

NDA 18-776/S-023

Organon Inc.
375 Mt. Pleasant Avenue
West Orange, NJ 07052

AUG 24 2000

Attention: Don L. Glassner
Manager, Regulatory Affairs

Dear Ms. Glassner:

Please refer to your supplemental new drug application dated September 5, 1997, received September 9, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Norcuran (vecuronium bromide) for Injection.

This supplemental new drug application provides for revised labeling in accordance with the Federal Register published on December 13, 1994, which revised the "Pediatric Use" subsection of the labeling for human prescription drugs.

We have completed the review of this supplemental application and it is approved effective on the date of this letter with the following minor editorial revision.

Remove the references from the package insert at the next printing.

The final printed labeling (FPL) must be identical, and include the minor editorial revisions indicated, to the submitted draft labeling (package insert submitted September 5, 1997).

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed to each application. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format - NDAs (January 1999). For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 18-776/S-023." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a 'Dear Health Care Practitioner' letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

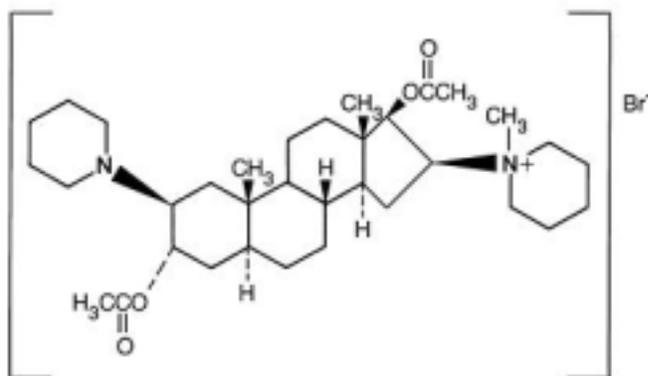
NORCURON®

(vecuronium bromide) for Injection

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

DESCRIPTION

NORCURON® (vecuronium bromide) for Injection is a nondepolarizing neuromuscular blocking agent of intermediate duration, chemically designated as piperidinium, 1-[(2 β , 3 α , 5 α , 16 β , 17 β)-3, 17-bis(acetyloxy)-2-(1-piperidiny) androstan-16-yl]-1-methyl-, bromide. The structural formula is:



Its chemical formula is C₃₄H₅₇BrN₂O₄ with molecular weight 637.74.

Norcuron® is supplied as a sterile nonpyrogenic freeze-dried buffered cake of very fine microscopic crystalline particles for intravenous injection only. Each 10 mL vial contains 10 mg vecuronium bromide, 20.75 mg citric acid anhydrous, 16.25 mg sodium phosphate dibasic anhydrous, 97 mg mannitol (to adjust tonicity), sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4. Each 20 mL vial contains 20 mg of vecuronium bromide, 41.5 mg citric acid anhydrous, 32.5 mg sodium phosphate dibasic anhydrous, 194 mg mannitol (to adjust tonicity), sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4. Bacteriostatic water for injection, USP, when supplied, contains 0.9% w/v BENZYL ALCOHOL, WHICH IS NOT FOR USE IN NEWBORNS.

CLINICAL PHARMACOLOGY

Norcuron® (vecuronium bromide) for Injection is a nondepolarizing neuromuscular blocking agent possessing all of the characteristic pharmacological actions of this class of drugs (curariform). It acts by competing for cholinergic receptors at the motor end-plate. The antagonism to acetylcholine is inhibited and neuromuscular block is reversed by acetylcholinesterase inhibitors such as neostigmine, edrophonium, and pyridostigmine. Norcuron® is about $\frac{1}{3}$ more potent than pancuronium; the duration of

neuromuscular blockade produced by Norcuron® is shorter than that of pancuronium at initially equipotent doses. The time to onset of paralysis decreases and the duration of maximum effect increases with increasing Norcuron® doses. The use of a peripheral nerve stimulator is recommended in assessing the degree of muscular relaxation with all neuromuscular blocking drugs. The ED₉₀ (dose required to produce 90% suppression of the muscle twitch response with balanced anesthesia) has averaged 0.057 mg/kg (0.049 to 0.062 mg/kg in various studies). An initial Norcuron® dose of 0.08 to 0.10 mg/kg generally produces first depression of twitch in approximately 1 minute, good or excellent intubation conditions within 2.5 to 3 minutes, and maximum neuromuscular blockade within 3 to 5 minutes of injection in most patients. Under balanced anesthesia, the time to recovery to 25% of control (clinical duration) is approximately 25 to 40 minutes after injection and recovery is usually 95% complete approximately 45-65 minutes after injection of intubating dose. The neuromuscular blocking action of Norcuron® is slightly enhanced in the presence of potent inhalation anesthetics. If Norcuron® is first administered more than 5 minutes after the start of the inhalation of enflurane, isoflurane, or halothane, or when steady state has been achieved, the intubating dose of Norcuron® may be decreased by approximately 15% (see **DOSAGE AND ADMINISTRATION** section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Norcuron®, the administration of Norcuron® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other nondepolarizing neuromuscular blocking agents on the activity of Norcuron® has not been studied (see **Drug Interactions**).

Repeated administration of maintenance doses of Norcuron® has little or no cumulative effect on the duration of neuromuscular blockade. Therefore, repeat doses can be administered at relatively regular intervals with predictable results. After an initial dose of 0.08 to 0.10 mg/kg under balanced anesthesia, the first maintenance dose (suggested maintenance dose is 0.010 to 0.015 mg/kg) is generally required within 25 to 40 minutes; subsequent maintenance doses, if required, may be administered at approximately 12 to 15 minute intervals. Halothane anesthesia increases the clinical duration of the maintenance dose only slightly. Under enflurane a maintenance dose of 0.010 mg/kg is approximately equal to 0.015 mg/kg dose under balanced anesthesia.

The recovery index (time from 25% to 75% recovery) is approximately 15-25 minutes under balanced or halothane anesthesia. When recovery from Norcuron® neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by Norcuron® is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate. Rapid recovery is a finding consistent with Norcuron® short elimination half-life, although there have been occasional reports of prolonged neuromuscular blockade in patients in the intensive care unit (See **PRECAUTIONS**).

The administration of clinical doses of Norcuron® is not characterized by laboratory or clinical signs of chemically mediated histamine release. This does not preclude the possibility of rare hypersensitivity reactions (See ADVERSE REACTIONS).

Pharmacokinetics: At clinical doses of 0.04-0.10 mg/kg, 60-80% of Norcuron® is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025-0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65-75 minutes in healthy surgical patients and in renal failure patients undergoing transplant surgery.

In late pregnancy, elimination half-life may be shortened to approximately 35-40 minutes. The volume of distribution at steady state is approximately 300-400 mL/kg; systemic rate of clearance is approximately 3-4.5 mL/minute/kg. In man, urine recovery of Norcuron® varies from 3-35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25-50% of a total intravenous dose of vecuronium may be excreted in bile within 42 hours. Only unchanged vecuronium has been detected in human plasma following use during surgery. In addition, one metabolite, 3-desacetyl vecuronium, has been rarely detected in human plasma following prolonged clinical use in the I.C.U. (See **PRECAUTIONS : Long Term Use in I.C.U.**). The 3-desacetyl vecuronium metabolite has been recovered in the urine of some patients in quantities that account for up to 10% of injected dose; 3-desacetyl vecuronium has also been recovered by T-tube in some patients accounting for up to 25% of the injected dose.

This metabolite has been judged by animal screening (dogs and cats) to have 50% or more of the potency of Norcuron®; equipotent doses are of approximately the same duration as Norcuron® in dogs and cats. Biliary excretion accounts for about half the dose of Norcuron® within 7 hours in the anesthetized rat. Circulatory bypass of the liver (cat preparation) prolongs recovery from Norcuron®. Limited data derived from patients with cirrhosis or cholestasis suggests that some measurements of recovery may be doubled in such patients. In patients with renal failure, measurements of recovery do not differ significantly from similar measurements in healthy patients.

Studies involving routine hemodynamic monitoring in good risk surgical patients reveal that the administration of Norcuron® in doses up to three times that needed to produce clinical relaxation (0.15 mg/kg) did not produce clinically significant changes in systolic, diastolic or mean arterial pressure. The heart rate, under similar monitoring, remained unchanged in some studies and was lowered by a mean of up to 8% in other studies. A large dose of 0.28 mg/kg administered during a period of no stimulation, while patients were being prepared for coronary artery bypass grafting, was not associated with alterations in rate-pressure-product or pulmonary capillary wedge pressure. Systemic vascular resistance was lowered slightly and cardiac output was increased insignificantly. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience with use of Norcuron® during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Unlike other nondepolarizing skeletal muscle relaxants, Norcuron® has no clinically significant effects on hemodynamic parameters. Norcuron® will not counteract those

hemodynamic changes or known side effects produced by or associated with anesthetic agents, other drugs or various other factors known to alter hemodynamics.

INDICATIONS AND USAGE

Norcuron® (vecuronium bromide) for Injection is indicated as an adjunct to general anesthesia, to facilitate endotracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

CONTRAINDICATIONS

Norcuron® (vecuronium bromide) for Injection is contraindicated in patients known to have a hypersensitivity to it.

WARNINGS

NORCURON® (vecuronium bromide) for Injection SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSAGE BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND THE POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING ITS USE. THE DRUG SHOULD NOT BE ADMINISTERED UNLESS FACILITIES FOR INTUBATION, ARTIFICIAL RESPIRATION, OXYGEN THERAPY, AND REVERSAL AGENTS ARE IMMEDIATELY AVAILABLE. THE CLINICIAN MUST BE PREPARED TO ASSIST OR CONTROL RESPIRATION. TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER POSSIBLE COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES BY OR UNDER THE SUPERVISION OF EXPERIENCED CLINICIANS WHO ARE FAMILIAR WITH ITS ACTIONS AND WHO ARE FAMILIAR WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES (see **PRECAUTIONS**). In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of Norcuron® 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.

PRECAUTIONS

Renal Failure: Norcuron® (vecuronium bromide) for Injection is well tolerated without clinically significant prolongation of neuromuscular blocking effect in patients with renal failure who have been optimally prepared for surgery by dialysis. Under emergency conditions in anephric patients some prolongation of neuromuscular blockade may occur; therefore, if anephric patients cannot be prepared for non-elective surgery, a lower initial dose of Norcuron® should be considered.

Altered Circulation Time: Conditions associated with slower circulation time in cardiovascular disease, old age, edematous states resulting in increased volume of distribution may contribute to a delay in onset time, therefore, dosage should not be increased.

Hepatic Disease: Experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in Norcuron® (vecuronium bromide) for Injection metabolism and excretion (**see Pharmacokinetics**). Data currently available do not permit dosage recommendations in patients with impaired liver function.

Long-term Use in I.C.U.: In the intensive care unit, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation may be associated with prolonged paralysis and/or skeletal muscle weakness, that may be first noted during attempts to wean such patients from the ventilator. Typically, such patients receive other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalance and diseases which lead to electrolyte imbalance, hypoxic episodes of varying duration, acid-base imbalance and extreme debilitation, any of which may enhance the actions of a neuromuscular blocking agent. Additionally, patients immobilized for extended periods frequently develop symptoms consistent with disuse muscle atrophy. The recovery picture may vary from regaining movement and strength in all muscles to initial recovery of movement of the facial and small muscles of the extremities then to the remaining muscles. In rare cases recovery may be over an extended period of time and may even, on occasion, involve rehabilitation. Therefore, when there is a need for long-term mechanical ventilation, the benefits-to-risk ratio of neuromuscular blockade must be considered.

Continuous infusion or intermittent bolus dosing to support mechanical ventilation, has not been studied sufficiently to support dosage recommendations. IN THE INTENSIVE CARE UNIT, APPROPRIATE MONITORING, WITH THE USE OF A PERIPHERAL NERVE STIMULATOR TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE IS RECOMMENDED TO HELP PRECLUDE POSSIBLE PROLONGATION OF THE BLOCKADE. WHENEVER THE USE OF NORCURON® OR ANY NEUROMUSCULAR BLOCKING AGENT IS CONTEMPLATED IN THE ICU, IT IS RECOMMENDED THAT NEUROMUSCULAR TRANSMISSION BE MONITORED CONTINUOUSLY DURING ADMINISTRATION AND RECOVERY WITH THE HELP OF A NERVE STIMULATOR. ADDITIONAL DOSES OF NORCURON® OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T₁ OR TO THE FIRST TWITCH. IF NO RESPONSE IS ELICITED, INFUSION ADMINISTRATION SHOULD BE DISCONTINUED UNTIL A RESPONSE RETURNS.

Severe Obesity or Neuromuscular Disease: Patients with severe obesity or neuromuscular disease may pose airway and/or ventilatory problems requiring special care before, during and after the use of neuromuscular blocking agents such as Norcuron® (vecuronium bromide) for Injection.

Malignant Hyperthermia: Many drugs used in anesthetic practice are suspected of being capable of triggering a potentially fatal hypermetabolism of skeletal muscle known as malignant hyperthermia. There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not Norcuron® (vecuronium bromide) for Injection is capable of triggering malignant hyperthermia.

C.N.S.: Norcuron® (vecuronium bromide) for Injection has no known effect on consciousness, the pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Drug Interactions: Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Norcuron® (vecuronium bromide) for injection and its duration of action. If succinylcholine is used before Norcuron® the administration of Norcuron® should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Norcuron® may be administered to produce complete neuromuscular block with clinical duration of action of 25-30 minutes (see **CLINICAL PHARMACOLOGY**). The use of Norcuron® before succinylcholine, in order to attenuate some of the side effects of succinylcholine, has not been sufficiently studied.

Other nondepolarizing neuromuscular blocking agents (pancuronium, d-tubocurarine, metocurine, and gallamine) act in the same fashion as does Norcuron®, therefore, these drugs and Norcuron® may manifest an additive effect when used together. There are insufficient data to support concomitant use of Norcuron® and other competitive muscle relaxants in the same patient.

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with Norcuron® (vecuronium bromide) for Injection will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Norcuron® may be the same as with balanced anesthesia unless the inhalational anesthetic has been administered for a sufficient time at a sufficient dose to have reached clinical equilibrium (see **CLINICAL PHARMACOLOGY**).

Antibiotics: Parenteral/intraperitoneal administration of high doses of certain antibiotics may intensify or produce neuromuscular block on their own. The following antibiotics have been associated with various degrees of paralysis: aminoglycosides (such as neomycin, streptomycin, kanamycin, gentamicin, and dihydrostreptomycin); tetracyclines; bacitracin; polymyxin B; colistin; and sodium colistimethate. If these or other newly introduced antibiotics are used in conjunction with Norcuron®, unexpected 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 Norcuron® (vecuronium bromide) for Injection. Norcuron® induced neuromuscular blockade has been counteracted by alkalosis and enhanced by acidosis in experimental animals (cat). Electrolyte imbalance and diseases which lead to electrolyte imbalance, such as adrenal cortical insufficiency, have been shown to alter neuromuscular blockade. Depending on the nature of the imbalance, either enhancement or inhibition may be expected. Magnesium salts, administered for the management of toxemia of pregnancy may enhance the neuromuscular blockade.

Drug/laboratory test interactions: None known

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Pregnancy: Pregnancy Category C: Animal reproduction studies have not been conducted with Norcuron® (vecuronium bromide) for Injection. It is also not known whether Norcuron® can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Norcuron® should be given to a pregnant woman only if clearly needed.

Labor and Delivery: The use of Norcuron® (vecuronium bromide) for Injection in patients undergoing cesarean section has been reported in the literature. Following tracheal intubation with succinylcholine, Norcuron® dosages of 0.04 mg/kg (n=11) and 0.06 to 0.08 mg/kg (n=20) were administered.^{1,2} The umbilical venous plasma concentrations were 11% of maternal concentrations at delivery and mean neonate APGAR scores at 5 minutes were ≥ 9 in both reports.^{1,2} The action of neuromuscular blocking agents may be enhanced by magnesium salts administered for the management of toxemia of pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Norcuron® (vecuronium bromide) for Injection is administered to a nursing woman.

Pediatric Use: Infants under 1 year of age but older than 7 weeks also tested under halothane anesthesia, are moderately more sensitive to Norcuron® (vecuronium bromide) for Injection on a mg/kg basis than adults and take about 1¹/₂ times as long to recover. See **Use in Pediatrics** subsection of **DOSAGE AND ADMINISTRATION** for recommendations for use in pediatric patients 7 weeks to 16 years of age. The safety and effectiveness of Norcuron® in pediatric patients less than 7 weeks of age have not been established.

ADVERSE REACTIONS

The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of the drug's pharmacological action beyond the time period needed. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiration insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with Norcuron® (vecuronium bromide) for Injection as with all curariform drugs. These adverse reactions are managed by manual or mechanical ventilation until recovery is judged adequate. Little or no increase in intensity of blockade or duration of action with Norcuron® is noted from the use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol. See **OVERDOSAGE** for discussion of other drugs used in anesthetic practice which also cause respiratory depression.

Prolonged to profound extensions of paralysis and/or muscle weakness as well as muscle atrophy have been reported after long-term use to support mechanical ventilation in the intensive care unit (see **PRECAUTIONS**). The administration of Norcuron® has been associated with rare instances of hypersensitivity reactions

(bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema); (see also **CLINICAL PHARMACOLOGY**).

OVERDOSAGE

The possibility of iatrogenic overdose can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation.

Excessive doses of Norcuron® (vecuronium bromide) for Injection produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with Norcuron® as with other neuromuscular blockers. This may be manifested by skeletal muscle weakness, decreased respiratory reserve, low tidal volume, or apnea. A peripheral nerve stimulator may be used to assess the degree of residual neuromuscular blockade from other causes of decreased respiratory reserve.

Respiratory depression may be due either wholly or in part to other drugs used during the conduct of general anesthesia such as narcotics, thiobarbiturates and other central nervous system depressants. Under such circumstances the primary treatment is maintenance of a patent airway and manual or mechanical ventilation until complete recovery of normal respiration is assured. Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Norcuron®. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and by adequacy of respiration. A peripheral nerve stimulator may also be used to monitor restoration of twitch height. Failure of prompt reversal (within 30 minutes) may occur in the presence of extreme debilitation, carcinomatosis, and with concomitant use of certain broad spectrum antibiotics, or anesthetic agents and other drugs which enhance neuromuscular blockade or cause respiratory depression of their own. Under such circumstances the management is the same as that of prolonged neuromuscular blockade. Ventilation must be supported by artificial means until the patient has resumed control of his respiration. Prior to the use of reversal agents, reference should be made to the specific package insert of the reversal agent.

The effects of hemodialysis and peritoneal dialysis on plasma levels of Norcuron® and its metabolite are unknown.

DOSAGE AND ADMINISTRATION

Norcuron® (vecuronium bromide) for 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. Dosage must be individualized in each case. The dosage information which follows is derived from studies based upon units of drug per unit of body weight and is intended to serve as a guide only, especially regarding enhancement of neuromuscular blockade of Norcuron® by volatile anesthetics and by prior use of succinylcholine (see **PRECAUTIONS /Drug Interactions**). Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

To obtain maximum clinical benefits of Norcuron® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of Norcuron® is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED₉₀) given as an intravenous bolus injection. This dose can be expected to produce good or excellent non-emergency intubation conditions in 2.5 to 3 minutes after injection. Under balanced anesthesia, clinically required neuromuscular blockade lasts approximately 25-30 minutes, with recovery to 25% of control achieved approximately 25 to 40 minutes after injection and recovery to 95% of control achieved approximately 45-65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of Norcuron® is enhanced. If Norcuron® is first administered more than 5 minutes after the start of inhalation agent or when steady-state has been achieved, the initial Norcuron® dose may be reduced by approximately 15%, i.e., 0.060 to 0.085 mg/kg.

Prior administration of succinylcholine may enhance the neuromuscular blocking effect and duration of action of Norcuron®. If intubation is performed using succinylcholine, a reduction of initial dose of Norcuron® to 0.04-0.06 mg/kg with inhalation anesthesia and 0.05-0.06 mg/kg with balanced anesthesia may be required.

During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of Norcuron® are recommended; after the initial Norcuron® injection, the first maintenance dose will generally be required within 25 to 40 minutes. However, clinical criteria should be used to determine the need for maintenance doses.

Since Norcuron® lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging approximately from 12 to 15 minutes under balanced anesthesia, slightly longer under inhalation agents. (If less frequent administration is desired, higher maintenance doses may be administered.)

Should there be reason for the selection of larger doses in individual patients, initial doses ranging from 0.15 mg/kg up to 0.28 mg/kg have been administered during surgery under halothane anesthesia without ill effects to the cardiovascular system being noted as long as ventilation is properly maintained (see **CLINICAL PHARMACOLOGY**).

Use by Continuous Infusion: After an intubating dose of 80-100 µg/kg, a continuous infusion of 1 µg/kg/min can be initiated approximately 20-40 min later. Infusion of Norcuron® should be initiated only after early evidence of spontaneous recovery from the bolus dose. Long-term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations. (see **PRECAUTIONS**).

The infusion of Norcuron® should be individualized for each patient. The rate of administration should be adjusted according to the patient's twitch response as determined by peripheral nerve stimulation. An initial rate of 1 µg/kg/min is recommended, with the rate of the infusion adjusted thereafter to maintain a 90%

suppression of twitch response. Average infusion rates may range from 0.8 to 1.2 µg/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 25-60 percent, 45-60 min after the intubating dose. Under halothane anesthesia it may not be necessary to reduce the rate of infusion.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Norcuron® infusion may be expected to proceed at rates comparable to that following a single bolus dose (see **CLINICAL PHARMACOLOGY**).

Infusion solutions of Norcuron® can be prepared by mixing Norcuron® with an appropriate infusion solution such as 5% glucose in water, 0.9% NaCl, 5% glucose in saline, or Lactated Ringers. Unused portions of infusion solutions should be discarded.

Infusion rates of Norcuron® can be individualized for each patient using the following table:

Drug Delivery Rate (µg/kg/min)	Infusion Delivery Rate (mL/kg/min)	
	0.1 mg/mL *	0.2 mg/mL **
0.7	0.007	0.0035
0.8	0.008	0.0040
0.9	0.009	0.0045
1.0	0.010	0.0050
1.1	0.011	0.0055
1.2	0.012	0.0060
1.3	0.013	0.0065

* 10 mg of Norcuron® in 100 mL solution

** 20 mg of Norcuron® in 100 mL solution

The following table is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

Amount of Drug µg/kg/min	NORCURON® INFUSION RATE --mL/MIN						
	Patient Weight--kg						
	40	50	60	70	80	90	100
0.7	0.28	0.35	0.42	0.49	0.56	0.63	0.70
0.8	0.32	0.40	0.48	0.56	0.64	0.72	0.80
0.9	0.36	0.45	0.54	0.63	0.72	0.81	0.90
1.0	0.40	0.50	0.60	0.70	0.80	0.90	1.00
1.1	0.44	0.55	0.66	0.77	0.88	0.99	1.10
1.2	0.48	0.60	0.72	0.84	0.96	1.08	1.20
1.3	0.52	0.65	0.78	0.91	1.04	1.17	1.30

NOTE: If a concentration of 0.2 mg/mL is used (20 mg in 100 mL), the rate should be decreased by one-half.

Use in Pediatrics: Pediatric patients (10 to 16 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way. Younger pediatric patients (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more often than adults.

Infants under 1 year of age but older than 7 weeks are moderately more sensitive to Norcuron® (vecuronium bromide) for Injection on a mg/kg basis than adults and take about 1¹/₂ times as long to recover. See also subsection of **PRECAUTIONS** titled **Pediatric Use**. Information presently available does not permit recommendation on usage in pediatric patients less than 7 weeks of age (see **PRECAUTIONS**). There are insufficient data concerning continuous infusion of vecuronium in pediatric patients, therefore, no dosing recommendations can be made.

COMPATIBILITY

Norcuron® is compatible in solution with:

0.9% NaCl solution

5% glucose in water

Sterile water for injection

5% glucose in saline

Lactated Ringers

Use within 24 hours of mixing with the above solutions.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

10 mL vials (10 mg of vecuronium bromide) and 10 mL prefilled syringes of diluent (bacteriostatic water for injection, USP) 22g 1¹/₄ [Prime] needle.

Boxes of 10 NDC No. 0052-0441-60

10 mL vials (10 mg vecuronium bromide) and 10 mL vials of diluent (bacteriostatic water for injection, USP).

Boxes of 10 NDC No. 0052-0441-17

10 mL vials (10 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.

Boxes of 10 NDC No. 0052-0441-15

20 mL vials (20 mg vecuronium bromide) only; DILUENT NOT SUPPLIED.

Boxes of 10 NDC No. 0052-0442-46

STORAGE

15-30°C (59-86°F). Protect from light.

AFTER RECONSTITUTION

- When reconstituted with supplied bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL, WHICH IS NOT INTENDED FOR USE IN NEWBORNS. Use within 5 days. May be stored at room temperature or refrigerated.

- When reconstituted with sterile water for injection or other compatible I.V. solutions: Refrigerate vial. Use within 24 hours. Single use only. Discard unused portion.

Rx only

ORGANON INC.

WEST ORANGE, NEW JERSEY 07052

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