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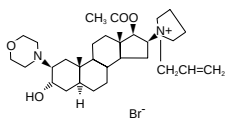
Injection ZEMURON® (rocuronium bromide)

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 anesthesia 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.

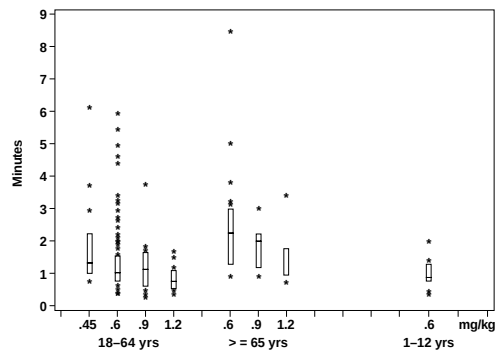


FIGURE 1: Time to ≥80% Block *vs.* Initial Dose of ZEMURON® by Age Group (Median, 25th and 75th percentile, and individual values)

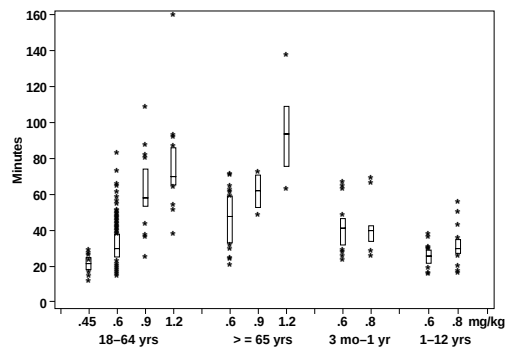


FIGURE 2: Duration of Clinical Effect *vs.* Initial Dose of ZEMURON® by Age Group (Median, 25th and 75th percentile, and individual values)

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).

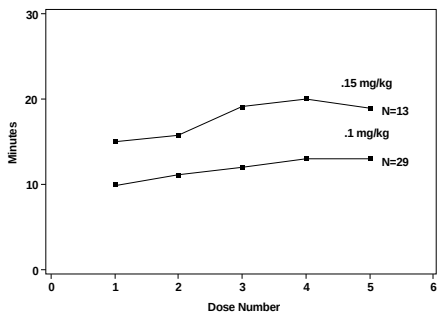


FIGURE 3: Duration of Clinical Effect *vs.* Number of ZEMURON® Maintenance Doses, by Dose

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 ($4 \times ED_{95}$) 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 the 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 Cl 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.

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 patient's 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 up-regulation 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-controll ed 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, determine 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 following 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

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

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

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

Use within 24 hours of mixing with the above solutions.

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.

℞ **only**

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Organon Inc.
West Orange, NJ 07052

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