1.6　外国における使用状況等に関する資料

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1.6　外国における使用状況等に関する資料

1.6.1　外国における承認・発売状況

本剤は，1994 年 3 月に米国（Zemuron®）で，1994 年 4 月にイギリス及びオランダ（Esmeron®）で承認され，2006 年 3 月現在では世界 88 カ国で承認されている．代表的な国における使用状況について 表 1.6-1に示した

表 1.6-1　主要な外国の承認・発売状況（2007 年 2 月現在）

国名	承認・発売状況	
オランダ	販　売　名：	Esmeron
	承　認　日：	1994 年 4 月 6 日
	剤型・含量：	注射液として 25 mg/2.5 mL，50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 急速導入並びに気管挿管を容易にするための全身麻酔の補助. 2. 手術時の骨格筋弛緩. 3. 集中治療室における挿管及び人工呼吸を容易にするための補助.
	用法・用量：	全般的な用法：個々の患者の状況にあわせた用量を投与する. **外科手術時** 標準的な気管挿管用量： 標準：0.6 mg/kg 急速導入：1.0 mg/kg 帝王切開時の急速導入：0.6 mg/kg 維持用量： 通常：0.15 mg/kg 吸入麻酔剤の長時間併用投与時：0.075～0.1 mg/kg 持続注入： 初回投与量 : 0.6 mg/kg ; その後の持続注入量は twitch response が対照の 10%となるよう維持する．（成人において静脈麻酔下では 0.3～0.6 mg/kg/h ; 吸入麻酔下では 0.3～0.4 mg/kg/h） 小児への使用 特に推奨投与法は設定されていない. 高齢者及び肝障害，胆道障害，腎障害患者への使用 標準的な気管挿管用量：0.6 mg/kg 急速導入：0.6 mg/kg（特に作用の遷延が懸念される患者） 維持用量：0.075～0.1 mg/kg または 0.3～0.4 mg/kg/h 過体重及び肥満患者への使用 投与量（mg/kg）は除脂肪体重（lean body mass）に基づいて計算する. **集中治療時（ICU）** 標準的な気管挿管用量：外科手術時と同用量 人工呼吸の補助： 初回投与量：0.6 mg/kg ; その後の持続注入量は twitch response が対照の 10%となるよう維持する．（初期には 0.3～0.6 mg/kg/h，次の 6～12 時間は徐々に減量する）

1.6　外国における使用状況に関する資料

表 1.6-1　主要な外国の承認・発売状況（2007 年 2 月現在）（続き）

国名	承認・発売状況	
英国	販　売　名：	Esmeron
	承　認　日：	1994 年 4 月 6 日
	剤型・含量：	注射液として 25 mg/2.5 mL，50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 急速導入並びに気管挿管を容易にするための麻酔の補助. 2. 手術時の骨格筋弛緩. 3. 集中治療室における挿管及び人工呼吸を容易にするための補助.
	用法・用量：	全般的な用法：個々の患者の状況にあわせた用量を投与する. **外科手術時** 標準気管挿管用量： 標準：0.6 mg/kg 急速導入：1.0 mg/kg 帝王切開時の急速導入：0.6 mg/kg 維持用量： 通常：0.15 mg/kg 吸入麻酔剤の長時間併用投与：0.075～0.1 mg/kg 持続注入： 初回投与量 0.6 mg/kg；その後の持続注入量は twitch response が対照の 10%となるよう維持する.（成人において静脈麻酔下では 0.3～0.6 mg/kg/h；吸入麻酔下では 0.3～0.4 mg/kg/h） 小児への使用 特に推奨投与法は設定されていない. 高齢者及び肝障害，胆道障害，腎障害患者への使用 標準的な気管挿管用量：0.6 mg/kg 急速導入：0.6 mg/kg（特に作用の遷延が懸念される患者） 維持用量：0.075～0.1 mg/kg または 0.3～0.4 mg/kg/h 過体重及び肥満患者への使用 投与量（mg/kg）は除脂肪体重（lean body mass）に基づいて計算する. **集中治療時（ICU）** 標準的な気管挿管用量：外科手術時と同用量 人工呼吸の補助： 初回投与量 : 0.6 mg/kg ; その後の持続注入量は twitch response が対照の 10%となるよう維持する.（初期には 0.3～0.6 mg/kg/h，次の 6～12 時間は徐々に減量する）

1.6　外国における使用状況に関する資料

表 1.6-1　主要な外国の承認・発売状況（2007 年 2 月現在）（続き）

国名	承認・発売状況	
フランス	販　売　名：	Esmeron
	承　認　日：	1994 年 11 月 14 日
	剤型・含量：	注射液として 25 mg/2.5 mL，50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 気管挿管を容易にするための麻酔の補助. 2. 骨格筋弛緩. 3. 人工呼吸を容易にするための補助.
	用法・用量：	全般的な用法：個々の患者の状況にあわせた用量を投与する. 標準気管挿管用量：0.6 mg/kg 維持用量（ボーラス投与）：通常 0.15 mg/kg, 吸入麻酔時の長時間併用時：0.075～0.1 mg/kg 持続注入：初回投与量：0.6 mg/kg； その後の持続注入量は twitch response が対照の 10%となるよう維持する.（成人において静脈麻酔下では 0.3～0.6 mg/kg/h；吸入麻酔下では 0.3～0.4 mg/kg/h）. 小児への使用 特に推奨投与法は設定されていない. 高齢者及び肝障害，胆道障害，腎障害患者への使用 気管挿管標準用量：0.6 mg/kg 維持用量：0.075～0.1 mg/kg または 0.3～0.4 mg/kg/h 過体重及び肥満患者への使用 投与量（mg/kg）は除脂肪体重（lean body mass）に基づいて計算する.
ドイツ	販　売　名：	Esmeron
	承　認　日：	1995 年 9 月 5 日
	剤型・含量：	注射液として 25 mg/2.5 mL，50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 気管挿管を容易にするための全身麻酔の補助. 2. 骨格筋弛緩. 3. 挿管困難が予想されない場合，急速導入時にサクシニルコリンの代わりとして
	用法・用量：	全般的な用法：個々の患者の状況にあわせた用量を投与する. 標準気管挿管用量： 標準：0.6 mg/kg 急速導入：1.0 mg/kg 維持用量（ボーラス投与）： 通常：0.15 mg/kg 吸入麻酔剤の長時間併用投与：0.075～0.1 mg/kg 持続注入： 初回投与量：0.6 mg/kg；その後の持続注入量は twitch response が対照の 10%となるよう維持する.（成人において静脈麻酔下では 0.3～0.6 mg/kg/h；吸入麻酔下では 0.3～0.4 mg/kg/h） 小児への使用 特に推奨投与法は設定されていない. 高齢者への使用 標準的な気管挿管用量：0.6 mg/kg 維持用量：0.075～0.1 mg/kg または 0.3～0.4 mg/kg/h 過体重及び肥満患者への使用 投与量（mg/kg）は除脂肪体重（lean body mass）に基づいて計算する.

1.6　外国における使用状況に関する資料

表 1.6-1　主要な外国の承認・発売状況（2007 年 2 月現在）（続き）

国名	承認・発売状況	
ノルウェー	販　売　名：	Esmeron
	承　認　日：	1996 年 8 月 13 日
	剤型・含量：	注射液 25 mg/2.5 mL，50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	とくに早い作用発現が求められる場合における通常麻酔における筋弛緩
	用法・用量：	全般的な用法：個々の患者の状況にあわせた用量を投与する． **外科手術時** 標準気管挿管用量： 標準：0.6 mg/kg 急速導入：1.0 mg/kg 維持用量： 通常：0.15 mg/kg 吸入麻酔剤の長時間併用投与：0.075～0.1 mg/kg 持続注入： 初回投与量 : 0.6 mg/kg ; その後の持続注入量は twitch response が対照の 10%となるよう維持する．（成人において静脈麻酔下では 0.3～0.6 mg/kg/h；吸入麻酔下では 0.3～0.4 mg/kg/h） 小児への使用 乳児，小児，青年：気管挿管時は成人と同用量の投与，急速導入は推奨しない．維持用量は成人と同用量．小児への持続注入速度は成人と同様である．新生児：十分なデータがない． 高齢者及び肝障害，胆道障害，腎障害患者への使用 標準的な気管挿管用量：0.6 mg/kg 急速導入：0.6 mg/kg 維持用量：0.075～0.1 mg/kg または 0.3～0.4 mg/kg/h 過体重及び肥満患者への使用 投与量（mg/kg）は除脂肪体重（lean body mass）に基づいて計算する．

1.6　外国における使用状況に関する資料

表 1.6-1　主要な外国の承認・発売状況（2007 年 2 月現在）（続き）

国名	承認・発売状況	
米国	販　売　名：	Zemuron
	承　認　日：	1994 年 3 月 17 日
	剤型・含量：	注射液として 50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 急速導入並びに気管挿管を容易にするための麻酔の補助. 2. 手術時の骨格筋弛緩. 3. 人工呼吸時の骨格筋弛緩.
	用法・用量：	全般的な用法：投与量は患者の状況にあわせる. 急速導入：0.6～1.2 mg/kg 標準的気管挿管：0.6 mg/kg 維持用量（ボーラス投与）：0.1～0.2 mg/kg 持続注入：初期投与は 10～12 μg/kg/min（0.6～0.72 mg/kg/h）とし，患者の反応に応じて投与量を調節する. 小児への使用 標準的気管挿管：0.6 mg/kg 維持用量：0.075～0.125 mg/kg 持続投与：初期投与は 12 μg/kg/min（0.72 mg/kg/h）とし，患者の反応に応じて投与量を調節する. 高齢者への使用 気管挿管標準用量：0.6～1.2 mg/kg 維持用量：0.1～0.15 mg/kg 過体重及び肥満患者への使用 投与量（mg/kg）は実体重に基づいて計算する.
カナダ	販　売　名：	Zemuron
	承　認　日：	1994 年 9 月 27 日
	剤型・含量：	静脈注射液として 50 mg/5 mL，100 mg/10 mL バイアル
	効能・効果：	1. 急速導入並びに通常の気管内挿管を容易にするための麻酔補助. 2. 手術時の骨格筋弛緩. 3. 人工呼吸時の骨格筋弛緩.
	用法・用量：	全般的な用法：投与量は個々の患者の状況にあわせること. 急速導入：0.6～1.2 mg/kg 標準的気管挿管：0.6 mg/kg 維持用量：0.1～0.2 mg/kg 持続注入：初回投与は 0.45～0.6 mg/kg，その後の維持投与量は 10～12 μg/kg/min (0.6～0.72 mg/kg/h）とし，患者の反応に応じて投与量を調節する. 小児への使用 標準的気管挿管：0.6 mg/kg 維持用量：0.075～0.125 mg/kg 持続投与：0.012 mg/kg/min (0.72 mg/kg/h)で開始し，患者の反応に応じて投与量を調節する. 高齢者への使用 気管挿管標準用量：0.6 mg/kg 以上，急速導入は推奨しない. 維持用量：0.1～0.15 mg/kg

1.6.2　1.6.2　外国の添付文書

本品の外国における添付文書の代表例として，米国の添付文書の原文及び和訳の概要を示した.

1.6.2.1　1.6.2.1　米国の添付文書（原文）

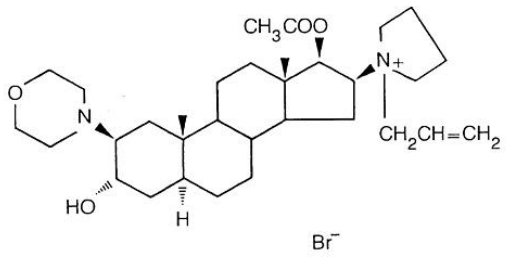
ZEMURON® (rocuronium bromide) Injection

THIS DRUG SHOULD BE ADMINISTERED BY ADEQUATELY-TRAINED INDIVIDUALS FAMILIAR WITH ITS ACTIONS, CHARACTERISTICS, AND HAZARDS.

DESCRIPTION

ZEMURON® (rocuronium bromide) Injection is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose and intermediate duration. Rocuronium bromide is chemically designated as 1-[17β-(acetyloxy)-3α-hydroxy-2β-(4-morpholinyl)-5α-androstan-16β-yl]-1- (2-propenyl) pyrrolidinium bromide.

The structural formula is:



The chemical formula is $C_{32}H_{53}BrN_2O_4$ with a molecular weight of 609.70. The partition coefficient of rocuronium bromide in n-octanol/water is 0.5 at 20°C.

ZEMURON® is supplied as a sterile, nonpyrogenic, isotonic solution that is clear, colorless to yellow/orange, for intravenous injection only. Each mL contains 10 mg rocuronium bromide and 2 mg sodium acetate. The aqueous solution is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide.

CLINICAL PHARMACOLOGY

ZEMURON® (rocuronium bromide) Injection is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose and intermediate duration. It acts by competing for cholinergic receptors at the motor end-plate. This action is antagonized by acetylcholinesterase inhibitors, such as neostigmine and edrophonium.

Pharmacodynamics

The ED_{95} (dose required to produce 95% suppression of the first [T_1] mechanomyographic [MMG] response of the adductor pollicis muscle [thumb] to indirect supramaximal train-of-four stimulation of the ulnar nerve) during opioid/nitrous oxide/oxygen anesthesia is approximately 0.3 mg/kg. Patient variability around the ED_{95} dose suggests that 50% of patients will exhibit T_1 depression of 91 to 97%.

Table 1 presents intubating conditions in patients with intubation initiated at 60 to 70 seconds.

TABLE 1: Percent of Excellent or Good Intubating Conditions and Median (Range) Time to Completion of Intubation in Patients with Intubation Initiated at 60 to 70 Seconds

ZEMURON® Dose (mg/kg) Administered over 5 sec	Percent of Patients With Excellent or Good Intubating Conditions	Time to Completion of Intubation (min)
Adults * 18 to 64 yrs		
0.45 (n=43)	86%	1.6 (1.0-7.0)
0.6 (n=51)	96%	1.6 (1.0-3.2)
Infants 3 mo to 1 yr		
0.6 (n=18)	100%	1.0 (1.0-1.5)
Pediatric 1 to 12 yrs		
0.6 (n=12)	100%	1.0 (0.5-2.3)

* Excludes patients undergoing cesarean section
Excellent intubating conditions = jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement
Good intubating conditions = same as excellent but with some diaphragmatic movement

Table 2: presents the time to onset and clinical duration for the initial dose of ZEMURON® (rocuronium bromide) Injection under opioid/nitrous oxide/oxygen anesthesia in adults and geriatric patients, and under halothane anes-thesia in pediatric patients.

TABLE 2: Median (Range) Time to Onset and Clinical Duration Following Initial (Intubating) Dose During Opioid/Nitrous Oxide/Oxygen Anesthesia (Adults) and Halothane Anesthesia (Pediatric Patients)

ZEMURON® Dose (mg/kg) Administered over 5 sec	Time to >/=80% Block (min)	Time to Maximum Block (min)	Clinical Duration (min)
Adults 18 to 64 yrs			
0.45 (n=50)	1.3 (0.8-6.2)	3.0 (1.3-8.2)	22 (12-31)
0.6 (n=142)	1.0 (0.4-6.0)	1.8 (0.6-13.0)	31 (15-85)
0.9 (n=20)	1.1 (0.3-3.8)	1.4 (0.8-6.2)	58 (27-111)
1.2 (n=18)	0.7 (0.4-1.7)	1.0 (0.6-4.7)	67 (38-160)
Geriatric >/=65 yrs			
0.6 (n=31)	2.3 (1.0-8.3)	3.7 (1.3-11.3)	46 (22-73)
0.9 (n=5)	2.0 (1.0-3.0)	2.5 (1.2-5.0)	62 (49-75)
1.2 (n=7)	1.0 (0.8-3.5)	1.3 (1.2-4.7)	94 (64-138)
Infants 3 mo to 1 yr			
0.6 (n=17)	-	0.8 (0.3-3.0)	41 (24-68)
0.8 (n=9)	-	0.7 (0.5-0.8)	40 (27-70)
Pediatric 1 to 12 yrs			
0.6 (n=27)	0.8 (0.4-2.0)	1.0 (0.5-3.3)	26 (17-39)
0.8 (n=18)	-	0.5 (0.3-1.0)	30 (17-56)

n = the number of patients who had time to maximum block recorded
Clinical duration = time until return to 25% of control T_1 . Patients receiving doses of 0.45 mg/kg who achieved less than 90% block (16% of these patients) had about 12 to 15 minutes to 25% recovery.

The time to >/=80% block and clinical duration as a function of dose are presented in Figures 1 and 2.

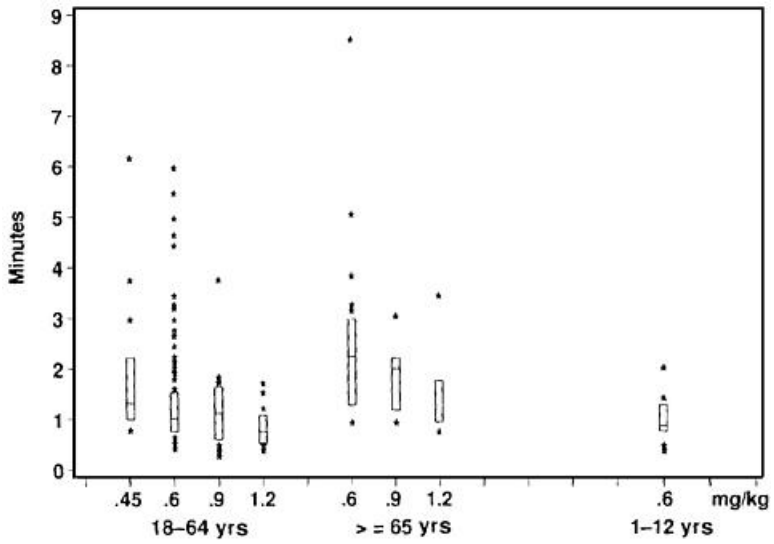


FIGURE 1: Time to >/=80% Block vs. Initial Dose of ZEMURON® by Age Group
(Median, 25th and 75th percentile, and individual values)

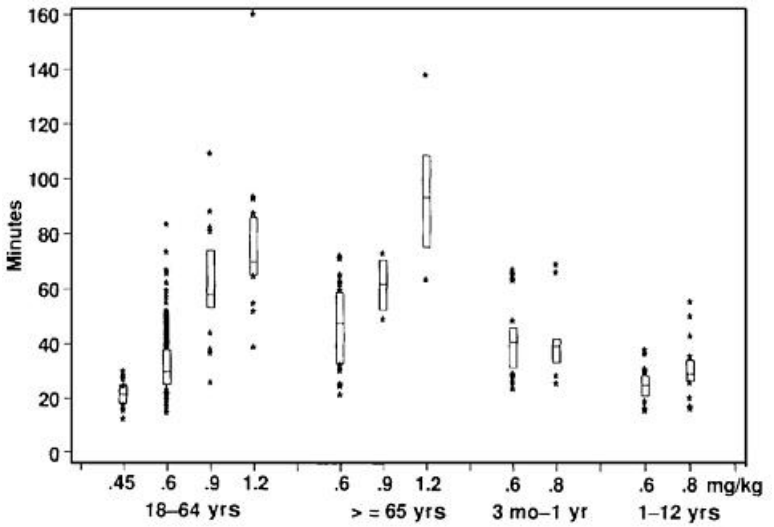


FIGURE 2: Duration of Clinical Effect vs. Initial Dose of ZEMURON® by Age Group
(Median, 25th and 75th percentile, and individual values)

The clinical durations for the first five maintenance doses, in patients receiving five or more maintenance doses are represented in Figure 3 (see DOSAGE AND ADMINISTRATION - Maintenance Dosing).

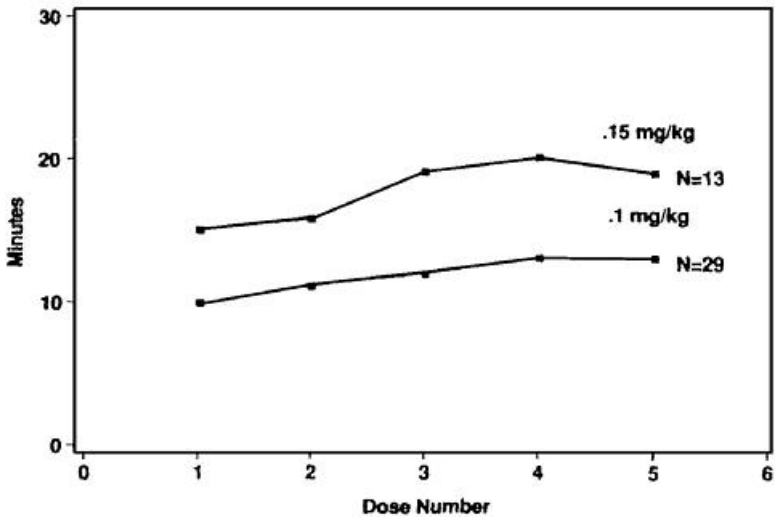


FIGURE 3: Duration of Clinical Effect vs. Number of ZEMURON® Maintenance Doses, by Dose

Once spontaneous recovery has reached 25% of control T_1, the neuromuscular block produced by ZEMURON® is readily reversed with anticholinesterase agents, e.g., edrophonium or neostigmine.

The median spontaneous recovery from 25 to 75% T_1 was 13 minutes in adult patients. When neuromuscular block was reversed in 36 adults at a T_1 of 22 to 27%, recovery to a T_1 of 89 (50-132)% and T_4 /T_1 of 69 (38-92)% was achieved within 5 minutes. Only five of 320 adults reversed received an additional dose of reversal agent. The median (range) dose of neostigmine was 0.04 (0.01-0.09) mg/kg and the median (range) dose of edrophonium was 0.5 (0.3-1.0) mg/kg.

In geriatric patients (n=51) reversed with neostigmine, the median T_4 /T_1 increased from 40 to 88% in 5 minutes.

Pediatric patients (n=27) who received 0.5 mg/kg edrophonium had increases in the median T_4 /T_1 from 37% at reversal to 93% after 2 minutes. Pediatric patients (n=58) who received 1 mg/kg edrophonium had increases in the median T_4 /T_1 from 72% at reversal to 100% after 2 minutes. Infants (n=10) who were reversed with 0.03 mg/kg neostigmine recovered from 25 to 75% T 1 within 4 minutes.

There were no reports of less than satisfactory clinical recovery of neuromuscular function.

The neuromuscular blocking action of ZEMURON® may be enhanced in the presence of potent inhalation anesthetics (see PRECAUTIONS - Inhalation Anesthetics).

Hemodynamics

There were no dose-related effects on the incidence of changes from baseline (>/=30%) in mean arterial blood pressure (MAP) or heart rate associated with ZEMURON® administration over the dose range of 0.12 to 1.2 mg/kg (4 × ED_{95}) within 5 minutes after ZEMURON® administration and prior to intubation. Increases or decreases in MAP were observed in 2 to 5% of geriatric and other adult patients, and in about 1% of pediatric

patients. Heart rate changes (>/=30%) occurred in 0 to 2% of geriatric and other adult patients. Tachycardia (>/=30%) occurred in 12 of 127 pediatric patients. Most of the pediatric patients developing tachycardia were from a single study where the patients were anesthetized with halothane and who did not receive atropine for induction (see CLINICAL PHARMACOLOGY - Clinical Trials - Pediatric Patients). In US studies, laryngoscopy and tracheal intubation following ZEMURON® administration were accompanied by transient tachycardia (>/=30% increases) in about one-third of adult patients under opioid/nitrous oxide/oxygen anesthesia. Animal studies have indicated that the ratio of vagal:neuromuscular block following ZEMURON® administration is less than vecuronium but greater than pancuronium. The tachycardia observed in some patients may result from this vagal blocking activity.

Histamine Release

In studies of histamine release, clinically significant concentrations of plasma histamine occurred in 1 of 88 patients. Clinical signs of histamine release (flushing, rash, or bronchospasm) associated with the administration of ZEMURON® were assessed in clinical trials and reported in 9 of 1137 (0.8%) patients.

Pharmacokinetics

In an effort to maximize the information gathered in the in vivo pharmacokinetic studies, the data from the studies was used to develop population estimates of the parameters for the subpopulations represented (e.g., geriatric, pediatric, renal, and hepatic insufficiency). These population based estimates and a measure of the estimate variability are contained in the following section.

Following intravenous administration of ZEMURON® (rocuronium bromide) Injection, plasma levels of rocuronium follow a three compartment open model. The rapid distribution half-life is 1 to 2 minutes and the slower distribution half-life is 14 to 18 minutes. Rocuronium is approximately 30% bound to human plasma proteins. In geriatric and other adult surgical patients undergoing either opioid/nitrous oxide/oxygen or inhalational anesthesia, the observed pharmacokinetic profile was essentially unchanged.

TABLE 3: Mean (SD) Pharmacokinetic Parameters in Adults (n=22; ages 27 to 58 yrs) and Geriatric (n=20; >/=65 yrs) During Opioid/Nitrous Oxide/Oxygen Anesthesia

PK Parameters	Adults (Ages 27 to 58 yrs)	Geriatrics (>/=65 yrs)
Clearance (L/kg/hr)	0.25 (0.08)	0.21 (0.06)
Volume of Distribution at Steady State (L/kg)	0.25 (0.04)	0.22 (0.03)
t 1/2 (beta) Elimination (hr)	1.4 (0.4)	1.5 (0.4)

In general, studies with normal adult subjects did not reveal any differences in the pharmacokinetics of rocuronium due to gender.

Studies of distribution, metabolism, and excretion in cats and dogs indicate that rocuronium is eliminated primarily by the liver. The rocuronium analog 17-desacetyl-rocuronium, a metabolite, has been rarely observed in the plasma or urine of humans administered single doses of 0.5 to 1 mg/kg with or without a subsequent infusion (for up to 12 hr) of rocuronium. In the cat, 17-desacetyl-rocuronium has approximately one-twentieth

the neuromuscular blocking potency of rocuronium. The effects of renal failure and hepatic disease on the pharmacokinetics and pharmacodynamics of rocuronium in humans are consistent with these findings.

In general, patients undergoing cadaver kidney transplant have a small reduction in clearance which is offset pharmacokinetically by a corresponding increase in volume, such that the net effect is an unchanged plasma half-life. Patients with demonstrated liver cirrhosis have a marked increase in their volume of distribution resulting in a plasma half-life approximately twice that of patients with normal hepatic function. Table 4 shows pharmacokinetic parameters in subjects with either impaired renal or hepatic function.

TABLE 4: Mean (SD) Pharmacokinetic Parameters in Adults with Normal Renal and Hepatic Function (n=10, ages 23 to 65), Renal Transplant Patients (n=10, ages 21 to 45) and Hepatic Dysfunction Patients (n=9, ages 31 to 67) During Isoflurane Anesthesia

PK Parameters	Normal Renal and Hepatic Function	Renal Transplant Patients	Hepatic Dysfunction Patients
Clearance (L/kg/hr)	0.16 (0.05) *	0.13 (0.04)	0.13 (0.06)
Volume of Distribution at Steady State (L/kg)	0.26 (0.03)	0.34 (0.11)	0.53 (0.14)
t 1/2 (beta) Elimination (hr)	2.4 (0.8) *	2.4 (1.1)	4.3 (2.6)

* Differences in the calculated t 1/2 (beta) and CI between this study and the study in young adults vs . geriatrics (>/=65 years) is related to the different sample populations and anesthetic techniques.

The net result of these findings is that subjects with renal failure have clinical durations that are similar to but somewhat more variable than the duration that one would expect in subjects with normal renal function. Hepatically impaired patients, due to the large increase in volume, may demonstrate clinical durations approaching 1.5 times that of subjects with normal hepatic function. In both populations the clinician should individualize the dose to the needs of the patient (see CLINICAL PHARMACOLOGY - Individualization of Dosage).

Tissue redistribution accounts for most (about 80%) of the initial amount of rocuronium administered. As tissue compartments fill with continued dosing (4 to 8 hours), less drug is redistributed away from the site of action and, for an infusion-only dose, the rate to maintain neuromuscular blockade falls to about 20% of the initial infusion rate. The use of a loading dose and a smaller infusion rate reduces the need for adjustment of dose.

Special Populations

Pediatrics

The clinical duration of effects of ZEMURON® (rocuronium bromide) Injection did not vary with age in patients 4 months to 8 years of age. The terminal half-life and other pharmacokinetic parameters of rocuronium in these pediatric patients are presented in Table 5.

TABLE 5: Mean (SD) Pharmacokinetic Parameters of Rocuronium in Pediatric Patients (ages 3 to <12 mos, n=6; 1 to <3 yrs, n=5; 3 to <8 yrs, n=7) During Halothane Anesthesia

PK Parameters	Patient Age Range		
	3 to <12 mos	1 to <3 yrs	3 to <8 yrs
Clearance (L/kg/hr)	0.35 (0.08)	0.32 (0.07)	0.44 (0.16)
Volume of Distribution at Steady State (L/kg)	0.30 (0.04)	0.26 (0.06)	0.21 (0.03)
t 1/2 (beta) Elimination (hr)	1.3 (0.5)	1.1 (0.7)	0.8 (0.3)

Clinical Trials

In US clinical trials, a total of 1137 patients received ZEMURON® (rocuronium bromide) Injection, including 176 pediatric, 140 geriatric, 55 obstetric, and 766 other adults. Most patients (90%) were ASA physical status I or II, about 9% were ASA III, and 10 patients (undergoing coronary artery bypass grafting or valvular surgery) were ASA IV. In European clinical trials, a total of 1394 patients received ZEMURON®, including 52 pediatric, 128 geriatric (>/=65 years) and 1214 other adults.

Adult Patients

Intubation using doses of ZEMURON® 0.6 to 0.85 mg/kg was evaluated in 203 adults in 11 clinical trials. Excellent to good intubating conditions were generally achieved within 2 minutes and maximum block occurred within 3 minutes in most patients. Doses within this range provide clinical relaxation for a median (range) time of 33 (14-85) minutes under opioid/nitrous oxide/oxygen anesthesia. Larger doses (0.9 and 1.2 mg/kg) were evaluated in two trials with 19 and 16 patients under opioid/nitrous oxide/oxygen anesthesia and provided 58 (27-111) and 67 (38-160) minutes of clinical relaxation, respectively.

Cardiovascular Disease

In one clinical trial, 10 patients with clinically significant cardiovascular disease undergoing coronary artery bypass graft received an initial dose of 0.6 mg/kg ZEMURON®. Neuromuscular block was maintained during surgery with bolus maintenance doses of 0.3 mg/kg. Following induction, continuous 8 mcg/kg/min infusion of ZEMURON® produced relaxation sufficient to support mechanical ventilation for 6 to 12 hours in the surgical intensive care unit (SICU) while the patients were recovering from surgery. Hypertension and tachycardia were reported in some patients but these occurrences were less frequent in patients receiving beta or calcium channel blocking drugs. In 7 of these 10 patients, ZEMURON® was associated with transient increases (>/=30%) in pulmonary vascular resistance. In another clinical trial of 17 patients undergoing abdominal aortic surgery, transient increases (>/=30%) in pulmonary vascular resistance were observed in 4 of 17 patients receiving ZEMURON® 0.6 or 0.9 mg/kg.

Rapid Sequence Intubation

Intubating conditions were assessed in 230 patients in six clinical trials where anesthesia was induced with either thiopental (3 to 6 mg/kg) or propofol (1.5 to 2.5 mg/kg) in combination with either fentanyl (2 to 5 mcg/kg) or alfentanil (1 mg). Most of the patients also received a premedication such as midazolam or temazepam. Most patients had intubation attempted within 60 to 90 seconds of administration of ZEMURON®

0.6 mg/kg or succinylcholine 1 to 1.5 mg/kg. Excellent or good intubating conditions were achieved in 119/120 (99% [95% confidence interval 95-99.9%]) patients receiving ZEMURON® and in 108/110 (98% [94-99.8%]) patients receiving succinylcholine. The duration of action of ZEMURON® 0.6 mg/kg is longer than succinylcholine and at this dose is approximately equivalent to the duration of other intermediate acting neuromuscular blocking drugs.

Geriatric Patients

ZEMURON® was evaluated in 55 geriatric patients (ages 65 to 80 years) in six clinical trials. Doses of 0.6 mg/kg provided excellent to good intubating conditions in a median (range) time of 2.3 (1-8) minutes. Recovery times from 25 to 75% after these doses were not prolonged in geriatric patients compared to other adult patients.

Pediatric Patients

ZEMURON® 0.6 or 0.8 mg/kg was evaluated for intubation in 75 pediatric patients (n=28; age 3 to 12 months, n=47; age 1 to 12 years) in three trials using halothane (1 to 5%) nitrous oxide (60 to 70%) in oxygen. Of the pediatric patients anesthetized with halothane who did not receive atropine for induction, about 80% experienced a transient increase (>/=30%) in heart rate after intubation. One of the 19 infants anesthetized with halothane and fentanyl who received atropine for induction experienced this magnitude of change.

Obese Patients

ZEMURON® was dosed according to actual body weight (ABW) in most clinical trials. The administration of ZEMURON® in the 47 of 330 (14%) patients who were at least 30% or more above their ideal body weight (IBW) was not associated with clinically significant differences in the onset, duration, recovery, or reversal of ZEMURON®-induced neuromuscular block.

In one clinical trial in obese patients, ZEMURON® 0.6 mg/kg was dosed according to ABW (n=12) or IBW (n=11). Obese patients dosed according to IBW had a longer time to maximum block, a shorter median (range) clinical duration of 25 (14-29) minutes, and did not achieve intubating conditions comparable to those dosed based on ABW. These results support the recommendation that obese patients be dosed based on actual body weight.

Obstetric Patients

ZEMURON® 0.6 mg/kg was administered with thiopental, 3 to 4 mg/kg (n=13) or 4 to 6 mg/kg (n=42), for rapid sequence induction of anesthesia for Cesarean section. No neonate had APGAR scores <7 at 5 minutes. The umbilical venous plasma concentrations were 18% of maternal concentrations at delivery. Intubating conditions were poor or inadequate in 5 of 13 women receiving 3 to 4 mg/kg thiopental when intubation was attempted 60 seconds after drug injection. Therefore, ZEMURON® is not recommended for rapid sequence induction in Cesarean section patients.

1.6　外国における使用状況に関する資料

Individualization of Dosage

DOSES OF ZEMURON® (rocuronium bromide) INJECTION SHOULD BE INDIVIDUALIZED AND A PERIPHERAL NERVE STIMULATOR SHOULD BE USED TO MEASURE NEUROMUSCULAR FUNCTION DURING ZEMURON® ADMINISTRATION IN ORDER TO MONITOR DRUG EFFECT, DETERMINE THE NEED FOR ADDITIONAL DOSES, AND CONFIRM RECOVERY FROM NEUROMUSCULAR BLOCK.

Based on the known actions of ZEMURON®, the following factors should be considered when administering ZEMURON®:

Renal or Hepatic Impairment

No differences from patients with normal hepatic and kidney function were observed for onset time at a dose of 0.6 mg/kg ZEMURON®. When compared to patients with normal renal and hepatic function, the mean clinical duration is similar in patients with end-stage renal disease undergoing renal transplant, and is about 1.5 times longer in patients with hepatic disease. Patients with renal failure may have a greater variation in duration of effect (see CLINICAL PHARMACOLOGY - Pharmacokinetics and PRECAUTIONS - Hepatic Disease and PRECAUTIONS - Renal Failure).

Reduced Plasma Cholinesterase Activity

No differences from patients with normal plasma cholinesterase activity are expected since rocuronium metabolism does not depend on plasma cholinesterase.

Drugs or Conditions Causing Potentiation of, or Resistance to, Neuromuscular Block

The neuromuscular blocking action of ZEMURON® is potentiated by isoflurane and enflurane anesthesia. Potentiation is minimal when administration of the recommended dose of ZEMURON® occurs prior to the administration of these potent inhalation agents. The median clinical duration of a dose of 0.57 to 0.85 mg/kg was 34, 38, and 42 minutes under opioid/nitrous oxide/oxygen, enflurane and isoflurane maintenance anesthesia, respectively. During 1 to 2 hours of infusion, the infusion rate of ZEMURON® required to maintain about 95% block was decreased by as much as 40% under enflurane and isoflurane anesthesia (see PRECAUTIONS - Inhalation Anesthetics).

When ZEMURON® is administered to patients chronically receiving anticonvulsant agents such as carbamazepine or phenytoin, shorter durations of neuromuscular block may occur and infusion rates may be higher due to the development of resistance to nondepolarizing muscle relaxants (see PRECAUTIONS - Anticonvulsants).

Pulmonary Hypertension

ZEMURON may be associated with increased pulmonary vascular resistance, so caution is appropriate in patients with pulmonary hypertension or valvular heart disease (see CLINICAL PHARMACOLOGY - Clinical Trials).

Obesity

In obese patients, the initial dose of ZEMURON® 0.6 mg/kg should be based upon the patients actual body weight (see CLINICAL PHARMACOLOGY - Clinical Trials - Obese Patients).

Based on the known actions of other nondepolarizing neuromuscular blocking agents, the following additional factors should be considered when administering ZEMURON®:

Drugs or Conditions Causing Potentiation of, or Resistance to, Neuromuscular Block

Resistance to nondepolarizing agents, consistent with up-regulation of skeletal muscle acetylcholine receptors, is associated with burns, disuse atrophy, denervation, and direct muscle trauma. Receptor up-regulation may also contribute to the resistance to nondepolarizing muscle relaxants which sometimes develops in patients with cerebral palsy, patients chronically receiving anticonvulsant agents such as carbamazepine or phenytoin or with chronic exposure to nondepolarizing agents (see PRECAUTIONS).

Other nondepolarizing neuromuscular blocking agents have been found to exhibit 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, a decrease from the recommended initial dose should be considered.

Certain antibiotics, magnesium salts, lithium, local anesthetics, procainamide, and quinidine have been shown to increase the duration of neuromuscular block and decrease infusion requirements of other neuromuscular blocking agents. In patients in whom potentiation of neuromuscular block may be anticipated, a decrease from the recommended initial dose should be considered (see PRECAUTIONS - Antibiotics and PRECAUTIONS - Other).

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

Burns

Patients with burns are known to develop resistance to nondepolarizing neuromuscular blocking agents, probably due to upregulation of post-synaptic skeletal muscle cholinergic receptors (see CLINICAL PHARMACOLOGY - Individualization of Dosage).

INDICATIONS AND USAGE

ZEMURON® (rocuronium bromide) Injection is a nondepolarizing neuromuscular blocking agent with a rapid to intermediate onset depending on dose and intermediate duration and is indicated for inpatients and outpatients as an adjunct to general anesthesia to facilitate both rapid sequence and routine tracheal intubation, and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS

ZEMURON® (rocuronium bromide) Injection is contraindicated in patients known to have hypersensitivity to rocuronium bromide.

WARNINGS

ZEMURON® (rocuronium bromide) INJECTION SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGES 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 FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND AN ANTAGONIST ARE IMMEDIATELY AVAILABLE. IT IS RECOMMENDED THAT CLINICIANS ADMINISTERING NEUROMUSCULAR BLOCKING AGENTS SUCH AS ZEMURON® EMPLOY A PERIPHERAL NERVE STIMULATOR TO MONITOR DRUG RESPONSE, NEED FOR ADDITIONAL RELAXANT, AND ADEQUACY OF SPONTANEOUS RECOVERY OR ANTAGONISM.

ZEMURON® HAS NO KNOWN EFFECT ON CONSCIOUSNESS, PAIN THRESHOLD, OR CEREBRATION. THEREFORE, ITS ADMINISTRATION MUST BE ACCOMPANIED BY ADEQUATE ANESTHESIA OR SEDATION.

In patients with myasthenia gravis or myasthenic (Eaton-Lambert) syndrome, small doses of nondepolarizing neuromuscular blocking agents may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of value in monitoring the response to administration of muscle relaxants.
ZEMURON®, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions) in the same syringe or administered simultaneously during intravenous infusion through the same needle.

Anaphylaxis

Although rare, severe anaphylactic reactions to neuromuscular blocking agents, including ZEMURON® (rocuronium bromide) Injection, have been reported. These reactions have, in some cases, been life threatening. Due to the potential severity of these reactions, the necessary precautions, such as the immediate availability of appropriate emergency treatment, should be taken.
Special precautions should be taken in patients who have had previous anaphylactic reactions to other neuromuscular blocking agents, since allergic cross-reactivity has been reported in this class of drugs.

PRECAUTIONS

Long-term Use in ICU

ZEMURON® (rocuronium bromide) Injection has not been studied for long-term use in the ICU. As with other nondepolarizing neuromuscular blocking drugs, apparent tolerance to ZEMURON® may develop rarely during chronic administration in the ICU. While the mechanism for development of this resistance is not known, receptor up-regulation may be a contributing factor. It is STRONGLY RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF ZEMURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN UNTIL THERE IS A DEFINITE RESPONSE (ONE TWITCH OF THE TRAIN-OF-FOUR) TO NERVE STIMULATION. Prolonged paralysis and/or skeletal muscle weakness may be noted during initial attempts to wean from the ventilator patients who have chronically received neuromuscular blocking drugs in the ICU. Therefore, ZEMURON® should only be used in this setting if, in the opinion of the prescribing physician, the specific advantages of the drug outweigh the risk.

Labor and Delivery

The use of ZEMURON® (rocuronium bromide) Injection in Cesarean section has been studied in a limited number of patients. ZEMURON® is not recommended for rapid sequence induction in Cesarean section patients (see CLINICAL PHARMACOLOGY - Clinical Trials).

Hepatic Disease

Since ZEMURON® (rocuronium bromide) Injection is primarily excreted by the liver, it should be used with caution in patients with clinically significant hepatic disease. ZEMURON® 0.6 mg/kg has been studied in a limited number of patients (n=9) with clinically significant hepatic disease under steady-state isoflurane anesthesia. After ZEMURON® 0.6 mg/kg, the median (range) clinical duration of 60 (35-166) minutes was moderately prolonged compared to 42 minutes in patients with normal hepatic function. The median recovery time of 53 minutes was also prolonged in patients with cirrhosis compared to 20 minutes in patients with normal hepatic function. Four of eight patients with cirrhosis, who received ZEMURON® 0.6 mg/kg under opioid/nitrous oxide/oxygen anesthesia, did not achieve complete block. These findings are consistent with the increase in volume of distribution at steady state observed in patients with significant hepatic disease (see CLINICAL PHARMACOLOGY - Pharmacokinetics). If used for rapid sequence induction in patients with ascites, an increased initial dosage may be necessary to assure complete block. Duration will be prolonged in these cases. The use of doses higher than 0.6 mg/kg has not been studied.

Renal Failure

Due to the limited role of the kidney in the excretion of ZEMURON® (rocuronium bromide) Injection, usual dosing guidelines should be adequate. ZEMURON® 0.6 mg/kg has been evaluated in three single center trials (n=30, ages 19 to 61 years) in patients undergoing renal transplant surgery, or shunt procedures in preparation for dialysis. After ZEMURON® 0.6 mg/kg, the time to maximum block was about 1 to 2 minutes and was not

different from patients without renal dysfunction. The mean (SD) clinical duration of 54 (22) minutes was not considered prolonged compared to 46 (12) minutes in normal patients; however, there was substantial variation (range, 22-90 minutes). The spontaneous recovery rate from 25 to 75% of control in renal dysfunction patients of 27 (11) minutes was similar to 28 (20) minutes in normal patients (see CLINICAL PHARMACOLOGY - Pharmacokinetics).

Anaphylaxis

There have been rare reports of severe anaphylactic reactions to ZEMURON® (rocuronium bromide) Injection, including some that have been life threatening. Clinicians should be prepared for the possibility of these reactions and take the necessary precautions, including the immediate availability of emergency treatment (see WARNINGS).

Malignant Hyperthermia (MH)

In an animal study in MH-susceptible swine, the administration of ZEMURON® (rocuronium bromide) Injection did not appear to trigger malignant hyperthermia. ZEMURON® has not been studied in MH-susceptible patients. Because ZEMURON® is always used with other agents, and the occurrence of malignant hyperthermia during anesthesia is possible even in the absence of known triggering agents, clinicians should be familiar with early signs, confirmatory diagnosis and treatment of malignant hyperthermia prior to the start of any anesthetic.

Altered Circulation Time

Conditions associated with slower circulation time, e.g., cardiovascular disease or advanced age, may be associated with a delay in onset time. Because higher doses of ZEMURON® (rocuronium bromide) Injection produce a longer duration of action, the initial dosage should usually not be increased in these patients to reduce onset time; instead, when feasible, more time should be allowed for the drug to achieve onset of effect.

Drug Interactions

The use of ZEMURON® (rocuronium bromide) Injection before succinylcholine, for the purpose of attenuating some of the side effects of succinylcholine, has not been studied.

If ZEMURON® is administered following administration of succinylcholine, it should not be given until recovery from succinylcholine has been observed. The median duration of action of ZEMURON® 0.6 mg/kg administered after a 1 mg/kg dose of succinylcholine when T_1 returned to 75% of control was 36 minutes (range 14-57, n=12) vs. 28 minutes (17-51, n=12) without succinylcholine.

There are no controlled studies documenting the use of ZEMURON® before or after other nondepolarizing muscle relaxants. Interactions have been observed when other nondepolarizing muscle relaxants have been administered in succession.

Inhalation Anesthetics

Use of inhalation anesthetics has been shown to enhance the activity of other neuromuscular blocking agents, enflurane > isoflurane > halothane.

Isoflurane and enflurane may also prolong the duration of action of initial and maintenance doses of ZEMURON® and decrease the average infusion requirement of ZEMURON® by 40% compared to opioid/nitrous oxide/oxygen anesthesia. No definite interaction between ZEMURON® and halothane has been demonstrated. In one study, use of enflurane in 10 patients resulted in a 20% increase in mean clinical duration of the initial intubating dose, and a 37% increase in the duration of subsequent maintenance doses, when compared in the same study to 10 patients under opioid/nitrous oxide/oxygen anesthesia. The clinical duration of initial doses of ZEMURON® of 0.57 to 0.85 mg/kg under enflurane or isoflurane anesthesia, as used clinically, was increased by 11% and 23%, respectively. The duration of maintenance doses was affected to a greater extent, increasing by 30 to 50% under either enflurane or isoflurane anesthesia. Potentiation by these agents is also observed with respect to the infusion rates of ZEMURON® required to maintain approximately 95% neuromuscular block. Under isoflurane and enflurane anesthesia, the infusion rates are decreased by approximately 40% compared to opioid/nitrous oxide/oxygen anesthesia. The median spontaneous recovery time (from 25 to 75% of control T_1) is not affected by halothane, but is prolonged by enflurane (15% longer) and isoflurane (62% longer). Reversal-induced recovery of ZEMURON® neuromuscular block is minimally affected by anesthetic technique.

Intravenous Anesthetics

The use of propofol for induction and maintenance of anesthesia does not alter the clinical duration or recovery characteristics following recommended doses of ZEMURON®.

Anticonvulsants

In 2 of 4 patients receiving chronic anticonvulsant therapy, apparent resistance to the effects of ZEMURON® was observed in the form of diminished magnitude of neuromuscular block, or shortened clinical duration. As with other nondepolarizing neuromuscular blocking drugs, if ZEMURON® is administered to patients chronically receiving anticonvulsant agents such as carbamazepine or phenytoin, shorter durations of neuromuscular block may occur and infusion rates may be higher due to the development of resistance to nondepolarizing muscle relaxants. While the mechanism for development of this resistance is not known, receptor up-regulation may be a contributing factor (see CLINICAL PHARMACOLOGY - Individualization of Dosage).

Antibiotics

Drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as ZEMURON® include certain antibiotics (e.g., aminoglycosides; vancomycin; tetracyclines; bacitracin; polymyxins; colistin; and sodium colistimethate). If these antibiotics are used in conjunction with ZEMURON®, prolongation of neuromuscular block should be considered a possibility.

Other

Experience concerning injection of quinidine during recovery from use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for ZEMURON®.

ZEMURON®-induced neuromuscular blockade was modified by alkalosis and acidosis in experimental pigs. Both respiratory and metabolic acidosis prolonged the recovery time. The potency of ZEMURON® was significantly enhanced in metabolic acidosis and alkalosis, but was reduced in respiratory alkalosis. In addition, experience with other drugs has suggested that acute (e.g., diarrhea) or chronic (e.g., adrenocortical insufficiency) electrolyte imbalance may alter neuromuscular blockade. Since electrolyte imbalance and acid-base imbalance are usually mixed, either enhancement or inhibition may occur. Magnesium salts, administered for the management of toxemia of pregnancy, may enhance neuromuscular blockade.

A local tolerance study in rabbits demonstrated that ZEMURON® was well tolerated following intravenous, intra-arterial and perivenous administration with only a slight irritation of surrounding tissues observed after perivenous administration. In humans, if extravasation occurs, it may be associated with signs or symptoms of local irritation; the injection or infusion should be terminated immediately and restarted in another vein (see DOSAGE AND ADMINISTRATION).

Drug/Laboratory Test Interactions

None known.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies in animals have not been performed to evaluate carcinogenic potential or impairment of fertility. Mutagenicity studies (Ames test, analysis of chromosomal aberrations in mammalian cells, and micronucleus test) conducted with ZEMURON® (rocuronium bromide) Injection did not suggest mutagenic potential.

Pregnancy

Pregnancy Category C

Developmental toxicology studies have been performed in pregnant, conscious, nonventilated rabbits and rats. Inhibition of neuromuscular function was the endpoint for high-dose selection. The maximum tolerated dose served as the high-dose and was administered intravenously three times a day to rats (0.3 mg/kg, 15 to 30% of human intubation dose of 0.6 to 1.2 mg/kg based on the body surface unit of mg/m 2) from day 6 to 17 and to rabbits (0.02 mg/kg, 25% human dose) from day 6 to 18 of pregnancy. High-dose treatment caused acute symptoms of respiratory dysfunction due to the pharmacological activity of the drug. Teratogenicity was not observed in these animal species. The incidence of late embryonic death was increased at the high-dose in rats most likely due to oxygen deficiency. Therefore, this finding probably has no relevance for humans because immediate mechanical ventilation of the intubated patient will effectively prevent embryo-fetal hypoxia. However, there are no adequate and well-controlled studies in pregnant women. ZEMURON® (rocuronium bromide) Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pediatric Use

The use of ZEMURON® (rocuronium bromide) Injection in pediatric patients less than 3 months of age and greater than 14 years of age has not been studied. See Pharmacodynamics subsection of CLINICAL PHARMACOLOGY and Use in Pediatrics subsection of DOSAGE AND ADMINISTRATION for clinical experience and recommendations for use in pediatric patients 3 months to 14 years of age.

Geriatric Use

ZEMURON® (rocuronium bromide) Injection was administered to 140 geriatric patients (>/=65 years) in US clinical trials and 128 geriatric patients in European clinical trials. The observed pharmacokinetic profile for geriatric patients (n=20) was similar to that for other adult surgical patients (see CLINICAL PHARMACOLOGY). Onset time and duration of action were slightly longer for geriatric patients (n=43) in clinical trials. For clinical experiences and recommendations for use in geriatric patients, see Pharmacodynamics and Clinical Trials subsections of CLINICAL PHARMACOLOGY and Use in Geriatrics subsection of DOSAGE AND ADMINISTRATION.

ADVERSE REACTIONS

Clinical studies in the US (n=1137) and Europe (n=1394) totaled 2531 patients. Prolonged neuromuscular block is associated with neuromuscular blockers as a class. Prolonged neuromuscular block (166 minutes) occurred after 0.6 mg/kg ZEMURON® (rocuronium bromide) Injection in an obese 67 year-old female with hepatic dysfunction who had received gentamicin before surgery. The patients exposed in the US clinical studies provide the basis for calculation of adverse reaction rates. The following adverse experiences were reported in patients administered ZEMURON® (all events judged by investigators during the clinical trials to have a possible causal relationship):

Adverse experiences in greater than 1% of patients: -- NONE

Adverse experiences in less than 1% of patients Probably Related or Relationship Unknown:

Cardiovascular:	arrhythmia, abnormal electrocardiogram, tachycardia
Digestive:	nausea, vomiting
Respiratory:	asthma (bronchospasm, wheezing, or rhonchi), hiccup
Skin and Appendages:	rash, injection site edema, pruritus

In the European studies, the most commonly reported adverse experiences were transient hypotension (2%) and hypertension (2%); it is in greater frequency than the US studies (0.1% and 0.1%). Changes in heart rate and blood pressure were defined differently from the US studies in which changes in cardiovascular parameters were not considered as adverse events unless judged by the investigator as unexpected, clinically significant, or thought to be histamine related.

In clinical practice, there have been reports, primarily from European sources, of severe allergic reactions (anaphylactic and anaphylactoid reactions and shock) with ZEMURON®, including some that have been life threatening and rarely fatal (see WARNINGS and PRECAUTIONS).

OVERDOSAGE

No cases of significant accidental or intentional overdose with ZEMURON® (rocuronium bromide) Injection have been reported. 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 Blockade).

Antagonism of Neuromuscular Blockade

ANTAGONISTS (SUCH AS NEOSTIGMINE) SHOULD NOT BE ADMINISTERED PRIOR TO THE DEMONSTRATION OF SOME SPONTANEOUS RECOVERY FROM NEUROMUSCULAR BLOCKADE. THE USE OF A NERVE STIMULATOR TO DOCUMENT RECOVERY AND ANTAGONISM OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED.

Patients should be evaluated for adequate clinical evidence of antagonism, e.g., 5 second head lift, adequate phonation, ventilation, and upper airway maintenance. Ventilation must be supported until no longer required.

Antagonism may be delayed in the presence of debilitation, carcinomatosis, and concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or separately cause respiratory depression. Under such circumstances the management is the same as that of prolonged neuromuscular blockade.

DOSAGE AND ADMINISTRATION

ZEMURON® (rocuronium bromide) INJECTION IS FOR INTRAVENOUS USE ONLY. THIS DRUG SHOULD BE ADMINISTERED BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS FAMILIAR WITH THE USE OF NEUROMUSCULAR BLOCKING AGENTS. INDIVIDUALIZATION OF DOSAGE SHOULD BE CONSIDERED IN EACH CASE (see CLINICAL PHARMACOLOGY - Individualization of Dosage).

The dosage information which follows is derived from studies based upon units of drug per unit of body weight. It is intended to serve as an initial guide to clinicians familiar with other neuromuscular blocking agents to acquire experience with ZEMURON®. The monitoring of twitch response is recommended to evaluate recovery from ZEMURON® and decrease the hazards of overdosage if additional doses are administered (see CLINICAL PHARMACOLOGY - Pharmacodynamics and DOSAGE AND ADMINISTRATION - Maintenance Dosing).

It is recommended that clinicians administering neuromuscular blocking agents such as ZEMURON® employ a peripheral nerve stimulator to monitor drug response, de-termine the need for additional relaxant and adequacy of spontaneous recovery or antagonism.

Rapid Sequence Intubation

In appropriately premedicated and adequately anesthetized patients, ZEMURON® (rocuronium bromide) Injection 0.6 to 1.2 mg/kg will provide excellent or good intubating conditions in most patients in less than 2 minutes (see CLINICAL PHARMACOLOGY - Clinical Trials).

Dose for Tracheal Intubation

The recommended initial dose regardless of anesthetic technique is 0.6 mg/kg. Neuromuscular block sufficient for intubation (>/=80% block) is attained in a median (range) time of 1 (0.4-6) minute(s) and most patients have intubation completed within 2 minutes. Maximum blockade is achieved in most patients in less than 3 minutes. This dose may be expected to provide 31 (15-85) minutes of clinical relaxation under opioid/nitrous oxide/oxygen anesthesia. Under halothane, isoflurane, and enflurane anesthesia, some extension of the period of clinical relaxation should be expected (see PRECAUTIONS - Inhalation Anesthetics).

A lower dose of ZEMURON® (rocuronium bromide) Injection (0.45 mg/kg) may be used. Neuromuscular block sufficient for intubation (>/=80% block) is attained in a median (range) time of 1.3 (0.8-6.2) minute(s) and most patients have intubation completed within 2 minutes. Maximum blockade is achieved in most patients in less than 4 minutes. This dose may be expected to provide 22 (12-31) minutes of clinical relaxation under opioid/nitrous oxide/oxygen anesthesia. Patients receiving this low dose of 0.45 mg/kg who achieve less than 90% block (about 16% of these patients) may have a more rapid time to 25% recovery, 12 to 15 minutes.

Should there be reason for the selection of a larger bolus dose in individual patients, initial doses of 0.9 or 1.2 mg/kg can be administered during surgery under opioid/nitrous oxide/oxygen anesthesia without adverse effects to the cardiovascular system. These doses will provide >/=80% block in most patients in less than 2 minutes, with maximum blockade occurring in most patients in less than 3 minutes. Doses of 0.9 and 1.2 mg/kg may be expected to provide 58 (27-111) and 67 (38-160) minutes, respectively, of clinical relaxation under opioid/nitrous oxide/oxygen anesthesia.

Maintenance Dosing

Maintenance doses of 0.1, 0.15, and 0.2 mg/kg ZEMURON® (rocuronium bromide) Injection, administered at 25% recovery of control T_1 (defined as 3 twitches of train-of-four), provide a median (range) of 12 (2-31), 17 (6-50) and 24 (7-69) minutes of clinical duration under opioid/nitrous oxide/oxygen anesthesia (see CLINICAL PHARMACOLOGY - Pharmacodynamics). In all cases, dosing should be guided based on the clinical duration following initial dose or prior maintenance dose and not administered until recovery of neuromuscular function is evident. A clinically insignificant cumulation of effect with repetitive maintenance dosing has been observed (see CLINICAL PHARMACOLOGY - Pharmacodynamics).

Use by Continuous Infusion

Infusion at an initial rate of 10 to 12 mcg/kg/min of ZEMURON® (rocuronium bromide) Injection should be initiated only after early evidence of spontaneous recovery from an intubating dose. Due to rapid redistribution (see CLINICAL PHARMACOLOGY - Pharmacokinetics) and the associated rapid spontaneous recovery, initiation of the infusion after substantial return of neuromuscular function (more than 10% of control T_1), may necessitate additional bolus doses to maintain adequate block for surgery.

Upon reaching the desired level of neuromuscular block, the infusion of ZEMURON® must be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as monitored with the use of a peripheral nerve stimulator. In clinical trials, infusion rates have ranged from 4 to 16 mcg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane, may enhance the neuromuscular blocking action of nondepolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to reduce the rate of infusion by 30 to 50%, at 45 to 60 minutes after the intubating dose.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of ZEMURON® infusion may be expected to proceed at rates comparable to that follow-ing comparable total doses administered by repetitive bolus injections (see CLINICAL PHARMACOLOGY - Pharmacodynamics).

Infusion solutions of ZEMURON® can be prepared by mixing ZEMURON® with an appropriate infusion solution such as 5% glucose in water or lactated Ringers (see DOSAGE AND ADMINISTRATION - Compatibility). Unused portions of infusion solutions should be discarded.

Infusion rates of ZEMURON® can be individualized for each patient using the following tables as guidelines:

TABLE 6: Infusion Rates Using ZEMURON® Injection (0.5 mg/mL) *

Patient Weight		Drug Delivery Rate (mcg/kg/min)									
(kg)	(lbs)	4	5	6	7	8	9	10	12	14	16
		Infusion Delivery Rate (mL/hr)									
10	22	4.8	6.0	7.2	8.4	9.6	10.8	12.0	14.4	16.8	19.2
15	33	7.2	9.0	10.8	12.6	14.4	16.2	18.0	21.6	25.2	28.8
20	44	9.6	12.0	14.4	16.8	19.2	21.6	24.0	28.8	33.6	38.4
25	55	12.0	15.0	18.0	21.0	24.0	27.0	30.0	36.0	42.0	48.0
35	77	16.8	21.0	25.2	29.4	33.6	37.8	42.0	50.4	58.8	67.2
50	110	24.0	30.0	36.0	42.0	48.0	54.0	60.0	72.0	84.0	96.0
60	132	28.8	36.0	43.2	50.4	57.6	64.8	72.0	86.4	100.8	115.2
70	154	33.6	42.0	50.4	58.8	67.2	75.6	84.0	100.8	117.6	134.4
80	176	38.4	48.0	57.6	67.2	76.8	86.4	96.0	115.2	134.4	153.6
90	198	43.2	54.0	64.8	75.6	86.4	97.2	108.0	129.6	151.2	172.8
100	220	48.0	60.0	72.0	84.0	96.0	108.0	120.0	144.0	168.0	192.0

TABLE 7: Infusion Rates Using ZEMURON® Injection (1 mg/mL) **

Patient Weight		Drug Delivery Rate (mcg/kg/min)									
(kg)	(lbs)	4	5	6	7	8	9	10	12	14	16
		Infusion Delivery Rate (mL/hr)									
10	22	2.4	3.0	3.6	4.2	4.8	5.4	6.0	7.2	8.4	9.6
15	33	3.6	4.5	5.4	6.3	7.2	8.1	9.0	10.8	12.6	14.4
20	44	4.8	6.0	7.2	8.4	9.6	10.8	12.0	14.4	16.8	19.2
25	55	6.0	7.5	9.0	10.5	12.0	13.5	15.0	18.0	21.0	24.0
35	77	8.4	10.5	12.6	14.7	16.8	18.9	21.0	25.2	29.4	33.6
50	110	12.0	15.0	18.0	21.0	24.0	27.0	30.0	36.0	42.0	48.0
60	132	14.4	18.0	21.6	25.2	28.8	32.4	36.0	43.2	50.4	57.6
70	154	16.8	21.0	25.2	29.4	33.6	37.8	42.0	50.4	58.8	67.2
80	176	19.2	24.0	28.8	33.6	38.4	43.2	48.0	57.6	67.2	76.8
90	198	21.6	27.0	32.4	37.8	43.2	48.6	54.0	64.8	75.6	86.4
100	220	24.0	30.0	36.0	42.0	48.0	54.0	60.0	72.0	84.0	96.0

TABLE 8: Infusion Rates Using ZEMURON® Injection (5 mg/mL) ***

Patient Weight		Drug Delivery Rate (mcg/kg/min)									
(kg)	(lbs)	4	5	6	7	8	9	10	12	14	16
		Infusion Delivery Rate (mL/hr)									
10	22	0.5	0.6	0.7	0.8	1.0	1.1	1.2	1.4	1.7	1.9
15	33	0.7	0.9	1.1	1.3	1.4	1.6	1.8	2.2	2.5	2.9
20	44	1.0	1.2	1.4	1.7	1.9	2.2	2.4	2.9	3.4	3.8
25	55	1.2	1.5	1.8	2.1	2.4	2.7	3.0	3.6	4.2	4.8
35	77	1.7	2.1	2.5	2.9	3.4	3.8	4.2	5.0	5.9	6.7
50	110	2.4	3.0	3.6	4.2	4.8	5.4	6.0	7.2	8.4	9.6
60	132	2.9	3.6	4.3	5.0	5.8	6.5	7.2	8.6	10.1	11.5
70	154	3.4	4.2	5.0	5.9	6.7	7.6	8.4	10.1	11.8	13.4
80	176	3.8	4.8	5.8	6.7	7.7	8.6	9.6	11.5	13.4	15.4
90	198	4.3	5.4	6.5	7.6	8.6	9.7	10.8	13.0	15.1	17.3
100	220	4.8	6.0	7.2	8.4	9.6	10.8	12.0	14.4	16.8	19.2

* 50 mg ZEMURON® in 100 mL solution
** 100 mg ZEMURON® in 100 mL solution
*** 500 mg ZEMURON® in 100 mL solution

Infusion solutions should be used within 24 hours of mixing. Unused portions of infusion solutions should be discarded.

Use in Pediatrics

Initial doses of 0.6 mg/kg in pediatric patients under halothane anesthesia produce excellent to good intubating conditions within 1 minute. The median (range) time to maximum block was 1 (0.5-3.3) minute(s). This dose will provide a median (range) time of clinical relaxation of 41 (24-68) minutes in 3 month to 1 year-old infants and 27 (17-41) minutes in 1 to 12 year-old pediatric patients. Maintenance doses of 0.075 to 0.125 mg/kg, administered upon return of T_1 to 25% of control, provide clinical relaxation for 7 to 10 minutes.

Spontaneous recovery proceeds at approximately the same rate in infants (3 months to 1 year) as in adults, but is more rapid in pediatric patients (1 to 12 years) than adults (see CLINICAL PHARMACOLOGY - Pharmacodynamics). A continuous infusion of ZEMURON® (rocuronium bromide) Injection initiated at a

rate of 12 mcg/kg/min upon return of T_1 to 10% of control (one twitch present in the train-of-four), may also be used to maintain neuromuscular blockade in pediatric patients. The infusion of ZEMURON® must be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as monitored with the use of a peripheral nerve stimulator. Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of ZEMURON® infusion may be expected to proceed at rates comparable to that following similar total exposure to single bolus doses (see CLINICAL PHARMACOLOGY - Pharmacodynamics).

Use in Obese Patients

An analysis across all US controlled clinical studies indicates that the pharmacodynamics of ZEMURON® (rocuronium bromide) Injection are not different between obese and non-obese patients when dosed based upon their actual body weight.

Use in Geriatrics

Geriatric patients (>/=65 years) exhibited a slightly prolonged median (range) clinical duration of 46 (22-73), 62 (49-75), and 94 (64-138) minutes under opioid/nitrous oxide/oxygen anesthesia following doses of 0.6, 0.9, and 1.2 mg/kg, respectively. Maintenance doses of 0.1 and 0.15 mg/kg ZEMURON® (rocuronium bromide) Injection, administered at 25% recovery of T_1 , provide approximately 13 and 33 minutes of clinical duration under opioid/nitrous oxide/oxygen anesthesia. The median (range) rate of spontaneous recovery of T_1 from 25 to 75% in geriatric patients is 17 (7-56) minutes which is not different from that in other adults (see CLINICAL PHARMACOLOGY - Pharmacokinetics and CLINICAL PHARMACOLOGY - Pharmacodynamics).

Compatibility

Diluent Compatibility

ZEMURON® (rocuronium bromide) Injection is compatible in solution with:

0.9% NaCl solution	sterile water for injection
5% glucose in water	lactated Ringers
5% glucose in saline	

ZEMURON® is compatible in the above solutions at concentrations up to 5 mg/mL for 24 hours at room temperature in plastic bags, glass bottles, and plastic syringe pumps.

Drug Admixture Incompatibility

ZEMURON® is physically incompatible when mixed with the following drugs:

amphotericin	hydrocortisone sodium succinate
amoxicillin	insulin
azathioprine	intralipid

cefazolin	ketorolac
cloxacillin	lorazepam
dexamethasone	methohexital
diazepam	methylprednisolone
erythromycin	thiopental
famotidine	trimethoprim
furosemide	vancomycin

Parenteral drug products should be inspected visually for particulate matter and clarity prior to administration whenever solution and container permit. Do not use solution if particulate matter is present.

Safety and Handling

There is no specific work exposure limit for ZEMURON® (rocuronium bromide) Injection. In case of eye contact, flush with water for at least 10 minutes.

HOW SUPPLIED

ZEMURON® (rocuronium bromide) Injection is available in the following:

ZEMURON® 5 mL multiple dose vials containing 50 mg rocuronium bromide injection (10 mg/mL)

Box of 10　　NDC 0052-0450-15

ZEMURON® 10 mL multiple dose vials containing 100 mg rocuronium bromide injection (10 mg/mL)

Box of 10　　NDC 0052-0450-16

The packaging of this product contains no natural rubber (latex).

Storage

ZEMURON® (rocuronium bromide) Injection should be stored in a refrigerator, 2-8°C (36-46°F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use ZEMURON® within 60 days. Use opened vials of ZEMURON® within 30 days.

1.6　外国における使用状況に関する資料

1.6.2.2　1.6.2.2　米国の添付文書（和訳の概要）

表 1.6-2に米国の添付文書の和訳の概要を示した.

表 1.6-2　米国の添付文書の和訳の概要

国　　名	米国
販　売　名	Zemuron
剤 型・含 量	注射剤 5 mL バイアル中 50 mg の臭化ロクロニウムを含有（10 mg/mL）。 10 mL バイアル中 100 mg の臭化ロクロニウムを含有（10 mg/mL）。
効 能・効 果	全身麻酔の補助として，急速導入並びに通常の気管内挿管を容易にし，手術時または人工呼吸時の骨格筋弛緩を生じさせる目的で本剤を使用する。
用 法・用 量	**用法** **本剤の使用は静脈内投与に限られる。筋弛緩薬の使用に明るく経験を積んだ医師により，または監督の元に本剤を投与すること。個々の症例を考慮して用量を定めること。** **用量** **急速導入**：適切に前投薬を投与され，十分な麻酔状態にある患者においては，本剤 0.6～1.2 mg/kg 投与 2 分後までに，大部分の患者で挿管状態が優秀または良好となる。 **気管内挿管用量**：麻酔方法に関係なく本剤の推奨初回量は 0.6 mg/kg である。低用量（0.45 mg/kg）を使用してもよい。高用量の投与を選択する理由のある場合，心血管系の副作用を伴わずに 0.9 又は 1.2 mg/kg を初回量として投与可能である。 **維持用量**：対照となる T_1収縮の 25%回復時に維持用量 0.1，0.15 又は 0.2 mg/kg を投与した場合作用持続時間はそれぞれ 12，17，24 分であった。臨床上問題とはならない程度の蓄積性が認められた。 **持続注入による使用**：挿管用量からの筋弛緩が自然回復し始めた時点で，初期速度 0.01～0.012 mg/kg/min で注入を始める。筋弛緩が目的のレベルに達した後，患者の筋収縮をモニターし注入速度を調節する。臨床試験において注入速度は 0.004～0.016 mg/kg/min の範囲であった。エンフルランまたはイソフルラン濃度が定常状態である場合，挿管のための投与 45～60 分後に 30～50%の注入速度の減量が必要かもしれない。 **小児への使用**：ハロタン麻酔下で 0.6 mg/kg の投与で 1 分以内に挿管スコアは良好以上になった。 **肥満患者への使用**：米国で行われた全ての臨床試験において，肥満患者と非肥満患者間での薬力学上の差は認められなかった。 **高齢者への使用**：0.6，0.9，1.2 mg/kg の投与量で作用持続時間がわずかに延長した。
使用上の注意	**禁忌** 本剤は，臭化ロクロニウムに対する過敏症の既往歴がある患者には禁忌である。 **警告** **本剤は，その作用及び使用時に生じうる合併症について熟知した経験を積んだ医師により，あるいはその監督下において，慎重に調節された用量を投与すること。挿管，人工呼吸及び酸素療法の設備，及び拮抗薬が直ちに利用できない場合には投与しないこと。本剤のような筋弛緩薬を使用する医師には，薬物の作用，追加投与の必要性，自然回復の過程，または拮抗薬の必要性をモニターするため末梢神経刺激装置の設置が推奨される。** **本剤の意識，痛覚閾値または脳機能に対する作用は不明であるため，適切な麻酔または鎮静下で使用すること。** 重症筋無力症又は筋無力性(Eaton-Lambert)症候群の患者では，少量の非脱分極性筋弛緩薬で十分な効果を示すことがある。少量の試験的用量で末梢神経刺激装置を使用し，筋弛緩薬投与に対する反応をモニターすることが有用である。 本剤は酸性であるため，バルビツール酸溶液などのアルカリ性溶液と同一シリンジ中で混合せず，また，同一の針を用いた持続注入による同時投与を行わないこと。 **使用上の注意** **集中治療病棟（ICU）での長時間使用**：本剤の ICU 内での長時間使用に関する試験は行われていない。他の非脱分極性筋弛緩薬と同様に，ICU での本剤の長時間使用時には，まれに見かけ上の耐性が生じることがある。 **投与時及び回復時には，神経刺激装置を用いて神経筋伝達を継続してモニターすること。神経刺激に対する明らかな反応（４連反応で単収縮が見られる）があるまで，本剤または他の筋弛緩薬の追加投与を行わないこと。** **妊婦及び産婦**：本剤の帝王切開における使用は少数の患者でしか試験されていない。帝王切開患者での急速導入は推奨できない。 **肝臓病**：本剤は主として肝臓により排泄されるため，臨床的に明らかな肝障害患者に対しては慎重に使用すること。定常状態のイソフルラン麻酔下での少数の肝障害患者における本剤 0.6 mg/kg 投与後の臨床的作用持続時間は正常肝機能患者と比較してやや延長した。

1.6　外国における使用状況に関する資料

使用上の注意 （続き）	**腎不全**：腎臓は本剤の主要排泄経路では無いので，通常の用量が妥当である。腎移植手術又は透析準備のための腎血流側路形成手術を受ける患者において本剤 0.6 mg/kg の効果を評価した時，作用発現時間は，腎障害のない患者と比べて差はなかった。作用持続時間は正常患者と比較して長いとは判断されなかったが，変動範囲は大きかった。腎障害患者の回復時間は正常患者と同等であった。 **悪性高熱症**：悪性高熱症ブタを用いた試験で本剤は悪性高熱症を誘発しなかったが，本剤は常に他剤と併用され，また麻酔時には既知の誘発因子が存在しない場合でも悪性高熱症が起こり得るため，医師は麻酔開始に当たっては予め悪性高熱症の初期徴候，確定診断法及び治療法を熟知していること。 **循環時間の変化**：心血管系疾患，高齢などの循環時間延長を伴う状態では，本剤の作用発現が延長することがある。本剤は高用量で持続時間を延長させるため，通例こうした患者では発現時間を短縮させるため，初回量を増量すべきではない。可能であれば，作用発現までに時間をかけること。 **他剤との相互作用**：本剤をサクシニルコリン投与後に投与する場合，サクシニルコリンからの回復が観察されるまでは投与しないこと。本剤の投与前後に他の非脱分極性筋弛緩薬を投与する臨床試験は行われていない。他の非脱分極性筋弛緩薬を後から投与した場合には相互作用がみられている。 吸入麻酔薬：他の筋弛緩薬において，吸入麻酔薬の使用により，エンフルラン＞イソフルラン＞ハロタンの順で神経筋遮断作用を増強させることが報告されている。 イソフルラン及びエンフルランは，本剤の初回量及び維持用量の持続時間を延長させることがあり，バランス麻酔（オピオイド/亜酸化窒素/酸素）と比較して平均注入速度を 40%減少させることがある。なお，拮抗薬による本剤の神経筋遮断からの回復に及ぼす麻酔方法の影響はわずかであった。 静脈麻酔薬：麻酔導入及び維持のためのプロポフォール使用により，推奨用量での本剤の持続時間及び自然回復時間は変化しない。 抗痙攣薬：他の非脱分極性筋弛緩薬と同様に，カルバマゼピン，フェニトインなどの抗痙攣薬を長期投与されている患者に本剤を投与する場合には，非脱分極性筋弛緩薬に対する抵抗性のために，臨床的持続時間の短縮がみられ、注入速度の増加を要することがある。 抗生物質：本剤等の非脱分極性筋弛緩薬の作用を増強させる可能性のある薬物として，ある種の抗生物質（アミノグリコシド類，バンコマイシン，テトラサイクリン類，バシトラシン，ポリミキシン類，コリスチン，コリスチメテートナトリウムなど）がある。これらの抗生物質を本剤と併用する場合は，神経筋遮断の延長が生じる可能性を考慮すること。 その他：他の筋弛緩薬で回復期間にキニジンを投与した場合，再発性麻痺が起こる可能性がある。本剤についてもこの可能性を考慮すること。 本剤の作用は代謝性アシドーシス及びアルカローシスにおいて著明に増強されるが，呼吸性アルカローシスにおいては減弱する。また，他の薬物に関する経験から急性（下痢など）又は慢性（副腎皮質不全など）の電解質異常が神経筋遮断を変化させることが推定される。妊娠中毒症へ投与されるマグネシウム塩は，神経筋遮断を増強させる可能性がある。 ヒトにおいては，血管外へ投与されると局所的炎症につながるため，直ちに投与または注入を中止し，別の静脈で投与を再開すること。 **薬物／臨床検査との相互作用**：知られているものはない。 **発癌性，変異原性及び受胎能**：発癌性試験または受胎能についての動物試験は行っていない。変異原性試験（Ames テスト，動物細胞での染色体異常及び小核試験）より，本剤の変異原性は認められなかった。 **妊娠カテゴリーC**：妊娠ラット及びウサギを用いた発生毒性試験を行った。高用量の投与により本剤の薬効による急性の呼吸障害が生じたが，これらの動物種において催奇形性は観察されなかった。また，高用量投与ラットにおいて発生後期の胎児死亡率が増加したが，おそらく酸素欠乏によると思われる。ヒトでは挿管患者は直ちに人工呼吸を行い胎児の低酸素症を防ぐので，この所見はヒトとの関連性はないと思われる。しかし妊婦において適切な臨床試験は行われていないので，妊婦に対しては，有用性が胎児に対する危険性を上回る場合にのみ本剤を使用すべきである。 **小児への使用**：3 か月未満及び 14 歳以上の小児への本剤の使用についての試験は行なわれていない。 **高齢者への使用**：高齢者の薬物動態プロフィルは外科的手術を受けた成人患者と類似していた。作用発現時間及び持続時間は高齢者でわずかに延長していた。 **副作用**：副作用頻度が 1%以上のものはなかった。副作用頻度が 1%未満のものは以下のとおりである。 心・血管障害：　不整脈，心電図異常，頻脈 消化管障害：　嘔気，嘔吐 呼吸器系障害：　喘息（気管支痙攣，喘鳴，ラ音），しゃっくり 皮膚・付属器障害：発赤，注射部位の浮腫，そう痒症 **過量投与**：本薬の過量投与例は報告されていない。神経筋遮断薬の過量投与は手術および麻酔に要する時間を越える筋弛緩作用を発現させる。初期投与では人工呼吸下で正常な神経筋機能の回復を確保しながら投与を行うこと。神経筋遮断作用からの回復を一度確認した後は，抗コリンエステラーゼ薬（ネオスチグミンあるいはエドロフォニウム等）の投与により回復を促進することができる。 **拮抗薬**：拮抗薬（ネオスチグミン等）は，神経筋弛緩からの回復の兆候が認められる前に投与しないこと。神経筋遮断からの回復と拮抗作用を記録するため，神経刺激装置の使用が推奨される。

C O N F I D E N T I A L

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