

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20098/S009**

**ADMINISTRATIVE DOCUMENTS**

DF  
MAY 19 1998

Division of Anesthetic, Critical Care, and Addiction Drug Products

CONSUMER SAFETY OFFICER  
LABELING REVIEW

**Application Number:** NDA 20-098/S-009

**Name of Drug:** MIVACRON (mivacurium chloride)

**Sponsor:** Glaxo-Wellcome

**CSO:** Ken Nolan

**Material Reviewed**

**Submission Date(s):** May 12 and May 20, 1998

**Receipt Date(s):** May 20, 1998

**Background and Summary Description:**

This supplemental application provides for labeling changes for MIVACRON based on Phase 4 studies commitments at the time of approval.

**Status Report**

**Reviews Completed:** Medical, Pharmacokinetics, Chemistry, Pharmacology

**CSO Review**

Please note, Labeling Review # 1 compares supplement 009, dated May 12, 1998 to S-002 approved March 2, 1994. Deleted text is lined through; added text is shaded.

Labeling Review # 2 contains the Agency's proposed revisions to the May 12, 1998 submission. Deleted text is lined through; added text is underlined.

The recommended draft labeling for attachment to the action letter is noted in labeling review # 2.

**Conclusion:** Recommend approval of labeling as stated in Labeling Review # 2.



FDA CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF ANESTHETIC, CRITICAL CARE, AND ADDICTION DRUG PRODUCTS  
HFD-170, Room 9B-45, 5600 Fishers Lane, Rockville MD 20857

Tel:(301)443-3741

---

---

MEMORANDUM

---

---

DATE: May 15, 1998

TO: Cynthia McCormick, M.D.  
Division Director, DACCADP

FROM: Bob A. Rappaport, M.D.  
Team Leader, Anesthetics and Analgesics

RE: NDA 20-098/S-009 Mivacron® (mivacurium chloride)  
Labeling Supplement

---

Mivacron®, a competitive non-depolarizing, neuromuscular blocking agent administered by intravenous injection, was approved for marketing in 1992. Mivacurium chloride is comprised of three stereoisomers: *cis-trans*, *trans-trans*, and *cis-cis*. The *cis-trans* and *trans-trans* isomers are equipotent and comprise about 92-96% of mivacurium. At the time of approval, the sponsor agreed to conduct a series of Phase IV studies to characterize the pharmacokinetics and pharmacodynamics of the individual stereoisomers. This submission consists of the final study reports for these evaluations and the proposed labeling changes based on these studies.

A total of eight studies are included in this submission. Dr. Roberta Kahn has completed a detailed clinical review of the seven studies with clinical data in the supplement. Dr. Suresh Doddapaneni has completed a thorough review of the seven studies which primarily address pharmacokinetic and pharmacodynamic issues.

At the time of NDA approval, the sponsor agreed to conduct the following studies:

1. PK/PD with long-term infusion
2. PK/PD in healthy subjects and in patients with renal and hepatic dysfunction
3. *In vitro* esterase hydrolysis studies

**Study TBZZ/93/0062**

The purpose of this study was to clarify and complete prior studies of *in vitro* esterase hydrolysis submitted in 1994. The data from those studies had been judged deficient by the reviewing pharmacokineticist. Dr. Doddapaneni reports that the data submitted to this supplement appears to be satisfactory. Although a batch with a higher concentration of the *cis-cis* isomer than the marketed product was used, Dr. Doddapaneni believes the sponsor's rationale to be reasonable, i.e. that the higher initial concentration was necessary in order to characterize the concentration as a function of time; and that the disappearance rates would not be affected by the relative differences in the isomer content.

The results of the study show that the pharmacologically active *trans-trans* and *cis-trans* isomers were rapidly hydrolyzed by plasma cholinesterase, while the *cis-cis* isomer disappeared much more slowly. Comparison of the *in vitro* results with *in vivo* half-lives in healthy surgical patients (Study 29) show that there is a longer *cis-cis* half-life for the *in vitro* (275 min.) compared to the *in vivo* (53 min.). These results suggest that another route of elimination, other than ester hydrolysis, is important for the *cis-cis* isomer *in vivo*.

Dr. Doddapaneni concludes that the sponsor's labeling statements on lines 195-202 of the package insert arising out of report TBZZ/93/0062 and Study 29 are acceptable.

**Study BLVS/93/0013: The Disposition of a Single Intravenous Bolus Dose of  $^{14}\text{C}$ -MIVACRON ( $^{14}\text{C}$ -mivacurium chloride) in Healthy Male Patients Undergoing Scheduled General Anesthesia (Study 12)**

In this open label study six male patients undergoing elective extraction of wisdom teeth, under nitrous oxide/oxygen/isoflurane anesthesia after induction with thiopentone, received a single dose of 0.15 mg/kg  $^{14}\text{C}$ -labeled mivacurium administered by iv. bolus injection.

Approximately 40% of the dose of  $^{14}\text{C}$  administered was recovered in the urine (mean percentage recovery) and 60% in the feces. While urinary excretion was complete by 24 hours, recovery in feces continued for up to 168 hours. Dr. Doddapaneni suggests that this may be due to the constipating effect of the opioid. There was no  $^{14}\text{C}$  excreted as  $^{14}\text{CO}_2$  during the course of anesthesia.

Five (5) percent of administered drug excreted in the urine was unchanged mivacurium; 36% and 10% as the quaternary monoester (879U84) and quaternary alcohol (141U86) metabolites, respectively. There was no evidence for plasma metabolites containing the  $^{14}\text{C}$  label other than 879U84 and 141U86. The major isomers of these metabolites were *cis*- and *trans*-879U84 and *trans*-141U86; *cis*-141U86 concentrations were negligible.

Dr. Doddapaneni concludes that the sponsor's labeling statement on lines 149-152 arising from Study 12 is acceptable.

Dr. Kahn reports that the only adverse effects were minor and representative of the histaminergic effects of the study drug.

**Study THRS/96/0002: Pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in healthy surgical patients receiving N2O/O2/narcotic anesthesia (Study 29)**

This was an open label study in 27 (up from 18 by protocol due to technical problems in obtaining plasma concentration data in 8 of the original patients) healthy male surgical patients undergoing procedures of low to moderate risk under N<sub>2</sub>O/O<sub>2</sub>/opioid anesthesia. After induction of anesthesia, mivacurium was administered by iv. infusion at 5 µg/kg/minute for 60 minutes followed by a rate of 10 µg/kg/minute for 60 minutes. Onset, depth and reversal of neuromuscular blockade were assessed by mechanomyography of the twitch and train-of-four responses of the adductor pollicis to supramaximal stimulus over the distal course of the ulnar nerve. The study was not designed to evaluate efficacy. However, the efficacy variables were used to identify clinically significant depth and duration of neuromuscular blockade.

The two active stereoisomers, *cis-trans* and *trans-trans*, were extensively metabolized by plasma cholinesterase with resultant high clearance values and short terminal half-life values. The *cis-cis* isomer had a much longer terminal half-life value. There was no correlation between this isomer and plasma cholinesterase activity. The presence of this isomer did not correlate with clinical evidence of neuromuscular blockade.

In her review, Dr. Kahn notes that the recovery indices documented in this study are consistent with those reported previously to be associated with shorter duration of mivacurium infusion. She suggests that this finding may indicate that recovery time from mivacurium is independent of dose size or infusion duration.

Dr. Kahn also reports that there were no adverse effects of clinical significance noted in this study.

Dr. Doddapaneni has recommended minor modifications in the sponsor's labeling statements on lines 186-188 and 195-210 of the package insert.

**Study BQRT/94/0023: A Pharmacokinetic and Pharmacodynamic Study of Mivacurium And its Metabolites in Surgical Patients with Normal Hepatic Function or Hepatic Dysfunction Receiving Mivacurium During N<sub>2</sub>O/O<sub>2</sub>/Isoflurane Anesthesia (Study 8)**

This was an open label, single center study in 22 patients undergoing surgical procedures of short duration. Patients were selected based on preoperative liver function and divided into three groups based on the Child's classification: A - 5 patients with mild hepatic dysfunction; B - 6 patients with moderate hepatic dysfunction; C - 1 patient with severe hepatic dysfunction. Ten patients with normal hepatic function were recruited as controls.

Anesthesia was induced with midazolam, fentanyl and thiopental. Mivacurium was then administered as an iv. infusion at 15  $\mu$ g/kg/minute for 10 minutes. Onset, depth and duration of neuromuscular blockade was monitored using standard mechanomyographic monitoring of the adductor pollicis. Recruitment of Child's C patients was discontinued after the first patient was enrolled due to the difficulty of enrolling patients with severe hepatic failure undergoing non-emergent surgery.

The results of this study indicate that the onset and depth of neuromuscular block were similar in healthy adults and in patients with mild or moderate hepatic dysfunction after administration of mivacurium 15  $\mu$ g/kg/min for 10 minutes (total dose of 0.15 mg/kg). The recovery profile data, however, indicated that there is a trend towards increasing recovery time which correlates with increasing severity of hepatic impairment. Although there was not a significant difference in recovery times between the normal patients and those with mild hepatic impairment, statistically significant differences in recovery times were documented between the normal patients and the patients with moderate hepatic impairment. Because only one patient was recruited into the Child's C group, there is insufficient information available from this study to assess the impact of this degree of disease upon the pharmacokinetics and pharmacodynamics of mivacurium.

The clearance of both *cis-trans* and *trans-trans* isomers decreased as a function of hepatic dysfunction. Moderate hepatic dysfunction resulted in an approximately 50% decrease from normals in the clearance of these isomers.  $C_{max}$  increased twofold for the isomers in the setting of moderate hepatic dysfunction. For the *cis-cis* isomer there was a trend (not statistically significant) toward increasing  $AUC_{0-\infty}$  and  $t_{1/2}$  with increasing hepatic dysfunction; however, this isomer is less dependent on plasma cholinesterase activity. For the quaternary monoester and quaternary alcohol metabolites,  $C_{max}$  was decreased slightly in patients with mild and moderate dysfunction due to reduced metabolic clearance of the parent compounds. The half-life was longer due to reduced organ clearance. These two factors resulted in a reduced maximum concentration, but an increased exposure.

Dr. Kahn reports that there were no adverse effects of clinical significance noted in this study.

Dr. Doddapaneni concludes that the sponsor's labeling statements on lines 311-316 arising from Study 8 are acceptable. However, he does recommend a modification of the sponsor's labeling statement on lines 328-324 (in Table 6) of the package insert.

The results of this study suggest that moderate hepatic dysfunction, and the resultant insufficient production of plasma cholinesterase, increase the recovery indices of patients under neuromuscular blockade with mivacurium when compared to those same indices in patients with normal hepatic function.

**Study BQRT/94/0025: A Pharmacokinetic and Pharmacodynamic Study of Mivacurium and its Metabolites in Surgical Patients with Normal Renal Function or Renal Dysfunction Receiving Mivacurium During N2O/O2/Narcotic Anesthesia (Study 11)**

This was an open label, single center study in 27 adult patients undergoing elective surgery of at least one hour in duration. Anesthesia was induced with midazolam, fentanyl and thiopental. Following induction, mivacurium was administered as an iv. infusion at 15  $\mu\text{g}/\text{kg}/\text{minute}$  for 10 minutes. The rate was then reduced to 7.5  $\mu\text{g}/\text{kg}/\text{minute}$  and maintained for another 10 minutes. Subsequent adjustments were made at the discretion of the investigator to maintain T1 suppression at  $95 \pm 4\%$ .

Patients were divided into three groups based on their serum creatinine levels: Group 1 - 11 patients with normal renal function (serum creatinine  $\leq 110 \mu\text{mol}/\text{L}$ ); Group 2 - 8 patients with mild to moderate renal function (serum creatinine 150-300  $\mu\text{mol}/\text{L}$ ); and, Group 3 - eight patients with severe renal dysfunction (serum creatinine  $> 700 \mu\text{mol}/\text{L}$ ).

No significant pharmacokinetic changes were found in association with renal impairment for the active *cis-trans* and *trans-trans* isomers as would be expected since they are primarily dependent upon plasma cholinesterase activity for clearance. There were, however, significant differences in the pharmacokinetic (clearance and half-life) parameters of the inactive *cis-cis* isomer and its metabolites. The differences were larger between Group 1 and 2 patients than between Group 1 and 3 patients. The only pharmacodynamic parameter showing a significant difference between the groups was the infusion rate requirement for maintenance of T1 suppression. This difference was between Group 1 and Group 2, with Group 2 requiring a higher mean infusion rate than Group 1 (and Group 3). The clinical significance of these findings is unclear and they may well represent artifact.

The half-lives of the quaternary monoester (*cis* and *trans*) and quaternary alcohol (*trans*) metabolites were significantly longer for both Groups 2 and 3 compared to the control

group. An insufficient quantity of the *cis*-141U86 isomer was obtained to characterize its pharmacokinetics.

Dr. Kahn reports that there were no adverse effects of clinical significance noted in this study.

Dr. Doddapaneni concludes that the sponsor's labeling statements on lines 253-316 arising from Study 11 are acceptable.

**Study BQRT/94/0026: A Study to Evaluate the Dose Response Relationship and Pharmacokinetics of Mivacurium Administered by Bolus Dose and Infusion to Adult and Elderly Surgical Patients During N<sub>2</sub>O/O<sub>2</sub>/Narcotic Anesthesia (Study 14)**

This was an open label, single center study in 36 young adult (18-40 years) and 35 elderly (age  $\geq 65$  years) patients undergoing elective surgery of at least 60 minutes duration. Each of the above two patient groups was further divided into four groups based on dosage. The young adult groups were 1-4 and the elderly groups were 5-8.

Groups 1 & 5:	0.04 mg/kg iv bolus
Groups 2 & 6:	0.06 mg/kg iv bolus
Groups 3 & 7:	0.08 mg/kg iv bolus*
Groups 4 & 8:	0.09 mg/kg iv bolus*

\*These two doses were reduced, by amendment, to 0.03 and 0.05 mg/kg, respectively, in order to ensure that four points were obtained on the dose-response curve.

Fourteen young adult and 15 elderly patients were selected for full pharmacokinetic evaluation.

After maximal block was achieved with the initial dose, each patient received a supplemental bolus to achieve a total dose of 0.1 mg/kg. Following recovery of T1 to 5-10% of baseline, an infusion of mivacurium at 6  $\mu$ g/kg/minute was started and adjusted to maintain 91-99% suppression of T1. General anesthesia was conducted by induction with fentanyl, diazepam and thiopental, followed by maintenance with the same agents plus N<sub>2</sub>O/O<sub>2</sub> by inhalation. Neuromuscular blockade was monitored by standard mechanomyographic technique and variables.

While the mean clearances and volumes of distribution were higher and the  $t_{1/2}$  longer for the elderly group, only the  $V_\beta$  for *trans-trans* mivacurium was significantly higher. There were no statistically significant differences in any pharmacokinetic parameters between the age groups for the mivacurium isomers.

There were no clinical efficacy differences observed between the two age groups. The spontaneous recovery profile for elderly patients was slightly prolonged compared to the young patients. There were no clinical safety differences between the two age groups. Seven adverse events were reported, three of which had possible relationships to the study drug. An episode of bronchospasm and an episode of hypotension may have been related to study drug, but are known potential side effects of mivacurium and resolved quickly with appropriate treatment. An episode of nodal bradycardia is, per Dr. Kahn, of unclear etiology and unlikely to be due to study drug. This event also responded to appropriate treatment.

Dr. Doddapaneni concludes that the sponsor's labeling statements on lines 236-237 arising from Study 14 are acceptable.

**Study RM1996/00132/00: Short- and Long-Term Infusions of Mivacron (mivacurium chloride) in Adult Surgical Patients During N<sub>2</sub>O/O<sub>2</sub>/Opioid Anesthesia (Study 33)**

This was an open label study of mivacurium 0.15 mg/kg administered as an iv bolus, followed by short-term (1-3 hours) or long-term (4-6 hours) infusion. The study population was divided into three groups based on age and duration of infusion:

- Group A: young adults (18-59 years) receiving short-term infusion, n = 12
- Group B1: young adults receiving long-term infusion, n = 20
- Group B2: elderly adults (60-81 years) receiving long-term infusion, n = 19

Patients were subcategorized by plasma cholinesterase activity and stability of infusion requirements over time. Standard electromechanomyographic monitoring was used to assess the efficacy of mivacurium. At 5% T1 recovery after the initial bolus, mivacurium infusion was initiated at 10 µg/kg/minute and adjusted to maintain 95 ± 4% T1 suppression.

The primary efficacy analyses were calculation of the average infusion rate needed to maintain neuromuscular block at 89-99% T1 suppression, and rate of spontaneous recovery after discontinuation of the infusion (25-75% recovery index).

Fifty-one patients were enrolled in the study. Two patients were excluded from efficacy analysis due to protocol violations (use of excluded drugs preoperatively). Two other patients had efficacy data excluded only from the time they received excluded drugs intraoperatively.

Sixteen patients required pharmacologic reversal of neuromuscular blockade. One of these patients received three doses of neostigmine and his data was excluded from the analysis of reversal data.

There were 11 patients who required decreasing doses of mivacurium. These patients were excluded from the average infusion rate analysis and were analyzed separately. Eight patients with low plasma cholinesterase activity were also analyzed separately.

Tables 6.1 and 6.2 in Dr. Kahn's review summarize the median and range values for efficacy variables for subgroups with normal and low plasma cholinesterase activity, respectively. Interpretation is limited by the small numbers in many cells. However, as Dr. Kahn points out, patients with low plasma cholinesterase activity exhibited substantially longer recovery times compared to patients with normal activity, as would be expected. The median recovery times of the young and the elderly patients were similar, as were those of the patients with decreasing and constant infusion requirements.

Dr. Kahn reports that there was only one adverse event. This was a young male who exhibited inverted T-waves in leads II and AVF over three hours after initiation of mivacurium infusion. The patient was treated and responded without sequellae. Dr. Kahn believes the event to be unrelated to study drug.

Dr. Doddapaneni reports that clearance of the *cis-trans* and *trans-trans* isomers was lower in the elderly patients compared to the young patients. Clearance values for the *cis-cis* isomer could not be calculated due to its long terminal half-life and the fact that infusion rates were changed in most patients within 160 minutes before steady state concentrations were achieved.

Dr. Doddapaneni concludes that the sponsor's labeling statements on lines 222-229 arising from Study 33 are acceptable.

**Study BQRT/94/0024: Evaluation of the Safety and Efficacy of Mivacurium Chloride in Patients with Ranging Degrees of Renal Dysfunction Under N<sub>2</sub>O/O<sub>2</sub>/Propofol Anesthesia**

This was an open label, parallel, single center study of 60 adult patients undergoing elective surgery of at least one hours duration. Based on preoperative estimated creatinine clearance, the patients were divided into three groups:

- Group 1: normal renal function, ASA 1 or 2 (n = 21)
- Group 2: mild-to-moderate renal dysfunction [creatinine clearance 21-50 ml/min (n = 19)]
- Group 3: severe renal dysfunction [creatinine clearance  $\leq$  20 ml/min] (n = 20)

Group 2 was further subdivided to acquire an equal number of patients with mild (36-50 ml/min) and moderate (21-35 ml/min) creatinine clearance.

Anesthesia was induced with propofol and fentanyl and maintained with N<sub>2</sub>O/O<sub>2</sub> supplemented with propofol and fentanyl. Mivacurium 0.15 mg/kg was administered iv over 20-30 seconds. Continuous infusion following intubation was started at 10 µg/kg/minute and was commenced at spontaneous recovery of T1 to 5% of baseline. The infusion was adjusted at no less than three minute intervals to maintain 95% suppression of T1 (5 ± 4% baseline). Maintenance bolus doses of 0.013-0.08 mg/kg were allowed in lieu of infusion for shorter procedures. Monitoring was performed using standard electromechanomyographic parameters.

Average infusion rate was determined by a minimum of five evaluable epochs (i.e. 3 minute intervals in which infusion rate is known and depth of neuromuscular blockade is stable at 91-95%) after the first five epochs. The average infusion rate was defined as the mean of the infusion rates for all evaluable epochs from the sixth to the last epoch, inclusive.

Some data was excluded from efficacy analyses based on the following: 1) patients received additional boluses of mivacurium during the infusion (3 patients), 2) loss of data (1 patient), and 3) prolonged neuromuscular block after the initial dose (1 patient).

Dr. Kahn reports that, "While mean rates of infusion required to maintain 95% T1 suppression were not affected by renal function, recovery after the termination of infusion was prolonged in patients with renal dysfunction compared to normal." Curiously, the recovery was more prolonged in the mild to moderate renal dysfunction group than in the severe renal dysfunction group.

Dr. Kahn also reports that the documented episodes of hypotension seen in six patients may be due to study drug but cannot definitely be attributed to a study drug effect. The other reported adverse events are either clearly unrelated to study drug, known and minor side effects of mivacurium, and/or responded quickly to standard treatment and there were no sequellae.

### **Post-Marketing Data**

Dr. Kahn has included information regarding adverse events of concern noted in recent post-marketing data reports. As these reports were not directly related to this submission, they will be reviewed elsewhere.

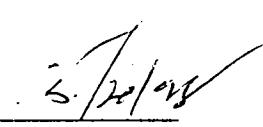
### **Conclusion:**

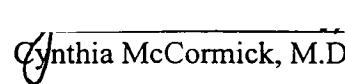
The sponsor has adequately fulfilled their Phase IV commitment to characterize the pharmacokinetics of the isomers and metabolites of mivacurium. No clinically significant results were found, other than those expected based on the pharmacology of

this drug. No significant new adverse events were uncovered during the evaluation process.

**Recommendations:**

The labeling changes which have been applied to the sponsor's draft labeling changes by Dr. Doddapaneni should be forwarded to the sponsor for final review. I have incorporated some of the labeling changes recommended by Dr. Kahn into Dr. Doddapaneni's draft label, a copy of which is attached to this memo.

  
Bob A. Rappaport, M.D. May 15, 1998

  
Cynthia McCormick, M.D. May 20, 1998

5/20/98

Cc: Original NDA  
Div. File  
HFD-170  
McCormick  
Rappaport  
Kahn  
Nolan  
HFD-870  
Hunt  
Doddapaneni

DEC 15 1997

**Division of Anesthetic, Critical Care, and Addictive Drug Products  
Labeling Supplement Review**

NDA # 20-098

Ref # S-009

Sponsor: GlaxoWellcome

Brand Name: Mivacron

Drug Category: Neuromuscular Blocking Agent

Original Receipt Date: May 12, 1997

Review Completed: December 15, 1997

Clinical Reviewer: Roberta C. Kahn, M.D.

**Background**

Mivacurium chloride is a competitive non-depolarizing neuromuscular blocking agent administered by intravenous injection. Mivacurium has an onset and duration of action which are intermediate between succinylcholine, the only ultra-short-acting neuromuscular blocking agent, and atracurium, cis-atracurium and other the intermediate-acting agents. Its relatively short duration of action is due to intravascular hydrolysis by plasma cholinesterase (pseudocholinesterase) as its primary elimination pathway. Mivacurium is a racemic mixture containing *cis-cis*, *cis-trans*, and *trans-trans* racemates. The latter two are the active isomers. Mivacron was approved by the agency on January 22, 1992. At the time of approval, detailed differences in the pharmacodynamics and pharmacokinetics of the individual isomeric forms had not been characterized.

This review details the final study reports based on the sponsor's commitment to Phase IV studies made at the time of approval, as well as proposed labeling changes based on the results of these studies.

**Material Reviewed**

The studies reported are as follows:

**THRS/96/0002: Pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in healthy surgical patients receiving N<sub>2</sub>O/O<sub>2</sub>/narcotic anesthesia.**

**BQRT/94/0026: A study to evaluate the dose-response relationship and pharmacokinetics of mivacurium administered by bolus dose and infusion to adult and elderly surgical patients during N<sub>2</sub>O/O<sub>2</sub>/narcotic anesthesia.**

**RM1996/00132/00: Short and long-term infusion of Miyacron (mivacurium chloride) in adult surgical patients during N<sub>2</sub>O/O<sub>2</sub>/opioid anesthesia.**

**BLVS/93/0013: The disposition of a single intravenous bolus dose of <sup>14</sup>C-Miyacron (<sup>14</sup>C-mivacurium chloride) in healthy male patients undergoing scheduled general anesthesia.**

**BQRT/94/0023: A pharmacokinetic and pharmacodynamic study of mivacurium and its metabolites in surgical patients with normal hepatic function or hepatic dysfunction receiving Miyacron during N<sub>2</sub>O/O<sub>2</sub>/isoflurane anesthesia.**

**BQRT/94/0025: A pharmacokinetic and pharmacodynamic study of mivacurium and its metabolites in surgical patients with normal renal function or renal dysfunction receiving mivacurium during N<sub>2</sub>O/O<sub>2</sub>/narcotic anesthesia.**

**BPRT/94/0024: Evaluation of the safety and efficacy of mivacurium chloride in patients with normal renal function and in patients with ranging degrees of renal dysfunction under N<sub>2</sub>O/O<sub>2</sub>/propofol anesthesia.**

### **Study Reports**

**THRS/96/0002: Pharmacokinetics and pharmacodynamics of the stereoisomers of mivacurium in healthy surgical patients receiving N<sub>2</sub>O/O<sub>2</sub>/narcotic anesthesia.**

27 healthy male surgical patients (ASA I and II) participated in this open label study of the pharmacokinetics of the individual stereoisomers of mivacurium as a continuous intravenous infusion.

Inclusion criteria were: male patients, age 18 years or older, ASA status I or II, scheduled for low to moderate risk surgery of more than 2.5 hours duration who consented to participate.

After induction of general anesthesia using a narcotic/nitrous oxide technique, each patient received an intravenous infusion of mivacurium at 5 mcg/kg/min for 60 minutes, followed by a rate of 10 mcg/kg/min for 60 minutes. Onset, depth of neuromuscular blockade, and reversal were assessed by mechanomyography of the twitch and train-of-four responses of the adductor pollicis to supramaximal stimulus over the distal course ulnar nerve. Vecuronium was administered to all patients requiring additional neuromuscular blockade following the termination of the mivacurium infusion.

Plasma samples for pharmacokinetic evaluation were obtained by sampling through an indwelling intravenous catheter in the arm opposite to the administration site of the mivacurium infusion. Blood samples were collected at time points 0,2,3,4,6,9,12,15,20,30,45, and 60 minutes after the initiation of infusion rate #1, at the same time points after the initiation of infusion rate #2, and at 1,2,3,4,6,8,12,20,30,45,60,90, and 120 minutes after the termination of the infusion. In some patients an additional sample at 240 minutes after the termination of the infusion was collected.

Two protocol amendments were submitted for approval and implemented during the course of the study. Amendment #1 provided for the inclusion of patients who were undergoing surgery of a shorter duration than stated in the original protocol, specifically 1.5-2.5 hours. However, it was not necessary for the investigator to enroll any patients under the terms of this aspect of the amendment. The second part of this amendment allowed for the reversal of exclusion of patients on the basis of the use of H1 and H2 receptor-blocking agents. This exclusion was felt to be unnecessary because of: 1) the unlikelihood that the use of cimetidine alone (or similar H2 receptor antagonist) would significantly mask the signs of mivacurium-induced histamine release, and 2) inhibition of hepatic microsomal function due to cimetidine was unlikely to have an effect on the metabolism and elimination of mivacurium.

Protocol amendment #2, added 9 patients to the original specification of 18 patients. This was because in eight of the original patients plasma concentration data could not be obtained because of technical problems. The amendment also allowed for a blood sample to be collected at 240 minutes after the termination of the infusion in order to better characterize the elimination  $t_{1/2\beta}$  of the cis-cis isomer.

Efficacy evaluation used standard criteria of mechanomyographic response:

- Percent suppression of twitch height compared to baseline.
- Maximal % twitch height reduction.
- Time to maximal twitch height suppression.
- Time to spontaneous recovery of T4:T1 to 5%, 10%, 25%, 50%, 75%, 90%, 95% after termination of the infusion.
- Time to T4:T1  $\geq$  75%.

This study was not designed to demonstrate efficacy, but rather these efficacy variables were used to identify that clinically significant neuromuscular blockade had been achieved and maintained by the doses that were administered intraoperatively.

Safety evaluation was by means of monitoring of vital signs, lead II ECG, body temperature, and continuous cardiac auscultation at baseline and 2.5, 5, 7.5, and 55 minutes after the start of each infusion rate. Any change in heart rate or systemic pressure that requires pharmacologic treatment with vasopressor agents were reported on the case report form. One hour following admission to and immediately prior to discharge from the \_\_\_\_\_ adequacy of neuromuscular function was assessed clinical by grip strength, and head lift. All adverse events observed during the course of the study period were recorded.

*Results:*

Of 27 patients who enrolled, 25 patients completed the protocol and 2 patients discontinued prematurely. 26 patients provided efficacy data and 27 patients provided safety data. One patient's data was excluded from efficacy and PK evaluation because of administration of gentamicin within 48 hours prior to baseline, since macrolide antibiotics have the potential to potentiate the effect of nondepolarizing NMB agents. One patient's efficacy and PK data was excluded because of pump malfunction. In 2 cases data was available for infusion #1 only because surgery was completed before infusion #2 was started. There were episodes of interruption of the infusion in 4 cases, resulting in exclusion of some data from analysis.

Table 1 summarizes steady state pharmacokinetic parameters for *trans-trans* and *cis-trans* isomers. These two isomers comprise 92-96% of the racemic mixture, and demonstrate  $t_{1/2} \beta = 2$  minutes. The *cis-cis* isomer has a slower clearance ( $CL = 4.6$  ml/min/kg;  $t_{1/2} \beta = 55$  min) but has minimal potency, as full return of twitch height is demonstrated despite persistence of this isomer in the circulation. The clearance of *trans-trans* and *cis-trans* isomers shows a direct correlation with plasma cholinesterase activity, while that of the *cis-cis* isomer does not.

Table 1. Steady-state Pharmacokinetics for the *trans-trans* and *cis-trans* isomers. (mean  $\pm$  SD) (Sponsor's Table 5)

	<i>trans-trans</i> mivacurium	<i>cis-trans</i> mivacurium
C <sub>ss</sub> (ng/ml)		
5 $\mu$ g/kg/min	60 $\pm$ 24	22 $\pm$ 9
10 $\mu$ g/kg/min	128 $\pm$ 41	44 $\pm$ 17
CL <sub>ss</sub> (ml/min/kg)		
5 $\mu$ g/kg/min	59.4 $\pm$ 26.7	100 $\pm$ 61.0
10 $\mu$ g/kg/min	53.2 $\pm$ 20.2	98.7 $\pm$ 45.3
V $\beta$ (L/kg)		
5 $\mu$ g/kg/min	0.160 $\pm$ 0.059	0.292 $\pm$ 0.227
10 $\mu$ g/kg/min	0.147 $\pm$ 0.052	0.276 $\pm$ 0.218

At the lower infusion rate, mean maximal twitch suppression was 83%. Time to maximal twitch suppression was 37.6 minutes. At the higher infusion rate, mean maximal twitch suppression was 99%, with time to maximal suppression of 17.6 minutes.

The mean time from termination of infusion #2 to the beginning of recovery was 4.2 minutes. Mean times for recovery indices were:

5%-25%	4.0 minutes
25%-75%	6.9 minutes
5%-95%	16.3 minutes

T4:T1  $\geq$  75%

26.5 minutes

These recovery indices are consistent with those reported previously with shorter durations of mivacurium infusion, suggesting that recovery from mivacurium is independent of the size of the dose and duration of infusion.

**Safety:**

No decreases in blood pressure greater than 30% were reported in the first 7.5 minutes of each infusion rate. These endpoints for systemic pressure and time interval were chosen because a hypotensive response of this magnitude within 5-10 minutes of drug administration is representative of a clinically significant histaminergic response. No other adverse experiences were temporally related to the infusion of mivacurium. A review of medications administered intraoperatively indicate no vasopressor therapy administered during surgery. There were two outliers in whom the maximal decreases in systolic pressure observed were 22.6% and 21.9%, and maximal decreases in diastolic pressure in these same patients were 41.5% and 21.7%, respectively. No clinically significant changes in heart rate were recorded. No other symptoms of histamine release were observed in any patients.

**Conclusions:**

The purpose of this study was to provide data to elucidate whether infusions of mivacurium of greater than one hour were associated with changes in the pharmacokinetic disposition of the parent molecule and metabolites. The study demonstrated that in healthy adults with documented normal plasma cholinesterase levels, normal renal and normal hepatic function, the pharmacokinetics of mivacurium after two hours of infusion at effective doses do not differ from previous observations with shorter infusion times. Analysis of the two active isomers, *cis-trans* and *trans-trans* mivacurium, demonstrate a small volume of distribution and rapid clearance consistent with elimination by ester hydrolysis by plasma cholinesterase. The *cis-cis* isomer has a  $t_{1/2}\beta$  of 55 minutes, which would not allow the assumption of steady-state conditions after an infusion of two hours' duration. The presence of this isomer in the circulation did not correlate with clinical evidence of neuromuscular blockade. The potential for greater activity of the *cis-cis* isomer over even longer durations of administration, or whether accumulation occurs due to renal or hepatic disease could not be evaluated under the conditions of this study. There were no adverse safety findings in this patient population associated with mivacurium in effective doses by infusion at 5 and 10 mcg/kg/min.

**BQRT/94/0026: A Study to Evaluate the Dose Response Relationship and Pharmacokinetics of Mivacurium Administered by Bolus Dose and Infusion to Adult and Elderly Surgical Patients During N2O/O2/Narcotic Anesthesia**

This was an open single-center study of 71 patients, ASA I, II, or III,

undergoing elective surgery of at least 60 minutes duration. Inclusion criteria were: consenting adults of either sex, scheduled for elective general surgery of low-to-moderate risk; female patients were not pregnant or not of child-bearing potential. Exclusion criteria were: likelihood of difficult intubation based on anatomic criteria, personal or family history of malignant hyperthermia, history of sensitivity to neuromuscular blocking agents, major thermal injury, chronic alcohol or drug use, reactive airway disease, renal or hepatic impairment, other significant organ system dysfunction, exposure to antibiotics, antidepressants, or anticonvulsants, prior recent drug study participation, or expectation of requirement for blood transfusion during surgery.

Patients were divided into two groups by age: thirty six patients aged 18-40 years, and thirty-five patients aged  $\geq 65$  years.

The younger age category was divided into groups 1-4, and the older age category were divided into groups 5-8, according to dose of mivacurium, as follows:

Groups 1,5:	0.04 mg/kg iv bolus
Groups 2,6:	0.06 mg/kg iv bolus
Groups 3,7:	0.08 mg/kg iv bolus*
Groups 4,8:	0.09 mg/kg iv bolus*

\*Under the terms of two amendments, these two doses were reduced to 0.03 and 0.05 mg/kg, respectively, in order to ensure that four points were obtained on the dose-response curve.

After maximum block was achieved with the initial dose, a supplemental bolus dose of mivacurium was administered to arrive at a final total dose of 0.1 mg/kg. Intubation was performed after the administration of the second dose.

After recovery of T1 to 5-10% of baseline, an infusion of mivacurium at 6  $\mu\text{g}/\text{kg}/\text{min}$  was started and adjusted to maintain 91-99% suppression of T1 throughout surgery. Patients were subsequently allowed to recover spontaneously. General anesthesia was conducted by induction with fentanyl 1-4  $\mu\text{g}/\text{kg}$ , diazepam 0.04- 0.14 mg/kg, and thiopental 2.38-6.67 mg/kg, followed by maintenance with the same intravenous agents as needed, with 66% N<sub>2</sub>O in O<sub>2</sub> by inhalation.

15 patients in group 1 and 16 patients in group 2 had blood samples drawn by venipuncture for pharmacokinetics of *cis-trans*, *trans-trans*, and *cis-trans* isomers at the following time points:

Initial bolus: pre-dose, +1,2,5 min.

Second bolus: predose, +1,2,5,10,20,30 min.

Infusion: predose, +1,2,5,10,15,20,30 min, then q 30 min until conclusion of the infusion. For a rate change: immediately prior, +1,2,5 min.

Post-infusion: pretermination (three samples q 5 min), +1,2,5,10,15,30,45,60, 120,180,240,360 min.

The degree of neuromuscular blockade was performed by the standard mechanomyographic technique of evoked response of the adductor pollicis in response to electrical stimulation over the ulnar nerve at the wrist. Monitoring variables related to block were: maximal T1 suppression, time to maximal suppression, T1 recovery to 5%, 10%, 25%, 50%, 75%, 90%, 95% of control,

time to T4:T1 recovery to  $\geq 50\%$  and 70%. As in other pharmacokinetic studies filed with this supplement, these efficacy variables were collected to document that clinically meaningful NMB was achieved at these doses.

Safety data was evaluated by intraoperative monitoring of vital signs, ECG, comparison of pre- and post-operative physical examination, vital signs, and compilation of adverse experience reports. Recovery from neuromuscular blockade was documented in the PACU by standard clinical assessments of grip strength and 5 second head lift. Patients who were assessed to have inadequate return of neuromuscular function in the post-treatment period were administered appropriate pharmacologic reversal, and were assessed by train-of-four before and after reversal. Patients who demonstrated inadequate spontaneous reversal were reported as adverse events and their recovery data was reported separately.

#### *Disposition:*

Seven patients were replaced for the following reasons: 5 patients received the higher doses in the original protocol, 1 patient received a lower dose than specified in the protocol due to a miscalculation, 1 patient was outside of the age limit at enrollment. All 71 patients contributed data to the safety analysis.

Although, as already noted, this study was not an efficacy study, the sponsor reports on the results of efficacy variables in order to validate the presence of clinical NMB at the administered doses. Efficacy data was excluded in two patients: one for protocol violation due to age, and one for abnormal dibucaine number, which would cause abnormal PK findings. Efficacy data was not available for the protocol infusion period only in three patients: unanticipated difficult intubation, administration of terbutaline for bronchospasm, and administration of isoflurane during maintenance. In the case of 13 patients who received additional boluses of mivacurium during the infusion period, efficacy data was excluded for the 30 minutes following the unscheduled bolus. Pharmacokinetic data was not available from four patients due to technical errors.

#### *Results:*

The demographics of the two groups are summarized in Table 2. All patients were Caucasian. There was a higher distribution of women into the younger age group. This difference is irrelevant to the results, as there is no evidence of a difference in the actions of neuromuscular blocking agents on the basis of sex. Systemic pressure was higher in the older age group.

Table 2. Demographics. (Means  $\pm$  SD) (Extracted from Sponsor's Table 5-7)

	Group 1: 18-40 years	Group 2: $\geq 65$ years
Age (yrs)	$31.1 \pm 6.6$	$71.5 \pm 5.2$
Weight (kg)	$74.7 \pm 13.2$	$70.4 \pm 12.1$
Height (cm)	$177.4 \pm 8.2$	$170.7 \pm 9.3$

Sex (M/F)	10/26	17/18
Systolic (mmHg)	127.4 ± 14.6	153 ± 20.3
Diastolic (mmHg)	79.4 ± 9.0	86.7 ± 9.2
Heart rate (bpm)	75.3 ± 9.2	75.7 ± 11.3

To calculate the ED<sub>95</sub> the common log of the initial dose was plotted against the probit of the maximum T1 suppression observed. The ED<sub>95</sub> corresponds to a probit of 6.64; for Group 1, the corresponding log dose is -1.274, or 0.053 mg/kg. For Group 2, the corresponding log dose is -1.240, or 0.058 mg/kg.

The mean infusion rate to maintain 91-99% T1 suppression was 7.1 µg/kg/min and 6.8 µg/kg/min for Groups 1 and 2 respectively.

Table 3 summarizes recovery data. Mean spontaneous recovery times for the older age group were approximately 2-5 minutes longer than in the younger age group.

Table 3. Summary of Spontaneous Recovery Variables. (Means ± SD) (Summarized from Sponsor's Tables 17-24,26-27)

Variables (min)	Group 1: 18-40 years	Group 2: ≥ 65 years
Reappearance of T1	1.8 ± 1.3	2.4 ± 1.8
5% T1 Recovery	3.4 ± 2.1	5.0 ± 4.0
10% T1 Recovery	4.3 ± 2.9	5.7 ± 3.1
25% T1 Recovery	6.5 ± 3.2	8.7 ± 4.0
50% T1 Recovery	10.2 ± 3.9	14.2 ± 4.9
75% T1 Recovery	14.3 ± 4.8	19.8 ± 7.2
90% T1 Recovery	17.8 ± 6.3	24.0 ± 8.8
95% T1 Recovery	18.0 ± 5.8	21.1 ± 5.6
T4:T1 ≥ 70%	17.2 ± 4.8	21.8 ± 6.6
25%-75% Recovery Index	7.8 ± 2.3	11.6 ± 4.1

After the initial bolus, t<sub>max</sub> for the active isomers occurs at 1-2 minutes after injection. C<sub>max</sub> demonstrates a dose-response relationship between the size of the initial bolus and C<sub>max</sub> for the active isomers. The relationship could not be characterized as linear or non-linear because of large variances in the data. Initial C<sub>max</sub> for the *cis-cis* isomer occurred at the same time as for the other two isomers; the concentration declined more rapidly than would be predicted for an elimination half-life of 55 minutes, suggesting the presence of a distribution phase.

After infusion, the active mivacurium isomers had a higher clearance, and higher volume of distribution in the elderly compared to the young. The differences

do not reach statistical significance, except  $V\beta$  for the *trans-trans* isomer, due to large variances. Table 4 summarizes this data.

Table 4. Pharmacokinetic Data After Mivacurium Infusion.  
(Means  $\pm$  SD) (Extracted from Sponsor's Tables 32- 34)

		Young	Elderly
CL <sub>ss</sub> (ml/kg/ min)	cis-cis*	----	----
	cis-trans	117.7 $\pm$ 51.4	186.4 $\pm$ 115.8
	trans-trans	64.4 $\pm$ 27.0	86.8 $\pm$ 41.1
$t_{1/2} \beta$ (min)	cis-cis	55.1 $\pm$ 13.5	66.0 $\pm$ 35.7
	cis-trans	2.6 $\pm$ 1.5	3.6 $\pm$ 2.9
	trans-trans	3.4 $\pm$ 2.5	4.6 $\pm$ 2.1
CL (ml/kg/ min)	cis-cis	4.3 $\pm$ 0.8	5.1 $\pm$ 2.2
	cis-trans	116.7 $\pm$ 79.0	208.8 $\pm$ 165.2
	trans-trans	58.1 $\pm$ 21.6	78.3 $\pm$ 40.2
$V\beta$ (ml/kg)	cis-cis	337 $\pm$ 77	430 $\pm$ 234
	cis-trans	424 $\pm$ 320	956 $\pm$ 898
	trans-trans	236 $\pm$ 129	508 $\pm$ 280

\* steady state conditions not met for cis-cis isomer

For the metabolites, *cis* 879U84, *trans* 879U84, and *trans* 141U86, there was a bi-exponential decline for the elimination phase. For *cis* 141U86 the plasma levels were too low to obtain reliable half-life or AUC data. The half-life of the first three metabolites was approximately 30% longer in the elderly. The differences were statistically significant for *cis* and *trans* 879. The estimated AUC, expressed per unit dose of mivacron given, for the metabolites showed a trend toward higher values of this variables in the elderly.

AUC/dose (ng/ml.h per mg/kg dose), means  $\pm$  SD.

	Young	Elderly
<i>cis</i> 879U84	1693 $\pm$ 361	2029 $\pm$ 533
<i>trans</i> 879U84	2229 $\pm$ 472	2615 $\pm$ 648
<i>trans</i> 141U86	1835 $\pm$ 655	2244 $\pm$ 548

Plasma cholinesterase activity correlated with clearance of the *cis-trans* and *trans-trans*, but not the *cis-cis* metabolite.

**Safety:**

Screening physical examination, hematologic and chemistries were not affected by the use of mivacurium. Reversal agents (neostigmine and atropine or glycopyrrolate) were administered to three patients (#54, 55, 61). All patients demonstrated full recovery of neuromuscular function as evidenced by post-operative clinical bedside testing.

There were 7 adverse events reported:

Pt# 15: age 34; postoperative bleeding; related to surgery.

26: age 28; bronchospasm; likely related to mivacurium; occurred after bolus and recurred after infusion; treated with terbutaline, without sequellae; other intraoperative meds: fentanyl, diazepam, N2O, O2, thiopental.

35: age 65; respiratory depression; reversed with naloxone.

45: age 77; late unconsciousness; recovered without sequellae.

55: age 67; intraoperative hypotension; possibly related to mivacurium or other meds; treated with ephedrine, without sequellae; other intraoperative meds: fentanyl, diazepam, N2O, O2, thiopental, alfentanil, enflurane, droperidol.

61: age 82; luxation of teeth; related to manipulation of the airway.

133<sup>1</sup>: age 78; nodal rhythm (2 min); possibly related to surgical manipulation (thyroidectomy) or mivacurium; treated with atropine, without sequellae; other meds: fentanyl, diazepam, N2O, O2, thiopental.

**Conclusions:**

This study's aim was to characterize the pharmacokinetics of the isomers and metabolites of mivacurium, and to identify pharmacokinetic and pharmacodynamic differences between the young and the elderly. The active isomer half-lives, 3-5 minutes, are slightly longer than the previously reported values (1-3 minutes). Tmax for major metabolites coincided with that of the parent molecule. Mean CL<sub>ss</sub> values for the active isomers were close to total CL values.

The ED<sub>95</sub> was calculated at 0.053 mg/kg for young patients and 0.058 mg/kg for elderly patients receiving N2O/narcotic anesthesia, which is a difference

---

<sup>1</sup>In Sponsor's Appendix B3, patient #52 is identified as receiving atropine for intraoperative bradycardia; patient #133 is not so identified. The sponsor has been contacted to clarify this discrepancy.

unlikely to have clinical relevance. There were no clinical (i.e., efficacy) differences observed between the two age groups. In both age groups, there was no relationship between the duration of infusion and the indices of recovery. The spontaneous recovery profile for elderly patients was slightly prolonged compared to young patients, for example,  $T_{4:1} \geq 70\%$  was 4.6 minutes greater in healthy elderly patients. This difference is clinically unimportant, as management is determined solely by objective evidence of recovery.

The relationship of clearance of active isomers to plasma cholinesterase activity is consistent with the established metabolic pathway of ester hydrolysis of mivacurium. The lack of relationship between the clearance of the *cis-cis* isomer and plasma cholinesterase activity implies an alternate pathway of elimination, prominently renal (study report in this review).

The safety evaluation does not indicate differences in the basis of age, based on the small number of adverse events reported. No unusual adverse events were reported. There were 3/7 incidents having a possible relationship to the use of mivacurium. One case of bronchospasm, treated with terbutaline, was the result of mivacurium-induced histamine release. One case of hypotension of short duration, reversed with ephedrine, may have possibly been related to the use of mivacurium, but was equally or more likely to have been related to the administration of droperidol and enflurane. In addition, the episode of hypotension occurred while the patient was already receiving an established infusion of mivacurium, whereas hypotension due to mivacurium-induced histamine release is more likely to occur after a bolus administration. A case of nodal bradycardia reversed with atropine cannot be evaluated based on the information supplied. Bradyarrhythmia is not a characteristic of either mivacurium's effect on the cholinergic receptor nor of the side effect of histamine release. It is also possible that the episode of bradycardia was due to stimulation of the carotid sinus during thyroidectomy; however, more information would need to be supplied.

#### **RM1996/00132/00: Short- and Long-Term Infusions of Mivacron (mivacurium chloride) in Adult Surgical Patients During N<sub>2</sub>O/O<sub>2</sub>/Opioid Anesthesia**

This was an open-label efficacy, safety and pharmacokinetic study of mivacurium 0.15 mg/kg administered as an intravenous bolus, followed by short-term (1-3 hours) or long-term (4-6 hours) infusion. The study population was divided into three treatment groups, based on age and duration of infusion:

- Group A: young adults receiving short-term infusion, n = 12
- Group B1: young adults receiving long-term infusion, n = 20
- Group B2: elderly adults receiving long-term infusion, n = 19

Within these groups, patients were subclassified by plasma cholinesterase activity (normal vs low) and stability of infusion requirements over time (constant vs decreasing). This subclassification was made prior to the final data analysis, as it became evident that the pharmacokinetic results depended on individual patients plasma cholinesterase activity and infusion requirements. Standard

electromechanomyographic monitoring was used to monitor the efficacy of mivacurium, i.e., stimulation of the ulnar nerve using surface electrodes to apply a supramaximal stimulus for twitch and train-of-four response of the adductor pollicis to monitor depth of block and recovery, respectively. Blood samples for pharmacokinetics were collected prior to the initial bolus administration every 30 minutes during infusion, and at discontinuation of the infusion. Blood sampling and administration of mivacurium were from intravenous cannulas placed at sites in contralateral arms.

The primary efficacy analyses were calculation of the average infusion rate needed to maintain neuromuscular block at 89-99% T1 suppression, and rate of spontaneous recovery after discontinuation of the infusion (25-75% recovery index). Primary pharmacokinetic measurements were of plasma concentrations of the isomers of mivacurium during infusion and after cessation of infusion. Derived pharmacokinetic variables were EC<sub>95</sub> (dose associated with 95% suppression of T1), Cmax, Tmax, plasma CL for the active isomers and metabolites, AUC estimate for the cis-cis isomer and metabolites, corrected for differences in total dose.

Safety assessments were conducted by tabulation of adverse events, monitoring of vital signs according to standard of practice during general anesthesia, and comparison of preoperative and postoperative screening physical examinations and laboratory data (complete blood count and routine chemistries).

Infusion data for individual patients were divided into consecutive 3 minute epochs commencing with the initiation of the infusion. Patients in Group A were included in the average infusion rate analysis if their infusions were 1 hour or longer with at least 5 evaluable epochs after the initial 45 minutes of infusion. Patients in Group B1 and B2 were included in the average infusion rate analysis if their infusions were 4 hours or longer with at least 5 evaluable epochs after the initial 225 minutes of infusion. An evaluable epoch was one inwhich the rate of infusion was known and T1 suppression was in the range of 89-99% of baseline. The average infusion rate was the mean of all infusion rates for all evaluable epochs from the sixth through the last complete epoch.

Inclusion criteria were male and female ASA I and II patients scheduled for low-to-moderate risk surgery, who consented to participate. Female patients were either not pregnant, using contraception, or not of childbearing potential. Age ranges for Groups A and B1 were 18-59 years, and for Group B2  $\geq$  60 years. Exclusion criteria were consistent with those already listed for other studies in this report.

The anesthesiologist was not restricted in choice of intravenous hypnotic agent or narcotic for maintenance of anesthesia. No inhalation agents other than N2O/O2 were administered. The patient received 0.15 mg/kg mivacurium over 5-10 seconds for initial muscular relaxation prior to endotracheal intubation. Twitch response was recorded continuously from the time of hypnosis prior to administration of mivacurium and thereafter. At the point of 5% T1 recovery, the infusion of mivacurium was initiated at 10  $\mu$ g/kg/min and adjusted to maintain 95  $\pm$  4% T1 suppression.