Zemuron advertisement.

[s.l.]: [s.n.], 1996

THE LEADING NEUROMUSCULAR BLOCKING AGENT ON THE MARKET[1]

FOR A FAST, SURE START... TAKE CONTROL WITH ZEMURON™

ZEMURON™ provides advantages at both critical stages of anesthesia...

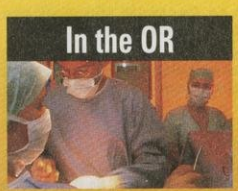
Onset

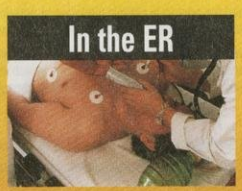
- Only rapid onset* nondepolarizing neuromuscular blocking agent[2]
- Indicated for rapid-sequence intubation†‡[2]
- Cardiovascular§ stability, low risk of histamine release‖¶[2]

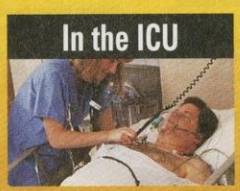
Reversal

- Dose-responsive duration[2]
- Recovery in under 5 minutes after neostigmine or edrophonium administration once spontaneous recovery has reached 25% of T_1 with train-of-four monitoring[2]

...which makes ZEMURON™ right at every site:







Please see following page for brief summary of full prescribing information.

* Under opioid/nitrous oxide/oxygen anesthesia in adult patients: At the initial recommended dose of 0.6 mg/kg, the median time to ≥80% blockade is 60 seconds with a range of 0.4 to 6.0 minutes, providing a median clinical duration of 31 minutes with a range of 15 to 85 minutes. At 0.45 mg/kg, the median time to ≥80% blockade is 78 seconds with a range of 0.8 to 6.2 minutes, providing a median clinical duration of 22 minutes with a range of 12 to 31 minutes. At 0.9 mg/kg, the median time to ≥80% blockade is 66 seconds with a range of 0.3 to 3.8 minutes, providing a median clinical duration of 58 minutes with a range of 27 to 111 minutes.

† At higher dosage range (0.6 mg/kg to 1.2 mg/kg) in most patients who are appropriately premedicated and adequately anesthetized.

‡ ZEMURON™ is not recommended for rapid-sequence induction in cesarean section patients.

§ Clinically significant changes in heart rate or blood pressure unlikely; heart rate changes (≥30%) occurred in 0% to 2% of geriatric and other adult patients. Tachycardia (≥30%) occurred in 12 of 127 children. Since ZEMURON™ may be associated with increased pulmonary vascular resistance, caution is appropriate in patients with pulmonary hypertension or valvular heart disease.

‖ Histamine release unlikely at doses up to 4 x ED_{95}.

¶ Signs of histamine release were observed in 0.8% of 1137 patients in clinical trials.

Injection

ZEMURON™

(rocuronium bromide)

Fast start...smooth finish

Injection

ZEMURON™
(rocuronium bromide)

Before prescribing, please consult full prescribing information, a summary of which follows:

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.

PRECAUTIONS
Long-term Use in I.C.U.: ZEMURON™ (rocuronium bromide) Injection has not been studied for long-term use in the I.C.U. As with other nondepolarizing neuromuscular blocking drugs, apparent tolerance to ZEMURON™ may develop rarely during chronic administration in the I.C.U. 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 I.C.U. 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 Trials subsection of CLINICAL PHARMACOLOGY).

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 Pharmacokinetics subsection of CLINICAL PHARMACOLOGY). 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 19–61 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 1–2 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 Pharmacokinetics subsection of CLINICAL PHARMACOLOGY).

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™ (rocuronium bromide) Injection 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 0.57–0.85 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™ (rocuronium bromide) Injection.

Anticonvulsants: In 2 of 4 patients receiving chronic anticonvulsant therapy apparent resistance to the effects of ZEMURON™ (rocuronium bromide) Injection 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 INDIVIDUALIZATION OF DOSAGE).

Antibiotics: Drugs which may enhance the neuromuscular blocking action of nondepolarizing agents such as ZEMURON™ (rocuronium bromide) Injection 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™ (rocuronium bromide) Injection.

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 Category B: A teratogenicity study has been conducted in rats using intravenously administered doses of ZEMURON™ (rocuronium bromide) Injection approximating the clinical dose in humans (0.3 mg/kg). No teratogenic effects were observed in this study. There are no adequate and well-controlled studies in pregnant women. ZEMURON™ 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.

ADVERSE REACTIONS
Clinical studies in the U.S. (n=1,137) and Europe (n=1,394) totaled 2,531 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 U.S. clinical studies provide the basis for calculation of adverse reaction rates. The following adverse experiences were reported in patients administered ZEMURON™ Injection (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 U.S. studies (0.1% and 0.1%). Changes in heart rate and blood pressure were defined differently from the U.S. 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 rare reports of allergic reactions (anaphylactic and anaphylactoid) with ZEMURON™ (rocuronium bromide) Injection.

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 sec 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.

HOW SUPPLIED
ZEMURON™ (rocuronium bromide) Injection is available in the following forms:

ZEMURON™ 5 mL multiple dose vials containing 50 mg rocuronium bromide injection (10 mg/mL)
Boxes of 10 — NDC No. 0052-0450-15

ZEMURON™ 10 mL multiple dose vials containing 100 mg rocuronium bromide injection (10 mg/mL)
Boxes of 10 — NDC No. 0052-0450-16

Storage: ZEMURON™ (rocuronium bromide) Injection should be stored under refrigeration, 2° to 8°C (36° to 46°F). DO NOT FREEZE. Upon removal from refrigeration to room temperature storage conditions (25°C/77°F), use ℞ **only** ZEMURON™ within 60 days. Use opened vials of ZEMURON™ within 30 days.

5310153 3/98

REFERENCES

1. National Prescription Audit Plus™. Therapeutic Class Report. Plymouth Meeting, Pa: IMS America; January 1998.
2. ZEMURON™ (rocuronium bromide) Injection prescribing information.

Organon
ORGANON INC.
WEST ORANGE
NEW JERSEY 07052

A Leader in the Research and Development of Neuromuscular Blocking Agents

ORG-43931 PRINTED IN USA MARCH 1998