

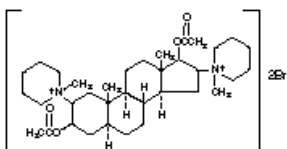
## PAVULON®

(pancuronium bromide) injection

**NOT FOR USE IN NEONATES  
CONTAINS BENZYL ALCOHOL**

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

**DESCRIPTION:** PAVULON® (pancuronium bromide) injection is a nondepolarizing neuromuscular



blocking agent chemically designated as the aminosteroid 2  $\beta$ , 16  $\beta$  - dipiperidino-5 $\alpha$ -androstane-3 $\alpha$ , 17- $\beta$  diol diacetate dimethobromide. The structural formula is:

PAVULON® is supplied as a sterile, isotonic, nonpyrogenic solution for injection. Each mL contains 1 mg or 2 mg pancuronium bromide, 2 mg sodium acetate and 1% benzyl alcohol as preservative. The solution is adjusted to isotonicity with sodium chloride and to a pH of 4 with acetic acid and/or sodium hydroxide; water is used as the solvent.

**CLINICAL PHARMACOLOGY:** PAVULON® 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 anticholinesterase agents such as pyridostigmine, neostigmine, and edrophonium. PAVULON® is approximately 1/3 less potent than vecuronium and approximately 5 times as potent as d-tubocurarine; the duration of neuromuscular blockade produced by PAVULON® is longer than that of vecuronium at initially equipotent doses. The ED<sub>95</sub> (dose required to produce 95% suppression of muscle twitch response) is approximately

0.05 mg/kg under balanced anesthesia and 0.03 mg/kg under halothane anesthesia. These doses produce effective skeletal muscle relaxation (as judged by time from maximum effect to 25% recovery of control twitch height) for approximately 22 minutes; the duration from injection to 90% recovery of control twitch height is approximately 65 minutes. The intubating dose of 0.1 mg/kg (balanced anesthesia) will effectively abolish twitch response within approximately 4 minutes; time from injection to 25% recovery from this dose is approximately 100 minutes.

Supplemental doses to maintain muscle relaxation slightly increase the magnitude of block and significantly increase the duration of block. The use of a peripheral nerve stimulator is of benefit in assessing the degree of neuromuscular blockade.

The most characteristic circulatory effects of pancuronium, studied under halothane anesthesia, are a moderate rise in heart rate, mean arterial pressure and cardiac output; systemic vascular resistance is not changed significantly and central venous pressure may fall slightly. The heart rate rise is inversely related to the rate immediately before administration of pancuronium, is blocked by prior administration of atropine, and appears unrelated to the concentration of halothane or dose of pancuronium.

Data on histamine assays and available clinical experience indicate that hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions commonly associated with histamine release are rare. (**see ADVERSE REACTIONS**).

**Pharmacokinetics:** The elimination half-life of pancuronium has been reported to range between 89–161 minutes. The volume of distribution ranges from 241–280 mL/kg and plasma clearance is approximately 1.1–1.9 mL/minute/kg. Approximately 40% of the total dose of pancuronium has been recovered in urine as unchanged pancuronium and its metabolites while approximately 11% has been recovered in bile. As much as 25% of an injected dose may be recovered as 3-hydroxy metabolite, which is half as potent a blocking agent as pancuronium. Less than 5% of the injected dose is recovered as 17-hydroxy metabolite and 3.17-dihydroxy metabolite, which have been judged to be approximately 50 times less potent than pancuronium. Pancuronium exhibits strong

binding to gamma globulin and moderate binding to albumin. Approximately 13% is unbound to plasma protein. In patients with cirrhosis the volume of distribution is increased by approximately 50%, the plasma clearance is decreased by approximately 22% and the elimination half-life is doubled. Similar results were noted in patients with biliary obstruction, except that plasma clearance was less than half the normal rate. The initial total dose to achieve adequate relaxation may thus be high in patients with hepatic and/or biliary tract dysfunction, while the duration of action is greater than usual.

The elimination half-life is doubled and the plasma clearance is reduced by approximately 60% in patients with renal failure. The volume of distribution is variable, and in some cases elevated. The rate of recovery of neuromuscular blockade, as determined by peripheral nerve stimulation is variable and sometimes very much slower than normal.

**INDICATIONS AND USAGE:** PAVULON® (pancuronium bromide) injection is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation.

**CONTRAINDICATIONS:** PAVULON® is contraindicated in patients known to be hypersensitive to the drug. PAVULON® is contraindicated for use in neonates, including premature infants, because the formulation contains benzyl alcohol (see **WARNINGS** and **PRECAUTIONS:**

***Pediatric Use***).

**WARNINGS:** PAVULON® SHOULD BE ADMINISTERED IN CAREFULLY ADJUSTED DOSES 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.

***Anaphylaxis:*** Severe anaphylactic reactions to neuromuscular blocking agents, including

PAVULON<sup>®</sup>, have been reported. These reactions have, in some cases, been life-threatening and fatal. Due to the potential severity of these reactions, the necessary precautions, such as the 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, both depolarizing and non-depolarizing, has been reported.

In patients who are known to have myasthenia gravis or the myasthenic (Eaton-Lambert) syndrome, small doses of PAVULON<sup>®</sup> 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.

PAVULON<sup>®</sup> contains benzyl alcohol, which is potentially toxic when administered locally to neural tissue. Exposure to excessive amounts of benzyl alcohol has been associated with toxicity (hypotension, metabolic acidosis), particularly in neonates, and an increased incidence of kernicterus, particularly in small preterm infants. There have been rare reports of deaths, primarily in preterm infants, associated with exposure to excessive amounts of benzyl alcohol. The amount of benzyl alcohol from medications is usually considered negligible compared to that received in flush solutions containing benzyl alcohol. Administration of high dosages of medications containing this preservative must take into account the total amount of benzyl alcohol administered. The amount of benzyl alcohol at which toxicity may occur is not known. If the patient requires more than the recommended dosages or other medications containing this preservative, the practitioner must consider the daily metabolic load of benzyl alcohol from these combined sources (see **WARNINGS** and **PRECAUTIONS: Pediatric Use**).

**PRECAUTIONS:** USE OF A PERIPHERAL NERVE STIMULATOR WILL USUALLY BE OF VALUE FOR MONITORING OF NEUROMUSCULAR BLOCKING EFFECT, AVOIDING OVERDOSAGE AND ASSISTING IN EVALUATION OF RECOVERY.

**General:** Although PAVULON<sup>®</sup> has been used successfully in many patients with pre-existing pulmonary, hepatic, or renal disease, caution should be exercised in these situations.

**Anaphylaxis:** Since allergic cross-reactivity has been reported in this class, request information from your patients about previous anaphylactic reactions to other neuromuscular blocking agents. In addition, inform your patients that severe anaphylactic reactions to neuromuscular blocking agents, including PAVULON<sup>®</sup>, have been reported.

**Renal Failure:** A major portion of pancuronium, as well as an active metabolite, are recovered in urine. The elimination half-life is doubled and the plasma clearance is reduced in patients with renal failure; at the same time, the rate of recovery of neuromuscular blockade is variable and sometimes very much slower than normal (**see Pharmacokinetics**). This information should be taken into consideration if pancuronium is selected, for other reasons, to be used in a patient with renal failure.

**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 and/or Biliary Tract Disease:** The doubled elimination half-life and reduced plasma clearance determined in patients with hepatic and/or biliary tract disease, as well as limited data showing that recovery time is prolonged an average of 65% in patients with biliary tract obstruction, suggests that prolongation of neuromuscular blockade may occur. At the same time, these conditions are characterized by an approximately 50% increase in volume of distribution of pancuronium, suggesting that the total initial dose to achieve adequate relaxation may in some cases be high. The possibility of slower onset, higher total dosage and prolongation of neuromuscular blockade must be taken into consideration when pancuronium is used in these patients (**see also Pharmacokinetics**).

**Long-term Use in I.C.U.:** In the intensive care unit, in rare cases, 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. 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.

UNDER THE ABOVE CONDITIONS, APPROPRIATE MONITORING, SUCH AS USE OF A PERIPHERAL NERVE STIMULATOR, TO ASSESS THE DEGREE OF NEUROMUSCULAR BLOCKADE, MAY PRECLUDE INADVERTANT EXCESS DOSING.

**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 PAVULON®.

**C.N.S.:** PAVULON® has no known effect on consciousness, the pain threshold or cerebation. Administration should be accompanied by adequate anesthesia or sedation.

**Drug Interactions:** Prior administration of succinylcholine may enhance the neuromuscular blocking effect of PAVULON® and increase its duration of action. If succinylcholine is used before PAVULON® the administration of PAVULON® should be delayed until the patient starts recovering from succinylcholine-induced neuromuscular blockade.

If a small dose of PAVULON® is given at least 3 minutes prior to the administration of succinylcholine, in order to reduce the incidence and intensity of succinylcholine-induced fasciculations, this dose may induce a degree of neuromuscular block sufficient to cause respiratory depression in some patients.

Other nondepolarizing neuromuscular blocking agents (vecuronium, atracurium, d-tubocurarine, metocurine, and gallamine) behave in a clinically similar fashion to PAVULON®. The combinations of PAVULON®-metocurine and PAVULON®-d-tubocurarine are significantly more potent than the

additive effects of each of the individual drugs given alone; however, the duration of blockade of these combinations is not prolonged. There are insufficient data to support concomitant use of pancuronium and the other three above mentioned muscle relaxants in the same patients.

**Inhalational Anesthetics:** Use of volatile inhalational anesthetics such as enflurane, isoflurane, and halothane with PAVULON® will enhance neuromuscular blockade. Potentiation is most prominent with use of enflurane and isoflurane.

With the above agents, the intubating dose of PAVULON® 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. The relatively long duration of action of pancuronium should be taken into consideration when the drug is selected for intubation in these circumstances.

Clinical experience and animal experiments suggest that pancuronium should be given with caution to patients receiving chronic tricyclic antidepressant therapy who are anesthetized with halothane because severe ventricular arrhythmias may result from this combination. The severity of the arrhythmias appears in part related to the dose of pancuronium.

**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 preoperatively or in conjunction with PAVULON®, 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 PAVULON® (pancuronium bromide) injection.

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 performed. It is not known whether PAVULON<sup>®</sup> can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. PAVULON<sup>®</sup> should be given to a pregnant woman only if the administering clinician decides that the benefits outweigh the risks.

PAVULON<sup>®</sup> may be used in operative obstetrics (Cesarean section), but reversal of pancuronium may be unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy, because magnesium salts enhance neuromuscular blockade. Dosage should usually be reduced, as indicated, in such cases. It is also recommended that the interval between use of pancuronium and delivery be reasonably short to avoid clinically significant placental transfer.

***Pediatric Use:*** Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Due to the potential toxicity of benzyl alcohol in neonates, solutions containing benzyl alcohol must not be used in this patient population (see CONTRAINDICATIONS).

This product contains benzyl alcohol as a preservative. Benzyl alcohol, a component of this product, has been associated with serious adverse events and death, particularly in pediatric patients. The “gaspings syndrome”, (characterized by central nervous system depression, metabolic acidosis, gasping respirations, and high levels of benzyl alcohol and its metabolites found in the blood and urine) has been associated with benzyl alcohol dosages >99 mg/kg/day in neonates and low-birth-weight neonates. Additional symptoms may include gradual neurological deterioration, seizures, intracranial hemorrhage, hematologic abnormalities, skin breakdown, hepatic and renal failure, hypotension, bradycardia, and cardiovascular collapse. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are



substantially lower than those reported in association with the “gaspings syndrome”, the minimum amount of benzyl alcohol at which toxicity may occur is not known. Premature and low-birth-weight infants, as well as patients receiving high dosages, may be more likely to develop toxicity. Practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources.

**ADVERSE REACTIONS: Neuromuscular:** The most frequent adverse reaction to nondepolarizing blocking agents as a class consists of an extension of 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 respiratory insufficiency or apnea.

Inadequate reversal of the neuromuscular blockade is possible with PAVULON<sup>®</sup> as with all curariform drugs. These adverse experiences are managed by manual or mechanical ventilation until recovery is judged adequate.

Prolonged paralysis and/or skeletal muscle weakness have been reported after long-term use to support mechanical ventilation in the intensive care unit.

**Cardiovascular:** See discussion of circulatory effects in **CLINICAL PHARMACOLOGY**.

**Gastrointestinal:** Salivation is sometimes noted during very light anesthesia, especially if no anticholinergic premedication is used.

**Skin:** An occasional transient rash is noted accompanying the use of PAVULON<sup>®</sup>.

**Other:** Although histamine release is not a characteristic action of PAVULON<sup>®</sup>, rare hypersensitivity reactions such as bronchospasm, flushing, redness, hypotension, tachycardia, and other reactions possibly mediated by histamine release have been reported.

**Post-Marketing:** There have been post-marketing reports of severe allergic reactions (anaphylactic and anaphylactoid reactions) associated with the use of neuromuscular blocking agents, including PAVULON<sup>®</sup>. These reactions, in some cases, have been life-threatening and fatal. Because these reactions were reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (**see WARNINGS and PRECAUTIONS**).

**OVERDOSAGE:** The possibility of iatrogenic overdosage can be minimized by carefully monitoring the muscle twitch response to peripheral nerve stimulation.

Excessive doses of PAVULON® produce enhanced pharmacological effects. Residual neuromuscular blockade beyond the time period needed may occur with PAVULON® 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.

Regonol® (pyridostigmine bromide) injection, neostigmine, or edrophonium, in conjunction with atropine or glycopyrrolate, will usually antagonize the skeletal muscle relaxant action of PAVULON®. 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 response.

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.

**DOSAGE AND ADMINISTRATION: NOTE: CONTAINS BENZYL ALCOHOL (see CONTRAINDICATIONS, WARNINGS and PRECAUTIONS: *Pediatric Use*)**

PAVULON® (pancuronium bromide) injection is for intravenous use only. This drug should be administered by or under the supervision of experienced clinicians familiar with the use of neuromuscular blocking agents. 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. Since potent inhalational anesthetics or prior use of

succinylcholine may enhance the intensity and duration of PAVULON® (**see PRECAUTIONS: Drug Interactions**), the lower end of the recommended initial dosage range may suffice when PAVULON® is first used after intubation with succinylcholine and/or after maintenance doses of volatile liquid inhalational anesthetics are started. To obtain maximum clinical benefits of PAVULON® and to minimize the possibility of overdosage, the monitoring of muscle twitch response to a peripheral nerve stimulator is advised.

In adults under balanced anesthesia the initial intravenous dosage range is 0.04 to 0.1 mg/kg. Later incremental doses starting at 0.01 mg/kg may be used. These increments slightly increase the magnitude of the blockade and significantly increase the duration of blockade, because a significant number of myoneural junctions are still blocked when there is clinical need for more drug.

If PAVULON® is used to provide skeletal muscle relaxation for endotracheal intubation, a bolus dose of 0.06 to 0.1 mg/kg are recommended. Conditions satisfactory in intubation are usually present within 2 to 3 minutes. (**see PRECAUTIONS**).

**Dosage in Children:** Dose response studies in children indicate that, with the exception of neonates, dosage requirements are the same as for adults. Due to the potential toxicity of benzyl alcohol in neonates, solutions containing benzyl alcohol must not be used in this patient population (see CONTRAINDICATIONS).

**Cesarean Section:** The dosage to provide relaxation for intubation and operation is the same as for general surgical procedures. The dosage to provide relaxation, following usage of succinylcholine for intubation (**see PRECAUTIONS: Drug Interactions**), is the same as for general surgical procedures.

**Compatibility:** PAVULON® is compatible in solution with:

0.9% sodium chloride injection	5% dextrose and sodium chloride injection
5% dextrose injection	Lactated Ringer's injection

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

When mixed with the above solutions in glass or plastic containers, PAVULON® will remain stable in

solution for 48 hours with no alteration in potency or pH; no decomposition is observed and there is no absorption to either the glass or plastic container.

**HOW SUPPLIED:** PAVULON® is packaged in the following forms:

2 mL ampuls — 2 mg/mL — boxes of 25, NDC#0052-0444-26;

5 mL ampuls — 2 mg/mL — boxes of 25, NDC#0052-0444-25;

10 mL vials — 1 mg/mL — boxes of 25, NDC#0052-0443-25.

**STORAGE:** Both concentrations of PAVULON® will maintain full clinical potency for six months if kept at a room temperature of 18° to 22°C (65° to 72°F); or for 3 years when refrigerated at 2° to 8°C (36° to 46°F).

**CAUTION:** Federal law prohibits dispensing without prescription.



**ORGANON INC. - WEST ORANGE, NEW JERSEY 07052**

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