avoid exposure to direct ultraviolet light. DO NOT FREEZE.

Recommended storage for MIVACRON Premixed Infusion is room temperature (15° to 25°C/59° to 77°F). Avoid excessive heat. Avoid exposure to direct ultraviolet light. Protect from freezing.