

PRODUCT MONOGRAPH

for

VECURONIUM BROMIDE FOR INJECTION

10 mg/vial, 20 mg/vial

Non Depolarizing Skeletal Neuromuscular Blocking Agent

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Control No. 162432

PRODUCT MONOGRAPH

NAME OF DRUG

VECURONIUM BROMIDE FOR INJECTION

THERAPEUTIC CLASSIFICATION

Non depolarizing Skeletal Neuromuscular Blocking Agent

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

ACTIONS AND CLINICAL PHARMACOLOGY

VECURONIUM BROMIDE FOR INJECTION is a non depolarizing neuromuscular blocking agent of intermediate duration 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 reversed by acetylcholinesterase inhibitors such as neostigmine. Vecuronium bromide is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by vecuronium bromide 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 vecuronium bromide doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

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 vecuronium bromide 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. After the administration of an intubating dose under balanced anesthesia, the clinical duration (time to 25% recovery of the control twitch response) is approximately 25 to 40 minutes, while 95% recovery is usually complete in 45 to 65 minutes. The neuromuscular blocking action of vecuronium bromide is slightly enhanced in the presence of potent inhalation anesthetics. If vecuronium bromide 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 vecuronium bromide may be decreased by approximately 15% (see **DOSAGE AND ADMINISTRATION**).

Prior administration of succinylcholine may enhance the neuromuscular blocking effect of vecuronium bromide and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04 to 0.06 mg/kg of vecuronium bromide will produce complete neuromuscular block with clinical duration of action of 25 to 30 minutes. If succinylcholine is used prior to vecuronium bromide, the administration of vecuronium bromide should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade. The effect of prior use of other non depolarizing neuromuscular blocking agents on the activity of vecuronium bromide has not been studied (see **PRECAUTIONS - Drug Interactions**).

Repeated administration of maintenance doses of vecuronium bromide 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 anesthesia a maintenance dose of 0.010 mg/kg is approximately equal to a 0.015 mg/kg dose under balanced anesthesia. The recovery index (time from 25 to 75% recovery) is approximately 15 to 25 minutes under balanced or halothane anesthesia. When recovery from the vecuronium bromide neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the neuromuscular block produced by vecuronium bromide is readily reversed with various anticholinesterase agents, e.g. pyridostigmine, neostigmine, or edrophonium in conjunction with an anticholinergic agent such as atropine or glycopyrrolate.

Pharmacokinetics

At clinical doses of 0.04 to 0.10 mg/kg, 60 to 80% of vecuronium bromide is usually bound to plasma protein. The distribution half-life following a single intravenous dose (range 0.025 to 0.280 mg/kg) is approximately 4 minutes. Elimination half-life over this same dosage range is approximately 65 to 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 to 40 minutes. The volume of distribution at steady state is approximately 300 to 400 mL/kg; systemic rate of clearance is approximately 3 to 4.5 mL/minute/kg. Urinary recovery of vecuronium bromide varies from 3 to 35% within 24 hours. Data derived from patients requiring insertion of a T-tube in the common bile duct suggests that 25 to 50% of a total intravenous dose of vecuronium may be excreted in the bile within 42 hours. Only unchanged vecuronium bromide has been detected in human plasma following clinical use.

One metabolite, 3-deacetyl vecuronium, has been recovered in the urine of some patients in quantities that account for up to 10% of the injected dose; 3-deacetyl 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 vecuronium bromide. Equipotent doses are of approximately the same duration as vecuronium bromide in dogs and cats. 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 low risk surgical patients reveal that the administration of vecuronium bromide in doses up to 3 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 in a clinically insignificant manner. (The drug has not been studied in patients with hemodynamic dysfunction secondary to cardiac valvular disease). Limited clinical experience (3 patients) with use of vecuronium bromide during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Vecuronium bromide has no clinically significant effect on hemodynamic parameters. Vecuronium bromide 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.

In one clinical study, the duration of action of vecuronium bromide was increased 5-fold during hypothermic cardiopulmonary bypass.

INDICATIONS AND CLINICAL USE

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

VECURONIUM BROMIDE FOR INJECTION is contraindicated in patients known to have a hypersensitivity to it.

In newborn infants (children less than one month of age), benzyl alcohol has been associated with an increased incidence of neurological and other complications which are, sometimes, fatal. Vecuronium bromide, when reconstituted with bacteriostatic water for injection, contains benzyl alcohol and should not be used in newborn infants.

WARNINGS

General

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. A peripheral nerve stimulator should be employed to monitor drug response, need for additional relaxant, and adequacy of spontaneous recovery or anticholinesterase antagonism.

Intensive Care Unit

TO REDUCE THE POSSIBILITY OF PROLONGED NEUROMUSCULAR BLOCKADE AND OTHER COMPLICATIONS THAT MIGHT OCCUR FOLLOWING LONG-TERM USE IN THE ICU, VECURONIUM BROMIDE FOR INJECTION 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 WITH APPROPRIATE PERIPHERAL NERVE STIMULATOR MUSCLE MONITORING TECHNIQUES.

Neuromuscular Disease

In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of vecuronium bromide may have profound effects. In such patients, a peripheral nerve stimulator and use of a small test dose may be of particular value in assessing and monitoring dosage requirements.

PRECAUTIONS

General

The administration of VECURONIUM BROMIDE FOR INJECTION has been associated with rare instances of hyper-sensitivity reactions (bronchospasm, hypotension and/or tachycardia, sometimes associated with acute urticaria or erythema).

As with all other neuromuscular blocking agents, VECURONIUM BROMIDE FOR INJECTION should be used with caution in patients with renal, hepatic, or pulmonary impairment. Vecuronium bromide should be used with extreme caution, if at all, in patients with myasthenia gravis.

Patients with carcinomatosis especially associated with bronchial carcinoma may exhibit a marked sensitivity to this agent, and the neuromuscular block produced may respond poorly to neostigmine.

Cardiovascular

As vecuronium bromide has no significant effects on heart rate in the recommended dosage range, it will not counteract the bradycardia produced by many anesthetic agents or vagal stimulation.

Renal Failure

Vecuronium bromide 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 vecuronium bromide should be considered.

Hepatic Disease

Limited experience in patients with cirrhosis or cholestasis has revealed prolonged recovery time in keeping with the role the liver plays in vecuronium bromide metabolism and excretion (see **Pharmacokinetics**). Data currently available do not permit dosage recommendations in patients with impaired liver function.

Increased Volume of Distribution

The onset of action of neuromuscular blocking agents may be delayed in patients who have increased volumes of distribution as a result of old age, edematous states, or cardiovascular

disease. More time should be permitted for the drug to achieve its maximal effect in these patients. Dosage should not be increased.

Long-term Use in I.C.U.

Limited information is available concerning the efficacy and safety of long-term (days to weeks) intravenous vecuronium bromide infusion to facilitate mechanical ventilation in the intensive care unit. In rare cases, long-term use of neuromuscular blocking drugs to facilitate mechanical ventilation in ICU settings may be associated with prolonged paralysis and/or skeletal muscle weakness, that may be first noted during attempts to wean patients from the ventilator. Typically, such patients have received other drugs such as broad spectrum antibiotics, narcotics and/or steroids and may have electrolyte imbalances and diseases which lead to electrolyte imbalances, 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.

WHENEVER THE USE VECURONIUM BROMIDE 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 VECURONIUM BROMIDE OR ANY OTHER NEUROMUSCULAR BLOCKING AGENT SHOULD NOT BE GIVEN BEFORE THERE IS A DEFINITE RESPONSE TO T_1 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 vecuronium bromide.

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. Heredity appears to be a factor in this reaction, because several families have been shown to have high incidence of

hyperthermia. VECURONIUM BROMIDE FOR INJECTION should therefore either not be used in such patients or if necessary, patients should be carefully monitored.

There are insufficient data derived from screening in susceptible animals (swine) to establish whether or not vecuronium bromide is capable of triggering malignant hyperthermia.

C.N.S.

Vecuronium bromide has no known effect on consciousness, pain threshold or cerebation. Administration must be accompanied by adequate anesthesia or sedation.

Hypothermia

Hypothermia (25 to 28°C) has been associated with a decreased requirement for non depolarizing neuromuscular blocking agents.

Burns

Resistance to non depolarizing neuromuscular blocking agents may develop in patients with burns, depending upon the time elapsed since the injury and the size of the burn.

Sensitivity / Resistance

Anaphylaxis

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. These reactions have in some cases been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as immediate availability of appropriate emergency treatment, should be taken. Precautions should also be taken in those individuals who have had previous anaphylactic reactions to other neuromuscular blocking agents since cross-reactivity between neuromuscular blocking agents has been reported in this class of drugs.

Use in Pregnancy and Lactation

Animal studies have not been conducted with vecuronium bromide. It is not known whether vecuronium bromide can cause fetal harm when administered to a pregnant woman, or if it can affect reproductive capacity. It is not known whether vecuronium bromide is secreted in breast milk and therefore it is not recommended in lactating women.

Use in Obstetrics

It is not known whether muscle relaxants administered during vaginal delivery have immediate or delayed adverse effects on the fetus, or increase the likelihood that resuscitation of the newborn will be necessary. The possibility that a forceps delivery will be necessary may increase.

The possibility of respiratory depression in the newborn infant should always be considered following cesarean section during which a neuromuscular blocking agent has been administered.

Pediatric Use

Infants under 1 year of age but older than 7 weeks also tested under halothane anesthesia, are moderately more sensitive to vecuronium bromide on a mg/kg basis than adults and take about 1% times as long to recover. Information presently available does not permit recommendations for usage in neonates (see **INSTRUCTIONS FOR USE**).

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been performed to evaluate carcinogenic or mutagenic potential or impairment of fertility.

Drug Interactions

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

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

Inhalational Anesthetics: Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with vecuronium bromide will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of vecuronium bromide 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 **ACTIONS AND CLINICAL PHARMACOLOGY**).

Antibiotics: The following antibiotics may enhance the neuromuscular blocking action of non depolarizing agents such as vecuronium bromide: 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 vecuronium bromide during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

Thiopental: Reconstituted vecuronium, which has an acid pH, should not be mixed with alkaline solutions (e.g., barbiturate solutions such as thiopental) in the same syringe or administered simultaneously during intravenous infusion through the same needle or same intravenous line.

Other: Experience concerning injection of quinidine during recovery from the use of other muscle relaxants suggests that recurrent paralysis may occur. This possibility must also be considered for vecuronium bromide. Vecuronium bromide 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.

ADVERSE REACTIONS

Neuromuscular: The most frequent adverse reaction to nondepolarizing neuromuscular blocking agents as a class consists of an extension of their pharmacological actions beyond the time period needed for surgery and anesthesia. This may vary from skeletal muscle weakness to profound and prolonged skeletal muscle paralysis resulting in respiratory insufficiency or apnea. Appropriate treatment should be instituted. (See PRECAUTIONS: PEDIATRIC USE).

VECURONIUM BROMIDE FOR INJECTION may cause respiratory depression (See **WARNINGS**).

Inadequate reversal of the neuromuscular blockade is possible with vecuronium, as with all curariform drugs. These adverse experiences are managed by manual or mechanical ventilation until recovery is judged adequate. The concomitant use of thiobarbiturates, narcotic analgesics, nitrous oxide, or droperidol is associated with little or no increase in intensity of blockade or duration of action of vecuronium bromide. Prolonged paralysis and / or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit (see **PRECAUTIONS**).

Cardiovascular: Cardiovascular changes and bronchospasm, should they occur, are difficult to assess as these can be influenced by other factors such as premedication, induction agent, intubation, presence of an endotracheal tube, inhalation agent, pre-existing disease and dosage.

Gastrointestinal: Excessive salivation is sometimes noted during very light anesthesia, particularly in children or if no anticholinergic premedication is used.

Skin: An occasional transient rash is noted accompanying the use of VECURONIUM BROMIDE FOR INJECTION.

Miscellaneous: Rare hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia and other reactions possibly mediated by histamine release have been reported.

Prolonged apnea may occur when a depolarizing agent such as succinylcholine is used for intubation prior to administration of vecuronium (see DRUG INTERACTIONS).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of vecuronium bromide can be expected to produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed for surgery and anesthesia may occur with vecuronium bromide 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 and help to differentiate 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. Pyridostigmine, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of vecuronium bromide. Satisfactory reversal can be judged by adequacy of skeletal muscle tone and 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 on 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 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 VECURONIUM BROMIDE FOR INJECTION and its metabolite are unknown.

For management of a suspected drug overdose, contact your Regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

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

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 vecuronium bromide by volatile anesthetics and by prior use of succinylcholine (see **PRECAUTIONS- Drug Interactions**).

To obtain maximum clinical benefit from vecuronium bromide and to minimize the possibility of overdosage, the monitoring of muscle twitch response to peripheral nerve stimulation is advised.

The recommended initial dose of vecuronium bromide 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 to 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 to 65 minutes after injection. In the presence of potent inhalation anesthetics, the neuromuscular blocking effect of vecuronium bromide is enhanced. If vecuronium bromide is first administered more than 5 minutes after the initiation of an inhalation agent or during steady-state inhalation anesthesia, the initial vecuronium bromide 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 vecuronium bromide. If intubation is performed using succinylcholine, a reduction of the initial dose of vecuronium bromide to 0.04 to 0.06 mg/kg with inhalation anesthesia or 0.05 to 0.06 mg/kg with balanced anesthesia may be required. The administration of vecuronium bromide should be delayed until signs of recovery from the succinylcholine effect are evident. During prolonged surgical procedures, maintenance doses of 0.010 to 0.015 mg/kg of vecuronium bromide are recommended.

After the initial injection of vecuronium bromide, 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 vecuronium bromide lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administered at relatively regular intervals for each patient, ranging from approximately 12 to 15 minutes under balanced anesthesia. Under the conditions of anesthesia with inhalation agents, intervals between maintenance doses are slightly longer. (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 to 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 **ACTIONS AND CLINICAL PHARMACOLOGY**).

Use by Infusion: Following the administration of a recommended initial bolus dose of vecuronium bromide, a diluted solution of vecuronium bromide, can be administered by continuous infusion to adults for maintenance of neuromuscular blockade during extended surgical procedures. Long term intravenous infusion to support mechanical ventilation in the intensive care unit has not been studied sufficiently to support dosage recommendations (see **PRECAUTIONS**).

Infusion of vecuronium bromide should be individualized for each patient. The rate of administration should be adjusted according to the patient's response as determined by peripheral nerve stimulation.

Infusion of vecuronium bromide should be initiated only after early evidence of spontaneous recovery from the bolus dose (typically 10 to 20% recovery of the initial twitch response). During balanced anesthesia, an initial infusion rate of 1 µg/kg/min is recommended with subsequent rate adjustments to maintain a 90% suppression of the twitch response. Individual infusion rates may range from 0.6 to 1.8 µg/kg/min.

Inhalation anesthetics, particularly enflurane and isoflurane may enhance the neuromuscular blocking action of non depolarizing muscle relaxants. In the presence of steady-state concentrations of enflurane or isoflurane, it may be necessary to use infusion rates which are 25 to 60% lower than those recommended during balanced anesthesia. Reduced infusion rates may not be required during halothane anesthesia.

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of vecuronium bromide infusion may be expected to proceed at rates comparable to those following single bolus doses (see **ACTIONS AND CLINICAL PHARMACOLOGY**).

Infusion solutions of vecuronium bromide can be prepared by mixing vecuronium bromide with an appropriate infusion solution such as 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP, 5% Dextrose and 0.9% Sodium Chloride Injection, USP; or Lactated Ringer's Injection, USP. Use within 24 hours of mixing with the above solutions. Unused portions of infusion solutions should be discarded.

Infusion rates of vecuronium bromide can be individualized for each patient using Table 1.

Table 1 VECURONIUM BROMIDE FOR INJECTION Infusion Rates		
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 VECURONIUM BROMIDE FOR INJECTION in 100 mL solution		
+ 20 mg of VECURONIUM BROMIDE FOR INJECTION in 100 mL solution		

Table 2 is a guideline for mL/min delivery for a solution of 0.1 mg/mL (10 mg in 100 mL) with an infusion pump.

Table 2 VECURONIUM BROMIDE FOR INJECTION Infusion Rates – mL/MIN							
Amount of Drug (µg/kg/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.							

Dosage in Children:

Older children (10 to 17 years of age) have approximately the same dosage requirements (mg/kg) as adults and may be managed the same way.

Younger children (1 to 10 years of age) may require a slightly higher initial dose and may also require supplementation slightly more than adults.

Infants under one year of age but older than 7 weeks are moderately more sensitive to VECURONIUM BROMIDE FOR INJECTION on a mg/kg basis than adults and take about 1% times as long to recover. See also **PRECAUTIONS - Pediatric Use**. Information presently available does not permit recommendation on usage in neonates (see **PRECAUTIONS**). There are insufficient data concerning continuous infusion of vecuronium bromide in children; therefore, no dosing recommendation can be made.

PHARMACEUTICAL INFORMATION

Drug Substance

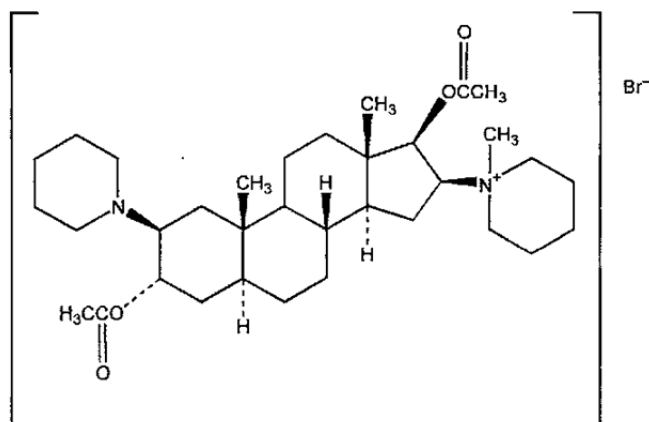
Proper Name: vecuronium bromide

Chemical Name: piperidinium, (1-2 β ,3 α ,5 α ,16 β ,17 β)-3,17-bis(acetyloxy)-2(1-piperidinyl)androstan-16-yl-1-methyl-bromide.

Molecular Formula: C₃₄H₅₇BrN₂O₄

Molecular Weight: 637.74

Structural Formula:



Description: Vecuronium is a white or almost white, odorless crystalline powder. It is soluble in alcohol and chloroform, slightly soluble in acetone; forms a gel with water which at 1% concentration is fluid. The drug has a pKa of 8.99 in distilled water at 25°C.

Composition:

10 mg/vial: Each vial contains vecuronium bromide 10 mg, citric acid anhydrous 20.75 mg, sodium phosphate dibasic 16.25 mg, mannitol 97 mg(to adjust tonicity), May contain sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4.

20 mg/vial: Each vial contains vecuronium bromide 20 mg, citric acid anhydrous 32.5 mg, sodium phosphate dibasic 32.5 mg, mannitol 194 mg (to adjust tonicity), sodium hydroxide and/or phosphoric acid to buffer and adjust to a pH of 4.

SHAKE WELL UNTIL DISSOLVED. ASSURE COMPLETE DISSOLUTION BEFORE MEASURING AND TRANSFERRING EACH INDIVIDUAL DOSE.

INSTRUCTIONS FOR USE

Reconstituted solutions

Reconstitute with Bacteriostatic Water for Injection, USP or one of the recommended diluents. (See table below)

Reconstitution Table		
Vial Size	Volume to be Added to Vial	Approximate Average Concentration
10 mg	10 mL	1 mg/mL
20 mg	20 mL	1 mg/mL

VECURONIUM BROMIDE FOR INJECTION has been shown to be compatible when administered with the following recommended diluents:

- 0.9% Sodium Chloride Injection, USP
- 5% Dextrose Injection, USP
- 5% Dextrose and 0.9% Sodium Chloride Injection, USP
- Sterile Water for Injection, USP
- Lactated Ringer's Injection, USP

After reconstitution: When reconstituted with Bacteriostatic Water for Injection, use within 5 days. When reconstituted with Sterile Water for Injection or other compatible i.v. solutions: Use within 24 hours. Single use only. Discard unused portion.

The reconstituted and diluted solutions should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

When reconstituted with bacteriostatic water for injection: CONTAINS BENZYL ALCOHOL WHICH IS NOT FOR USE IN NEWBORNS.

Stability and Storage Recommendations:

Store dry powder between 15 and 25°C. PROTECT FROM LIGHT.

AVAILABILITY OF DOSAGE FORMS

VECURONIUM BROMIDE FOR INJECTION is supplied in single dose vials as follows:

- 10 mL vial containing 10 mg vecuronium bromide, cartons of 5 vials.
- 25 mL vial containing 20 mg vecuronium bromide, cartons of 5 vials.

PHARMACOLOGY

Pharmacodynamics

In various animal models, including the rat, cat and monkey, VECURONIUM BROMIDE FOR INJECTION has a more rapid onset and shorter duration of neuromuscular blocking action than pancuronium. It had less accumulation on repeated administration than pancuronium or tubocurarine and was readily reversed by cholinesterase inhibitors. Vecuronium bromide has negligible ganglion-blocking activity and there is a wide margin in the neuromuscular and vagal blocking doses. In animals, the relative neuromuscular blocking potency of vecuronium bromide ranged from 3.4 times less potent in the rat to 1.5 times less potent in the monkey than pancuronium.

In dogs and cats doses up to 20 times the therapeutic doses had no cardiovascular effects.

Compared to pancuronium and tubocurarine, the intracutaneous injection of vecuronium bromide caused significantly less histamine release in human volunteers. Inhalation anesthetics were found to augment the neuromuscular blocking action of vecuronium bromide in several animal species. In the rat the order of their potentiating effect was enflurane>isoflurane>halothane.

Pharmacokinetics

Animal: In the dog, i.v. administration of vecuronium bromide had a mean distribution half-life of 3.0 minutes and a mean elimination half-life of 22 minutes. Similar values were found for the cat. Circulatory bypass of the liver in the cat prolongs recovery from vecuronium bromide. In cholestatic rats the neuromuscular blocking action of vecuronium bromide was increased about 3 fold. A similar effect was observed when bile salts were infused concomitantly. In rats only about 3.5% of an administered dose of vecuronium bromide was eliminated in the urine. Biliary excretion accounted for 46% of the dose in 7 hours. In the rabbit the placental transfer to the fetus was limited, accounting for less than 0.1% of the dose up to 20 minutes after dosing.

TOXICOLOGY

Acute Toxicity

In halothane anesthetised cats (4 male and 4 female) five i.v. injections of VECURONIUM BROMIDE FOR INJECTION were given 30 minutes apart for total doses of 2.5, 7.5 and 22.5 mg/kg body weight. All doses caused neuromuscular blockade with a dose-related duration of action. All the cats in the high dose group died within 24 hours. No deaths occurred in the other dose groups. Gross pathology, histopathology and various evaluations did not reveal any drug related abnormalities. The same doses of vecuronium bromide given to similar groups of cats under thiopental anesthesia resulted in the death of 2 of 8 animals at the high dose. No drug related effects were observed on tissue pathology or clinical chemistry and hematological parameters.

Four male and four female dogs under halothane anesthesia were given total doses of 2.5, 6.75 and 22.5 mg/kg. Two male dogs from the high dose group were killed in a moribund state and 1

female died spontaneously. Clinical chemistry, hematological as well as gross pathology and histopathology did not reveal any drug related abnormality. A similar study in dogs under thiopental anaesthesia resulted in the death of 1 male and 2 females in the high dose group with no other drug related toxicological changes.

Subacute Toxicity

Groups of Beagle dogs (3/sex/group) were given saline placebo, 14 µg/kg, 42 µg/kg or 140 µg/kg (the latter dose was 10 times the ED₉₀) twice weekly for 3 weeks. No overt signs of toxicity were seen, other than transient respiratory arrest in the animals in the two highest dose groups. No drug related blood biochemical or hematological changes were observed; there were no histopathological changes caused by drug treatment.

Three male and 3 female cats were given i.v. bolus doses of vecuronium bromide of 40 µg/kg, 400 µg/kg, 2000 µg/kg or saline daily for 21 days. Three cats in the high dose group died during recovery on days 2, 4 and 6 and 1 from the 400 µg/kg group on day 3. Death appeared to be due to respiratory and/or cardiac suppression. No treatment-related gross or microscopic tissue changes were found in survivors.

Mutagenicity

Concentrations of vecuronium bromide up to 1000 µg/mL gave negative results in the Ames Salmonella test.

Carcinogenicity

Long term studies in animals have not been performed to evaluate carcinogenic potential.

Reproductive toxicity

Animal reproduction studies have not been conducted with vecuronium bromide.

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PART III: CONSUMER INFORMATION

Vecuronium Bromide For Injection

This leaflet is part III of a three-part "Product Monograph" This leaflet is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Vecuronium Bromide For Injection. Contact your doctor or nurse if you have any questions about this drug.

Your medical history can influence the way that Vecuronium Bromide For Injection is given to you.

BEFORE you receive Vecuronium Bromide For Injection talk to your doctor if you have:

- myasthenia gravis or myasthenic (Eaton-Lambert) syndrome or other neuromuscular diseases.
- cancer, particularly lung cancer
- a decreased kidney function or kidney disease
- a heart disease or heart valve disease
- severe obesity,
- have a recent burn
- pulmonary hypertension or lung disease
- oedema (fluid retention for example at the ankles)
- recent, severe vomiting, diarrhea, and "water pill" use
- a liver or gallbladder disease or decreased liver function
- diseases affecting nerves or muscles
- an allergy to muscle relaxants
- a history or family history of malignant hyperthermia (very high body temperature with increased breathing heart rate, and stiff muscles)

Tell your doctor if you have any other medical conditions, as they may influence how Vecuronium Bromide For Injection works.

Driving and Using Machines

Your doctor will inform you when it is safe to drive and operate potentially dangerous machinery after you have been administered Vecuronium Bromide For Injection.

ABOUT THIS MEDICATION

What the medication is used for:

Vecuronium Bromide For Injection is used as part of the general anesthetic. It relaxes muscles during an operation, including cesarean section. It can also be used to ease mechanical ventilation which helps you breathe.

What it does:

Vecuronium Bromide For Injection blocks the nerve impulses to move your muscles. Because the muscles needed for breathing also become relaxed, you will need help breathing (mechanical ventilation) during and after your operation until you can breathe on your own. At the end of surgery, the effects of Vecuronium Bromide For Injection will wear off so you can start breathing on your own.

When it should not be used:

- if you have had an allergic reaction to vecuronium, to bromide or any of the other ingredients in Vecuronium Bromide For Injection.
- if you are pregnant or breastfeeding.
- in newborns less than 1 month of age. Vecuronium Bromide For Injection when reconstituted with bacteriostatic water for injection contains benzyl alcohol, a preservative that has been associated with fatal complications including "gasping syndrome" in premature infants.

What the medicinal ingredient is:

Vecuronium bromide.

What the nonmedicinal ingredients are:

Citric acid anhydrous, mannitol, sodium phosphate dibasic. May also contain phosphoric acid and/or sodium hydroxide.

What dosage forms it comes in:

Vials of 10 mg and 20 mg.

INTERACTIONS WITH THIS MEDICATION

It is very important to tell your doctor about any medications you may be taking including medicines obtained without a prescription. This will help your doctor to decide the correct dose of Vecuronium Bromide For Injection for you.

Be sure to tell about any antibiotics and medications for diseases which lead to electrolyte imbalance such as adrenal cortical insufficiency or medication to counter electrolyte imbalance such as magnesium salts.

PROPER USE OF THIS MEDICATION

Usual dose:

The dose given is decided by the doctor based on the clinical need and your physical condition.

Only an adequately trained health care professional may give Vecuronium Bromide For Injection.

Overdose:

As medical personnel will be monitoring your condition during the procedure it is unlikely that you will be given too much Vecuronium Bromide For Injection. However, if this happens artificial

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

As for all drugs used during an operation, this drug should be administered only in a facility prepared to give resuscitation and life support by adequately trained health care professionals familiar with its actions, characteristics, and hazards.

respiration will be continued until you are able to breathe again on your own. It is possible to counteract the effects of (too much) Vecuronium Bromide For Injection and speed-up your recovery by giving you a drug that reverses the effects of Vecuronium Bromide For Injection.

Vecuronium Bromide For Injection will be given under the supervision of a qualified physician who will manage your condition in the event of an overdose.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Vecuronium Bromide For Injection can have side effects. **Your anaesthetist or intensive care doctor will care for you if any of the following side effects or any other undesirable events occur.**

For the following serious side effects, you must seek immediate emergency medical treatment.

- Allergic reactions (rash, swelling of the face, throat, lips, difficulty breathing).
- Feeling cold and/or clammy
- Difficulty breathing/choking/wheezing
- Muscle weakness or paralysis
- Rapid or slow heart beat
- Sudden fever with stiffness, pain and weakness in your muscles
- Seizure/seizure-like activity

For the following serious side effects, call your doctor or pharmacist.

- Dizziness especially upon standing up quickly
- Lowering of blood pressure if measured
- Severe itching
- Jaundice/yellowing of the skin/eyeballs
- Problems with your vision
- Excessive salivation (drooling)
- Skin rash

This is not a complete list of side effects. For any unexpected effects after receiving Vecuronium Bromide For Injection, contact your doctor or nurse.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
 - Fax toll-free to 1-866-678-6789, or
 - Mail to: Canada Vigilance Program
Health Canada
Postal Locator 0701E
Ottawa, ON K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor, Hospira Healthcare Corporation, at: 1-866-488-6088, Option 4.

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