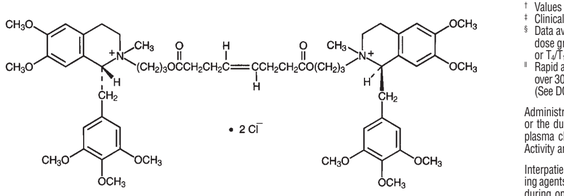
MIVACURIUM CHLORIDE INJECTION

Rx only

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

DESCRIPTION

Mivacurium chloride is a short-acting, nondepolarizing skeletal muscle relaxant for intravenous (IV) 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.

Mivacurium chloride 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 pH.

CLINICAL PHARMACOLOGY

Mivacurium chloride (a mixture of three stereoisomers) binds competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine.

Pharmacodynamics: The time to maximum neuromuscular block is similar for recommended doses of mivacurium chloride 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 chloride (a mixture of three stereoisomers) 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 twitch response to ulnar nerve stimulation) of mivacurium is 0.07 mg/kg (range: 0.05 to 0.09) in adults receiving opioid/nitrous oxide/oxygen anesthesia. The pharmacodynamics of doses of mivacurium ≥ED_{95} administered over 5 to15 seconds during opioid/nitrous oxide/oxygen anesthesia are summarized in Table 1. The mean time for spontaneous recovery of the twitch response from 25% to 75% of control amplitude is about 6 minutes (range: 3 to 9, n=32) following an initial dose of 0.15 mg/kg mivacurium and 7 to 8 minutes (range: 4 to 24, n=85) following initial doses of 0.20 or 0.25 mg/kg mivacurium.

Volatile anesthetics may decrease the dosing requirement for mivacurium chloride and prolong the duration of action; the magnitude of these effects may be increased as the concentration of the volatile agent is increased. Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC [Minimum Alveolar Concentration]) may decrease the effective dose of mivacurium by as much as 25% and may prolong the clinically effective duration of action and decrease the average infusion requirement by as much as 35% to 40%. At equivalent MAC values, halothane has little or no effect on the ED_{50} of mivacurium, but may prolong the duration of action and decrease the average infusion requirement by as much as 20% (see CLINICAL PHARMACOLOGY: Individualization of Dosages subsection and PRECAUTIONS: Drug Interactions).

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

Initial Dose of mivacurium* (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 mivacurium 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 mivacurium over 30 to 60 seconds does not alter the time to maximum neuromuscular block or the duration of action. The duration of action of mivacurium 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 mivacurium chloride as with other neuromuscular blocking agents. However, analysis of data from 224 patients in clinical studies receiving various doses of mivacurium during opioid/nitrous oxide/oxygen anesthesia with a variety of premedicants and varying lengths of surgery indicated that approximately 90% of the patients had clinically effective durations of block within 8 minutes of the median duration predicted from the dose-response data shown in Table 1. Variations in plasma cholinesterase activity, including values within the normal range and values as low as 20% below the lower limit of the normal range, were not associated with clinically significant effects on duration. The variability in duration, however, was greater in patients with plasma cholinesterase activity at or slightly below the lower limit of the normal range.

When administered during the induction of adequate anesthesia using thiopental or propofol, nitrous oxide/oxygen, and coinduction agents such as fentanyl and/or midazolam, doses of 0.15 mg/kg (2 X ED_{95}) mivacurium administered over 5 to 15 seconds or 0.20 mg/kg mivacurium 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 mivacurium 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.

Repeated administration of maintenance doses or continuous infusion of mivacurium 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. Based on pharmacokinetic studies in 82 adults receiving infusions of mivacurium for longer than 2.5 hours, spontaneous recovery of neuromuscular function after infusion is independent of the duration of infusion and comparable to recovery reported for single doses (Table 1).

Mivacurium chloride was administered as an infusion for as long as 4 to 6 hours in 20 adult patients and 19 geriatric patients. In most patients, after a brief period of adjustment, the rate of mivacurium required to maintain 89% to 99% T_1 suppression remained relatively constant over time. There was a subset of patients in each group whose infusion rates did not stabilize quickly and decreased (by ≥30%) over the period of infusion. The rate of spontaneous recovery in these patients was comparable with that of patients having stable infusion rates and not dependent on the duration of infusion. These patients, however, tended to have higher infusion requirements (i.e., >8 mcg/kg/min) during the first 30 minutes of infusion than patients with stable infusion rates, although their final infusion rates were similar to those with stable infusion rates. There were no clinically important differences in infusion rate requirements between geriatric and young patients (see Pharmacokinetics: Special Populations: Geriatric Patients).

The neuromuscular block produced by mivacurium chloride is readily antagonized by anticholinesterase agents. As seen with other nondepolarizing neuromuscular blocking agents, the more profound the neuromuscular block at the time of reversal, the longer the time and the greater the dose of anticholinesterase agent required for recovery of neuromuscular function.

In children (2 to 12 years), mivacurium 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 mivacurium. Recovery following reversal is faster in children than in adults (Table 1).

Hemodynamics: Administration of mivacurium 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 Mivacurium* (mg/kg)		% of Patients With ≥30% Change MAP Dec	MAP Inc	HR Dec	HR 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 mivacurium over 30 to 60 seconds (see CLINICAL PHARMACOLOGY: Individualization of Dosages subsection and PRECAUTIONS: General).

Analysis of 426 patients in clinical studies receiving initial doses of mivacurium up to and including 0.30 mg/kg during opioid/nitrous oxide/oxygen anesthesia showed that high initial doses and a rapid rate of injection contributed to a greater probability of experiencing a decrease of ≥30% in MAP after administration of mivacurium. Obese patients also had a greater probability of experiencing a decrease of ≥30% in MAP when dosed on the basis of actual body weight, thereby receiving a larger dose than if dosed on the basis of ideal body weight (see CLINICAL PHARMACOLOGY): Individualization of Dosages subsection and PRECAUTIONS: General).

Children experience minimal changes in MAP or HR after administration of doses of mivacurium up to and including 0.20 mg/kg over 5 to 15 seconds, but higher doses (≥0.25 mg/kg) may be associated with transient decreases in MAP (Table 2).

Following a dose of 0.15 mg/kg mivacurium administered over 60 seconds, adult patients with significant cardiovascular disease undergoing coronary artery bypass grafting or valve replacement procedures showed no clinically important changes in MAP or HR. Transient decreases in MAP were observed in some patients after doses of 0.20 to 0.25 mg/kg mivacurium administered over 60 seconds. The number of patients in whom these decreases in MAP required treatment was small.

Pharmacokinetics: Mivacurium chloride is a mixture of isomers which do not interconvert *in vivo*. The *cis-trans* and *trans-trans* isomers (92% to 96% of the mixture) are equipotent. The steady-state concentrations of the *cis-trans* and *trans-trans* isomers doubled after the infusion rate was increased from 5 to 10 mcg/kg/min, indicating that their pharmacokinetics is dose-proportional.

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 ($t_{1/2}$ 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 mivacurium 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* isomers is also small and averaged 335 mL/kg (range 192 to 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 metabolites were administered to cats and dogs suggest that each metabolite is unlikely to produce clinically significant neuromuscular, autonomic, or cardiovascular effects following administration of mivacurium chloride.

The mean ± S.D. *in vitro* $t_{1/2}$ values of the *trans-trans* and the *cis-trans* isomers were 1.3 ± 0.3 and 0.8 ± 0.2 minutes, respectively, in human plasma from healthy male (n=5) and female (n=5) volunteers. The mean *in vivo* $t_{1/2}$ values for the more potent *trans-trans* and *cis-trans* isomers in healthy surgical patients (Table 3) were similar to those found *in vitro*, suggesting that hydrolysis by plasma cholinesterase is the predominant elimination pathway for these isomers. The mean ± S.D. *in vitro* $t_{1/2}$ of the less potent *cis-cis* isomer was 276 ± 130 minutes, while the mean ± S.D. *in vivo* $t_{1/2}$ for the *cis-cis* isomer in healthy surgical patients was 53 ± 20 minutes. These data suggest that *in vivo*, pathways other than hydrolysis by plasma cholinesterase contribute to the elimination of the *cis-cis* isomer.

Elimination: The clearance (CL) values of the two more potent isomers, *cis-trans* and *trans-trans*, are very high and are dependent on plasma cholinesterase activity (Table 3). The combination of high CL and low distribution volume results in $t_{1/2}$ values of approximately 2 minutes for the two more potent isomers. The short $t_{1/2}$ and high CL of the more potent isomers are consistent with the short duration of action of mivacurium chloride.

The CL of the less potent *cis-cis* isomer is not dependent on plasma cholinesterase. The mean ± S.D. CL was 4.6 ± 1.1 mL/min/kg and $t_{1/2}$ was 53 ± 20 minutes in the 18 healthy surgical patients whose data are displayed in Table 3.

Renal and biliary excretion of unchanged mivacurium are minor elimination pathways; urine and bile are important elimination pathways for the two metabolites.

Special Populations: Geriatric Patients (≥65 years): Two pharmacokinetic/pharmacodynamic studies of mivacurium chloride have been conducted in geriatric patients. The first study compared the pharmacokinetics and pharmacodynamics of mivacurium in 19 geriatric patients with those in 20 adult patients receiving infusions for as long as 4 to 6 hours. The average infusion rate required to produce 89% to 99% T_1 suppression was slightly (~14%) lower in geriatric patients. This difference is not regarded as clinically important, but is most likely secondary to differences in pharmacokinetics (i.e., a lower CL of the *cis-trans* and *trans-trans* isomers in geriatric patients) (Table 4). The rate of post-infusion spontaneous recovery was not dependent on duration of infusion and appeared to be comparable in these geriatric patients and adult patients. Two pharmacodynamic studies in which patients received infusions for a shorter duration (2 to 3 hours) have shown that the infusion rate requirements were lower (by 38%) in geriatric patients (64 to 86 years of age) than in younger patients (18 to 41 years of age).

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

Parameter	Isomer	Adult Patients (n=12)	Geriatric 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 pharmacokinetic/pharmacodynamic 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 geriatric 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 geriatric patients than in young adult patients.

In a third study of the pharmacodynamics of 0.1 mg/kg mivacurium chloride administered to eight geriatric 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 geriatric patients than in adult patients. In addition, the clinical duration was slightly (~3 minutes, on average) longer in geriatric 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 geriatric patients. This difference does not lead to clinically important differences in the ED_{95} of mivacurium or the infusion rate of mivacurium required to produce 95% T_1 suppression in geriatric patients. However, the time to onset may be slower, the duration may be slightly longer, the rate of recovery may be slightly slower, therefore mivacurium requirements may be lower in geriatric patients.

Patients with Renal Disease: An early clinical trial showed that the clinically effective duration of action of 0.15 mg/kg mivacurium 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 moderate renal impairment, eight patients with severe renal dysfunction (not undergoing transplantation), and 11 patients with normal renal function. This study showed that the pharmacokinetics of the more potent (*cis-trans* and *trans-trans*) isomers were not statistically significantly affected by renal impairment or failure (Table 5). However, the CL of the *cis-cis* isomer was lower and the $t_{1/2}$ values of the *cis-cis* isomer and metabolites were longer in patients with renal impairment or failure than in patients with normal renal function. The second study also showed that there were no differences in the average infusion rate required to produce 89% to 99% T_1 suppression, nor were there any differences in the post-infusion recovery profile among these populations (Table 5). A third study in a similar population showed that patients with renal dysfunction had a longer duration and a slower rate of recovery than patients with normal renal function. This study did, however, confirm that there were no differences in the average infusion rate required to produce 89% to 99% T_1 suppression in these patient populations. Therefore, although there were minor differences in the pharmacokinetics of the *cis-cis* isomer and metabolites, there were no clinically significant differences in the infusion rate requirements of mivacurium chloride in patients with mild, moderate, or severe renal dysfunction receiving infusions of mivacurium chloride for an average of 1 to 2 hours; however, the duration may be longer and the rate of recovery may be slower following administration of mivacurium chloride in some patients with renal dysfunction.

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	203§ (97 – 776)	474 (284 – 908)	416¶ (64 – 902)
	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
n=7

Patients with Hepatic Disease: The clinically effective duration of action of 0.15 mg/kg mivacurium was three times longer in eight patients with end-stage liver disease (undergoing liver transplantation) than in eight healthy patients and is likely related to the markedly decreased plasma cholinesterase activity (30% of healthy patient values) which could decrease the clearance of the *trans-trans* and *cis-trans* isomers (see PRECAUTIONS: Reduced Plasma Cholinesterase Activity).

A separate study compared the pharmacokinetics and pharmacodynamics of mivacurium in patients with mild or moderate cirrhosis to healthy adults with normal hepatic function (Table 6). Although the number of patients in each group is small, the CL values of the more potent isomers, *trans-trans* and *cis-trans*, are lower in patients with mild to moderate cirrhosis as expected based on the marked decreases in plasma cholinesterase activity in this population (see PRECAUTIONS: Reduced Plasma Cholinesterase Activity).

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

Based on the known actions of mivacurium chloride (a mixture of three stereoisomers) and other neuromuscular blocking agents, the following factors should be considered when administering mivacurium:

Renal or Hepatic Impairment: A dose of 0.15 mg/kg mivacurium is recommended for facilitation of tracheal intubation in patients with renal or hepatic impairment. However, the clinically effective duration of block produced by this dose may be about 1.5 times longer in patients with end-stage kidney disease and about 3 times longer in patients with end-stage liver disease than in patients with normal renal and hepatic function. Infusion rates should be decreased by as much as 50% in patients with hepatic disease depending on the degree of hepatic impairment (see PRECAUTIONS: Renal and Hepatic Disease). No infusion rate adjustments are necessary in patients with renal impairment.

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of mivacurium chloride must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity. Mivacurium chloride should be used with great caution, if at all, in patients known or suspected of being homozygous for the atypical plasma cholinesterase gene (see WARNINGS). Doses of 0.03 mg/kg produced complete neuromuscular block for 26 to 128 minutes in three such patients; thus initial doses greater than 0.03 mg/kg are not recommended in homozygous patients. Infusions of mivacurium chloride are not recommended in homozygous patients.

Mivacurium chloride has been used safely in patients heterozygous for the atypical plasma cholinesterase gene and in genotypically normal patients with reduced plasma cholinesterase activity. After an initial dose of 0.15 mg/kg mivacurium, the clinically effective duration of block in heterozygous patients may be approximately 10 minutes longer than in patients with normal genotype and normal plasma cholinesterase activity. Lower infusion rates of mivacurium are recommended in these patients (see PRECAUTIONS: Reduced Plasma Cholinesterase Activity).

Drugs or Conditions Causing Potentiation of or Resistance to Neuromuscular Block: As with other neuromuscular blocking agents, mivacurium chloride may have profound neuromuscular blocking effects in cachectic or debilitated patients, patients with neuromuscular diseases, and patients with carcinomatosis. In these or other patients in whom potentiation of neuromuscular block or difficulty with reversal may be anticipated, the initial dose should be decreased. A test dose of not more than 0.015 to 0.020 mg/kg, which represents the lower end of the dose-response curve for mivacurium, is recommended in such patients (see PRECAUTIONS: General).

The neuromuscular blocking action of mivacurium chloride is potentiated by isoflurane or enflurane anesthesia. Recommended initial doses of mivacurium (see DOSAGE AND ADMINISTRATION) may be used for intubation prior to the administration of these agents. If mivacurium 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 mivacurium 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 mivacurium chloride may be expected with higher concentrations of enflurane or isoflurane. The use of halothane requires no adjustment of the initial dose of mivacurium, but may prolong the duration of action and decrease the average infusion rate by as much as 20% (see PRECAUTIONS: Drug Interactions).

When mivacurium chloride 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 rate requirements may be lower (see PRECAUTIONS: Drug Interactions).

When mivacurium chloride 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 mivacurium. 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 mivacurium 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 mivacurium 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: Hemodynamics subsection and PRECAUTIONS: General). Therefore, in obese patients, the initial dose should be determined using the patient's ideal body weight (IBW), according to the following formulae:

Men: IBW in kg=(106 + [6 x inches in height above 5 feet])/2.2
Women: IBW in kg=(106 + [5 x inches in height above 5 feet])/2.2

Allergy and Sensitivity: In patients with any history suggestive of a greater sensitivity to the release of histamine or related mediators (e.g., asthma), the initial dose of mivacurium should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS: General).

INDICATIONS AND USAGE

Mivacurium chloride is a short-acting neuromuscular blocking agent indicated for inpatients and outpatients, as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS

Mivacurium chloride is contraindicated in patients known to have an allergic hypersensitivity to mivacurium chloride or other benzylisoquinolinium agents, as manifested by reactions such as urticaria or severe respiratory distress or hypotension.

WARNINGS

MIVACURIUM CHLORIDE SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH THE DRUG'S ACTIONS AND THE POSSIBLE COMPLICATIONS OF ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS PERSONNEL AND FACILITIES FOR RESUSCITATION AND LIFE SUPPORT (TRACHEAL INTUBATION, ARTIFICIAL VENTILATION, OXYGEN THERAPY), AND AN ANTAGONIST OF MIVACURIUM CHLORIDE ARE IMMEDIATEDLY AVAILABLE. IT IS RECOMMENDED THAT A PERIPHERAL NERVE STIMULATOR BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING THE ADMINISTRATION OF MIVACURIUM CHLORIDE IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DRUG, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

MIVACURIUM CHLORIDE HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. TO AVOID DISTRESS TO THE PATIENT, NEUROMUSCULAR BLOCK SHOULD NOT BE INDUCED BEFORE UNCONSCIOUSNESS.

MIVACURIUM CHLORIDE 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.

Mivacurium chloride injection is 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).

PRECAUTIONS

General: Although mivacurium chloride (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 mivacurium chloride 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 mivacurium 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 mivacurium 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 mivacurium have no clinically significant effects on heart rate; therefore, mivacurium 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 of not more than 0.015 to 0.020 mg/kg mivacurium is recommended to assess the level of neuromuscular block and to monitor dosage requirements (see CLINICAL PHARMACOLOGY: Individualization of Dosages).

Mivacurium chloride has not been studied in patients with burns. Resistance to nondepolarizing 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 plasma cholinesterase activity which may offset this resistance (see CLINICAL PHARMACOLOGY: Individualization of Dosages).

Acid-base and/or serum electrolyte abnormalities may potentiate or antagonize the action of neuromuscular blocking agents. The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy (see CLINICAL PHARMACOLOGY: Individualization of Dosages).

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

Renal and Hepatic Disease: The possibility of prolonged neuromuscular block must be considered when mivacurium is used in patients with renal or hepatic disease (see CLINICAL PHARMACOLOGY: Pharmacokinetics). Most patients with chronic hepatic disease such as hepatitis, liver abscess, and cirrhosis of the liver exhibit a marked reduction in plasma cholinesterase activity. Patients with acute or chronic renal disease may also show a reduction in plasma cholinesterase activity (see CLINICAL PHARMACOLOGY: Individualization of Dosages).

Reduced Plasma Cholinesterase Activity: The possibility of prolonged neuromuscular block following administration of mivacurium chloride must be considered in patients with reduced plasma cholinesterase (pseudocholinesterase) activity.

Plasma cholinesterase activity may be diminished in the presence of genetic abnormalities of plasma cholinesterase (e.g., patients heterozygous or homozygous for the atypical plasma cholinesterase gene), pregnancy, liver or kidney disease, malignant tumors, infections, burns, anemia, decompensated heart disease, peptic ulcer, or myxedema. Plasma cholinesterase activity may also be diminished by chronic administration of oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors and by irreversible inhibitors of plasma cholinesterase (e.g., organophosphate insecticides, echothiophate, and certain antineoplastic drugs).

Mivacurium chloride has been used safely in patients heterozygous for the atypical plasma cholinesterase gene. At doses of 0.10 to 0.20 mg/kg mivacurium chloride, 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 (one in 2500 patients) are extremely sensitive to the neuromuscular blocking effect of mivacurium chloride. In three such adult patients, a small dose of 0.03 mg/kg (approximately the $ED_{10\text{-}20}$ 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 mivacurium 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, mivacurium chloride did not trigger MH. Mivacurium chloride 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 mivacurium chloride in patients undergoing mechanical ventilation in the ICU.

Drug Interactions: Although mivacurium chloride (a mixture of three stereoisomers) has been administered safely following succinylcholine-facilitated tracheal intubation, the interaction between mivacurium chloride 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 mivacurium chloride.

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

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

Isoflurane and enflurane (administered with nitrous oxide/oxygen to achieve 1.25 MAC) decrease the ED_{95} of mivacurium by as much as 25% (see CLINICAL PHARMACOLOGY: Pharmacodynamics and Individualization of Dosages). These agents may also prolong the clinically effective duration of action and decrease the average infusion requirement of mivacurium by as much as 35% to 40%. A greater potentiation of the neuromuscular blocking effects of mivacurium may be expected with higher concentrations of enflurane or isoflurane. Halothane has little or no effect on the ED_{95}, but may prolong the duration of action and decrease the average infusion requirement by as much as 20%.

Other drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as mivacurium chloride include certain antibiotics (e.g., aminoglycosides, tetracyclines, bacitracin, polymyxins, lincomycin, clindamycin, colistin, and sodium colistimethate), magnesium salts, lithium, local anesthetics, procainamide, and quinidine. The neuromuscular blocking effect of mivacurium chloride may be enhanced by drugs that reduce plasma cholinesterase activity (e.g., chronically administered oral contraceptives, glucocorticoids, or certain monoamine oxidase inhibitors) or by drugs that irreversibly inhibit plasma cholinesterase (see PRECAUTIONS: Reduced Plasma Cholinesterase Activity subsection).

Resistance to the neuromuscular blocking action of nondepolarizing neuromuscular blocking agents has been demonstrated in patients chronically administered phenytoin or carbamazepine. While the effects of chronic phenytoin or carbamazepine therapy on the action of mivacurium chloride are unknown, slightly shorter durations of neuromuscular block may be anticipated and infusion rate requirements may be higher.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis and fertility studies have not been performed. Mivacurium chloride was evaluated in a battery of four short-term mutagenicity tests. It was non-mutagenic in the Ames Salmonella assay, the mouse lymphoma assay, the human lymphocyte assay, and the *in vivo* rat bone marrow cytogenetic assay.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category C. Teratology testing in nonventilated pregnant rats and mice treated subcutaneously with maximum subparalyzing doses of mivacurium revealed no maternal or fetal toxicity or teratogenic effects. There are no adequate and well-controlled studies of mivacurium chloride in pregnant women. Because animal studies are not always predictive of human response, and the doses used were subparalyzing, mivacurium chloride should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The use of mivacurium chloride during labor, vaginal delivery, or cesarean section has not been studied in humans and it is not known whether mivacurium chloride administered to the mother has effects on the fetus. Doses of 0.08 and 0.20 mg/kg mivacurium given to female beagles undergoing cesarean section resulted in negligible levels of the stereoisomers in mivacurium chloride 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 mivacurium chloride to a nursing woman.

Pediatric Use: Mivacurium chloride 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: Mivacurium chloride was safely administered during clinical trials to 64 geriatric (≥65 years) patients, including 31 patients with significant cardiovascular disease (see PRECAUTIONS: General subsection). In general, the clearances of mivacurium chloride are most likely lower, the duration may be longer, the rate of recovery may be slower, therefore, mivacurium chloride requirements may be lower in geriatric patients (see CLINICAL PHARMACOLOGY: Special Populations: Geriatric Patients)

ADVERSE REACTIONS

Observed in Clinical Trials: Mivacurium chloride (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 three of 2074 patients administered mivacurium chloride. The most commonly reported adverse experience following the administration of mivacurium chloride was transient, dose-dependent cutaneous flushing about the face, neck, and/or chest. Flushing was most frequently noted after the initial dose of mivacurium and was reported in about 25% of adult patients who received 0.15 mg/kg mivacurium over 5 to 15 seconds. When present, flushing typically began within 1 to 2 minutes after the dose of mivacurium and lasted for 3 to 5 minutes. Of 105 patients who experienced flushing after 0.15 mg/kg mivacurium, 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 mivacurium. One of 332 (0.3%) healthy adults who received 0.15 mg/kg mivacurium over 5 to 15 seconds and none of 37 cardiac surgery patients who received 0.15 mg/kg mivacurium over 60 seconds were treated for a decrease in blood pressure in association with the administration of mivacurium. One to two percent of healthy adults given ≥0.20 mg/kg mivacurium 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 in 30 seconds by 0.10 mg/kg), and 2% to 4% of cardiac surgery patients given ≥0.20 mg/kg over 60 seconds were treated for a decrease in blood pressure. None of the 63 children who received the recommended dose of 0.20 mg/kg mivacurium was treated for a decrease in blood pressure in association with the administration of mivacurium.

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

Incidence Greater Than 1%-

Cardiovascular: Flushing (16%)

Incidence Less Than 1%-

Cardiovascular: Hypotension, tachycardia, bradycardia, cardiac arrhythmia, phlebitis
Respiratory: Bronchospasm, wheezing, hypoxemia
Dermatological: Rash, urticaria, erythema, injection site reaction
Nonspecific: Prolonged drug effect
Neurologic: Dizziness
Musculoskeletal: Muscle spasms

Observed in Clinical Practice: Based on initial clinical practice experience in patients who received mivacurium chloride, spontaneously reported adverse events are uncommon. Some of these events occurred at recommended doses and required treatment.

Anaphylaxis/Anaphylactoid Reaction: From post-marketing surveillance, mivacurium has been associated with reports of anaphylactic/anaphylactoid reactions. In some of these reports, sensitivity to mivacurium chloride was confirmed using skin test procedures.

Other adverse reaction data from clinical practice are insufficient to establish a casual relationship or to support an estimate of their incidence. These adverse events include:

Musculoskeletal: Diminished drug effect, prolonged drug effect
Cardiovascular: Hypotension (rarely severe), flushing
Respiratory: Bronchospasm
Integumentary: Rash

OVERDOSAGE

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 neuromuscular function is assured. Once evidence of recovery from neuromuscular block is observed, further recovery may be facilitated by administration of an anticholinesterase agent (e.g., neostigmine, edrophonium) in conjunction with an appropriate anticholinergic 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 ≥75% in about 10 minutes. The times from 25% recovery of the muscle twitch response to T_4/T_1 ratio ≥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 ≥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

MIVACURIUM CHLORIDE SHOULD ONLY BE ADMINISTERED INTRAVENOUSLY.

The dosage information provided below is intended as a guide only. Doses of mivacurium 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 ≥30% more than ideal body weight for height), asthma, reduction in plasma cholinesterase activity, and the presence of inhalational anesthetic agents.

When using mivacurium chloride 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.

The use of a peripheral nerve stimulator will permit the most advantageous use of mivacurium, minimize the possibility of overdosage or underdosage, and assist in the evaluation of recovery. 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 mivacurium chloride.

Adults: *Initial Doses:* Doses of 0.15 mg/kg administered over 5 to 15 seconds, 0.2 mg/kg administered over 30 seconds, or 0.25 mg/kg administered in divided doses (0.15 mg/kg followed in 30 seconds by 0.1 mg/kg) are recommended for facilitation of tracheal intubation for most patients (see Table 7).

Table 7: Recommended Initial Dosing Regimens for Adults

Dosing Paradigm*	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 to 3 min after completion of dose
0.2 mg/kg, I.V. (over 30 sec)	Thiopental/opioid/N_2O/O_2 or propofol/opioid	2 to 2.5 min after completion of dose
0.25 mg/kg, I.V.(0.15 mg/kg followed in 30 sec by 0.1 mg/kg)	Propofol/opioid	1.5 to 2 min after completion of 0.15 mg/kg dose

*Dosing instituted after induction of adequate general anesthesia.

The purpose of slowed or divided dosing of mivacurium chloride at doses above 0.15 mg/kg is to minimize the transient decreases in blood pressure 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 mivacurium chloride recommended in Table 7, 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 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 mivacurium should be 0.15 mg/kg or less, administered over 60 seconds (see PRECAUTIONS). No data are available on the use of doses of mivacurium 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 mivacurium administered to patients receiving opioid/nitrous oxide/oxygen anesthesia. The expected duration of clinically effective block and time to 95% spontaneous recovery following 0.2 mg/kg mivacurium are approximately 20 to 30 minutes, respectively and following 0.25 mg/kg mivacurium are approximately 25 to 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, 0.2, and 0.25 mg/kg mivacurium, respectively (see Table 1). Maintenance doses of 0.1 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 mivacurium chloride is potentiated by isoflurane or enflurane anesthesia. Recommended initial doses of mivacurium may be used to facilitate tracheal intubation prior to the administration of these agents; however, if mivacurium chloride 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 mivacurium may be reduced by as much as 25%. Greater reductions in the dose of mivacurium may be required with higher concentrations of enflurane or isoflurane. With halothane, which has only a minimal potentiating effect on mivacurium, a smaller dosage reduction may be considered.

Continuous Infusion: Continuous infusion of mivacurium chloride 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 range of 89% to 99% for extended periods in adults receiving opioid/nitrous oxide/oxygen anesthesia. In some patients, particularly those with higher infusion requirements (>8 mcg/kg/min) during the first 30 minutes, the infusion rate required to maintain 89% to 99% T_1 suppression may decrease gradually (by ≥30%) with time over a 4- to 6- hour period of infusion (see CLINICAL PHARMACOLOGY: Pharmacodynamics). Reduction of the infusion rate by up to 35% to 40% should be considered when mivacurium is administered during stable-state conditions of isoflurane or enflurane anesthesia (administered with nitrous oxide/oxygen to achieve 1.25 MAC). Greater reductions in the infusion rate of mivacurium may be required with greater concentrations of enflurane or isoflurane. With halothane, smaller reductions in infusion rate may be required.

Children: *Initial Doses:* Dosage requirements for mivacurium 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 dose of mivacurium for facilitating tracheal intubation in children 2 to 12 years of age is 0.2 mg/kg administered over 5 to 15 seconds. When administered during stable opioid/nitrous oxide/oxygen anesthesia, 0.2 mg/kg of mivacurium produces maximum neuromuscular block in an average of 1.9 minutes (range: 1.3 to 3.3) and clinically effective block for 10 minutes (range: 6 to 15). Maintenance doses are generally required more frequently in children than in adults. Administration of doses of mivacurium above the recommended range (>0.2 mg/kg) is associated with transient decreases in MAP in some children (see CLINICAL PHARMACOLOGY: Hemodynamics). Mivacurium has not been studied in pediatric patients below the age of 2 years.

Continuous Infusion: Children require higher infusion rates of mivacurium than adults. During opioid/nitrous oxide/oxygen anesthesia, the infusion rate required to maintain 89% to 99% neuromuscular block averages 14 mcg/kg/min (range: 5 to 31). The principles for infusion of mivacurium in adults are also applicable to children (see above).

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 mivacurium 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 8 provides guidelines for delivery in mL/hr (equivalent to microdrops/min when 60 microdrops= 1 mL) of mivacurium chloride injection, equivalent to 2 mg/mL mivacurium.

Table 8: Infusion Rates for Maintenance of Neuromuscular Block During Opioid/Nitrous Oxide/Oxygen Anesthesia Using Mivacurium Chloride Injection, equivalent to 2 mg/mL mivacurium.

	Drug Delivery Rate (mcg/kg/min)									
	4	5	6	7	8	10	14	16	18	20
Patient Weight (kg)	**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

Mivacurium Chloride Injection Compatibility and Admixtures: ***Y-site Administration:*** Mivacurium chloride injection may not be compatible with alkaline solutions having a pH greater than 8.5 (e.g., barbiturate solutions).

- Studies have shown that mivacurium chloride 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
- Sufenta® (sufentanil citrate) Injection, diluted as directed
- Alfenta® (alfentanil hydrochloride) Injection, diluted as directed
- Sublimaze® (fentanyl citrate) Injection, diluted as directed
- Versed® (midazolam hydrochloride) Injection, diluted as directed
- Inapsine® (droperidol) Injection, diluted as directed

Compatibility studies with other parenteral products have not been conducted.

Dilution Stability: Mivacurium chloride 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 (polyvinylchloride) 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 mivacurium should be prepared for single patient use only and used within 24 hours of preparation. The unused portion of diluted mivacurium 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

Mivacurium Chloride Injection, equivalent to 2 mg/mL mivacurium is supplied as follows:

SINGLE DOSE VIAL

NDC NUMBER	PACKAGING
66758-032-02	Carton of 10 x 5 mL Single Dose Vials
66758-032-04	Carton of 10 x 10 mL Single Dose Vials

Store under refrigeration between 2°C and 8°C (36°F and 46°F). Avoid exposure to direct ultraviolet light. Retain in carton until time of use. DO NOT FREEZE

Rx only

For Parenta customer service, call 1-800-898-9948

Manufactured for:
PARENTA® pharmaceuticals
an Ebewe Pharma Company
West Columbia, SC 29169

Manufactured by:
HollisterStier CONTRACT MANUFACTURING
Hollister-Stier Laboratories, LLC
Spokane, WA 99207

June 2008
875005-H01