PRODUCT MONOGRAPH

[Pr]VECURONIUM BROMIDE FOR INJECTION

Non-depolarizing Skeletal Neuromuscular Blocking Agent

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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 for Injection is about 1/3 more potent than pancuronium; the duration of neuromuscular blockade produced by Vecuronium Bromide for Injection 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 for Injection doses. The use of a peripheral nerve stimulator is of benefit in assessing the degree of muscular relaxation.

The ED_{90} (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 for Injection 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 anaesthesia, 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 approximately 45 to 65 minutes. The neuromuscular blocking action of Vecuronium Bromide for Injection is slightly enhanced in the presence of potent inhalation anesthetics. If Vecuronium Bromide for Injection 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 for Injection may be decreased by approximately 15% (see **DOSAGE AND ADMINISTRATION** section). Prior administration of succinylcholine may enhance the neuromuscular blocking effect of Vecuronium Bromide for Injection and its duration of action. With succinylcholine as the intubating agent, initial doses of 0.04-0.06 mg/kg of Vecuronium Bromide for Injection will produce complete neuromuscular block with clinical duration of action of 25-30 minutes. If succinylcholine is used prior to Vecuronium Bromide for Injection, the administration of Vecuronium Bromide for Injection 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 for Injection has not been studied (see **DRUG INTERACTIONS**).

Repeated administration of maintenance doses of Vecuronium Bromide for Injection 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 15-25 minutes under balanced or halothane anesthesia. When recovery from the Vecuronium Bromide for Injection neuromuscular blocking effect begins, it proceeds more rapidly than recovery from pancuronium. Once spontaneous recovery has started, the

neuromuscular block produced by Vecuronium Bromide for Injection 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 0.04-0.10 mg/kg, 60-80% of Vecuronium 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. Urinary recovery of Vecuronium Bromide for Injection 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 the bile within 42 hours. Only unchanged Vecuronium Bromide for Injection 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 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 for Injection. Equipotent doses are of approximately the same duration as Vecuronium Bromide for Injection 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 for Injection 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 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 for Injection during surgery for pheochromocytoma has shown that administration of this drug is not associated with changes in blood pressure or heart rate.

Vecuronium Bromide for Injection has no clinically significant effect on hemodynamic parameters. Vecuronium Bromide for Injection 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 for Injection was increased 5-fold during hypothermic cardiopulmonary bypass.

INDICATION

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.

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 NEUROMUSCLAR 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 for Injection 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

Limited data on histamine assay and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia and other reactions commonly associated with histamine release are unlikely to occur.

Cardiovascular

As Vecuronium Bromide for Injection 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 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 Vecuronium Bromide for Injection 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 for Injection 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 ICU

Limited information is available concerning the efficacy and safety of long-term (days to weeks) intravenous Vecuronium Bromide for Injection 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 OF VECURONIUM BROMIDE FOR INJECTION 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 FOR INJECTION 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 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 Vecuronium Bromide for Injection is capable of triggering malignant hyperthermia.

CNS

Vecuronium Bromide for Injection has no known effect on consciousness, pain threshold or cerebration. Administration must be accompanied by adequate anesthesia or sedation.

Hypothermia

Hypothermia (25-28°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.

Use in Pregnancy and Lactation

Animal studies have not been conducted with Vecuronium Bromide for Injection. It is not known whether Vecuronium Bromide for Injection can cause fetal harm when administered to a pregnant woman, or if it can affect reproductive capacity. It is not known whether Vecuronium

Bromide for Injection 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 for Injection on a mg/kg basis than adults and take about 1 1/2 times as long to recover. Information presently available does not permit recommendations for usage in neonates.

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 adminstration of succinylcholine may enhance the neuromuscular blocking effect of Vecuronium Bromide for Injection and its duration of action. If succinylcholine is used before Vecuronium Bromide for Injection, the administration of Vecuronium Bromide for Injection should be delayed until the succinylcholine effect shows signs of wearing off. With succinylcholine as the intubating agent, initial doses of 0.040-0.06 mg/kg of Vecuronium Bromide for Injection may be administered to produce complete neuromuscular block with a

clinical duration of action of 25-30 minutes (see **ACTIONS AND CLINICAL PHARMACOLOGY**). The use of Vecuronium Bromide for Injection 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 for Injection. Therefore, these drugs and Vecuronium Bromide for Injection may manifest an additive effect when used together. There are insufficient data to support concomitant use of Vecuronium Bromide for Injection 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 for Injection will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane. With the above agents the initial dose of Vecuronium Bromide for Injection 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 nondepolarizing agents such as Vecuronium Bromide for Injection: 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 for Injection during surgery, unexpected prolongation of neuromuscular block should be considered a possibility.

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 for Injection. Vecuronium Bromide for Injection induced

neuromuscular blockade had 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

The most frequent adverse reaction for non-depolarizing blocking agents as a class consists of an extension of the drug's pharmacological action 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. Inadequate reversal of the neuromuscular blockade is possible with Vecuronium Bromide for Injection as with all curariform drugs.

Inadequate reversal is 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 for Injection. 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**).

Bronchospasm, flushing, redness, hypotension and tachycardia have been reported in rare instances.

OVERDOSAGE

The possibility of iatrogenic overdosage can be minimized by carefully monitoring muscle twitch response to peripheral nerve stimulation. Excessive doses of Vecuronium Bromide for

Injection 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 for Injection 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. Pyridostigmine, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate will usually antagonize the skeletal muscle relaxant action of Vecuronium Bromide for Injection. 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.

DOSAGE AND ADMINISTRATION

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 for Injection by volatile anesthetics and by prior use of succinylcholine (see **PRECAUTIONS/DRUG INTERACTIONS**).

To obtain maximum clinical benefit from Vecuronium Bromide for Injection 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 for Injection is 0.08 to 0.10 mg/kg (1.4 to 1.75 times the ED_{90}) 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 Vecuronium Bromide for Injection is enhanced. If Vecuronium Bromide for Injection is first administered more than 5 minutes after the initiation of an inhalation agent or during steady state inhalation anesthesia, the initial Vecuronium Bromide for Injection dose may be reduced by approximately 15% i.e., 0.060 to 0.085 mg/kg.

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

The administration of vercuronium 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 for Injection are recommended. After the initial Vecuronium Bromide for Injection 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 Vecuronium Bromide for Injection lacks clinically important cumulative effects, subsequent maintenance doses, if required, may be administrated 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 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 for Injection, a diluted solution of Vecuronium Bromide for Injection 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 for Injection 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 for Injection 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 anaesthesia, an initial infusion rate of 1 mcg/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 mcg/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 anaesthesia. Reduced infusion rates may not be required during halothane anesthesia

Spontaneous recovery and reversal of neuromuscular blockade following discontinuation of Vecuronium Bromide for Injection 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 for Injection can be prepared by mixing Vecuronium Bromide for Injection 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 hr of mixing with the above solutions. Unused portions of infusion solutions should be discarded.

Infusion rates of Vecuronium Bromide for Injection can be individualized for each patient using the following table:

Drug Delivery Rate (mcg/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

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.

VECURONIUM BROMIDE FOR INJECTION INFUSION RATE - mL/MIN

Amount of Drug	**Patient Weight - Kg**						
(mcg/kg/min)	**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	0.365	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 100mL), 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 often 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 1/2

times as long to recover. See also subsection of **PRECAUTIONS** titled **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 for Injection in children, therefore, no dosing recommendation can be made.

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: vecuronium bromide

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

Molecular Formula: $C_{34}H_{57}BrN_2O_4$

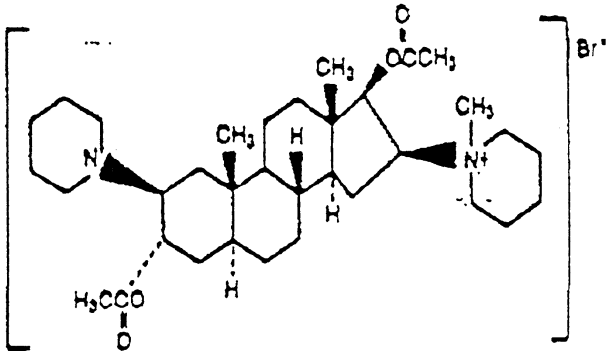
Molecular Weight: 637.74

Solubilities: Freely soluble in alcohol and in chloroform, slightly soluble in acetone. Forms a gel with water at 1% concentration in fluid.

Melting Point: 227-229°C

pH: Approximately 4

Structural Formula:



Physical Appearance: White or almost white crystals or crystalline powder, odourless.

COMPOSITION

Each 10 mg vial contains 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 mg vial contains 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.

STABILITY AND STORAGE RECOMMENDATIONS

PROTECT FROM LIGHT. Store at room temperature between 15 and 30°C (59°-86°F).

RECONSTITUTED SOLUTIONS

Reconstitute each 10 mg vial with 10 mL of bacteriostatic water for injection or 10 mL of compatible diluent to obtain a solution containing 1 mg/mL vecuronium bromide. Reconstitute each 20 mg vial with 20 mL of bacteriostatic water for injection or 20 mL of compatible diluent to obtain a solution containing 1 mg/mL vecuronium bromide. Compatible admixture/infusion preparation diluents (diluted to a strength of 0.1 mg/mL or 0.2 mg/mL) are:

0.9% Sodium Chloride Injection, USP
5% Dextrose Injection, USP
Lactated Ringer's Injection, USP
5% Dextrose and 0.9% Sodium Chloride Injection, USP

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

After reconstitution: When reconstituted with bacteriostatic water for injection, use within 5 days. When reconstituted with compatible I.V. solutions: Use within 24 hours. Single use only. Discard unused portion.

AVAILABILITY OF DOSAGE FORMS

Vecuronium Bromide for Injection is available in 10 mL vials containing 10 mg vecuronium bromide and in 20 mL vials containing 20 mg vecuronium bromide (note: the diluent is not supplied for either the 10 mL or 20 mL vial). Boxes of 10 vials.

Route of Administration: Intravenous

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 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 anesthesia 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 mcg/kg, 42 mcg/kg or 140 mcg/kg (the latter dose was 10 times the ED_{90}) 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 mcg/kg, 400 mcg/kg, 2000 mcg/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 mcg/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 mcg/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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