1. Name of the medicinal product

Pavulon, 4 mg=2 ml, solution for injection.

2. Qualitative and quantitative composition

Each ml Pavulon contains 2 mg pancuronium bromide.
For a full list of excipients, see 6.1.

3. Pharmaceutical form

Solution for injection.

4. Clinical particulars

4.1 Therapeutic indications
Pavulon is indicated as an adjunct to general anesthesia, to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgical procedures of intermediate and long duration.

4.2 Posology and method of administration
Dosage
Like other neuromuscular blocking agents, Pavulon should only be administered by or under supervision of experienced clinicians who are familiar with the action and use of these drugs.
As is the case for all other neuromuscular blocking agents, the dosage of Pavulon should be individualized in each patient.
The method of anesthesia, expected duration of surgery, possible interaction with other drugs that are administered before or during anesthesia and condition of the patient should be taken into account when determining the dose. The use of an appropriate neuromuscular monitoring technique is recommended for monitoring neuromuscular block and recovery.
Inhalational anesthetics do potentiate the neuromuscular blocking effects of Pavulon. This potentiation however, becomes clinically relevant in the course of anesthesia, when the volatile agents have reached the tissue concentrations required for this interaction. Consequently, adjustments with Pavulon should be made by administering smaller maintenance doses at less frequent intervals during procedures under inhalational anesthesia (see section 4.5).
In adult patients the following dosage recommendations may serve as a general guideline for tracheal intubation and muscle relaxation for intermediate to long lasting surgical procedures.

Tracheal intubation
The standard intubating dose during routine anesthesia is 0.08 to 0.1 mg pancuronium bromide per kg bodyweight. Clinically acceptable intubation conditions are established within 90 to 120 seconds after intravenous injection of a dose of 0.1 mg pancuronium bromide per kg bodyweight and within 120 to 180 seconds after a dose of 0.08 mg pancuronium bromide per kg bodyweight. Time from intravenous administration to 25 % recovery of control twitch height is approximately 75 minutes after a dose of 0.08 mg pancuronium bromide per kg bodyweight and approximately 100 minutes after a dose of 0.1 mg pancuronium bromide per kg bodyweight.

Doses of Pavulon for maintenance of muscle relaxation
The recommended maintenance dose is 0.01 to 0.02 mg pancuronium bromide per kg bodyweight. In order to limit cumulative effects, it is recommended to administer maintenance doses of Pavulon only when the twitch height has recovered to at least 25% of its control value.

Doses of Pavulon for surgical procedures after intubation with suxamethonium
The recommended dose is 0.04 to 0.06 mg pancuronium bromide per kg bodyweight. With these doses, the time from intravenous administration to 25% recovery of control twitch height is approximately 22 to 35 minutes, depending on the dose of suxamethonium administered. The administration of Pavulon should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Dosing in elderly patients
The same intubation and maintenance doses as for younger adults (0.08–0.1 mg/kg and 0.01–0.02 mg/kg, respectively) can be used. However, the duration of action is prolonged in elderly compared to younger subjects due to changes in pharmacokinetic mechanisms.

Dosing in pediatric patients
Clinical studies have demonstrated that the dose requirements for neonates (0–1 month) and infants (1–12 months) are comparable to adults. Due to a variable sensitivity to non-depolarizing neuromuscular blocking agents, it is recommended to use an initial test dose of 0.01–0.02 mg/kg in neonates. Children (1–14 years) are reported to require a higher dose (approximately 25%).

Dosing in overweight and obese patients
When used in overweight or obese patients (defined as patients with a body weight of 30% or more above the ideal body weight) doses should be reduced taking into account the ideal body weight.

Administration
Pavulon is administered intravenously only, preferably as a bolus injection into the line of a running infusion.

4.3 Contraindications
Former anaphylactic/ anaphylactoid reactions to pancuronium or the bromide ion or hypersensitivity to any of the excipients of Pavulon.

4.4 Special warnings and precautions for use
Since Pavulon causes paralysis of the respiratory muscles, ventilatory support is mandatory for patients treated with this drug until adequate spontaneous respiration is restored.
As with other neuromuscular blocking agents, residual curarization has been reported for Pavulon. In order to prevent complications resulting from residual curarization, it is recommended to extubate only after the patient has recovered sufficiently from neuromuscular block.
Other factors which could cause residual curarization after extubation in the post-operative phase (such as drug interactions or patient condition) should also be considered. If not used as part of standard clinical practice, the use of a reversal agent should be considered, especially in those cases where residual curarization is more likely to occur.
Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. Particularly in the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross-reactivity to neuromuscular blocking agents has been reported.
There are insufficient data to give recommendations for the use of Pavulon in the intensive care unit. In general, following long term use of muscle relaxants in the ICU, prolonged paralysis and/or skeletal muscle weakness has been noted. In order to help preclude possible prolongation of neuromuscular block and/or overdosage it is strongly recommended that neuromuscular transmission is monitored throughout the use of muscle relaxants. In addition, patients should receive adequate analgesia and sedation.
Furthermore, muscle relaxants should be titrated to effect in the individual patients by or under supervision of experienced clinicians who are familiar with their actions and with appropriate neuromuscular monitoring techniques.
Myopathy after long term administration of non-depolarizing neuromuscular blocking agents in the ICU in combination with corticosteroid therapy has been reported frequently. Therefore, for patients receiving both neuromuscular blocking agents and corticosteroids, the period of use of the neuromuscular blocking agent should be limited as much as possible.

The following conditions may influence the pharmacokinetics and/or pharmacodynamics of Pavulon:
Renal failure
Since renal excretion is the major elimination route of pancuronium, the elimination half-life is prolonged and the plasma clearance is reduced in patients with renal failure. The prolongation of elimination half-life in patients with renal failure is often but not always associated with an extended duration of neuromuscular blockade. In these patients the rate of recovery from neuromuscular block may also be decreased.

Hepatic and/or biliary tract disease
Despite the modest role of the liver in the elimination of pancuronium, major pharmacokinetic changes have been observed in patients with liver disease. Resistance to the neuromuscular blocking activity of Pavulon may occur, because of a considerable increase (up to 50 %) in the volume of distribution of the drug. At the same time hepatic and/or biliary tract disease can prolong the elimination half-life of pancuronium. The possibility of slower onset, higher total dosage requirements and prolongation of neuromuscular blockade and recovery time must be taken into consideration when Pavulon is used in these patients.

Prolonged circulation time
Conditions associated with prolonged circulation time, such as cardiovascular disease, old age, edematous states resulting in an increased volume of distribution, may contribute to an increase of onset time.

Neuromuscular disease
As is the case with other neuromuscular blocking agents, Pavulon should be used with extreme caution in patients with neuromuscular disease or after poliomyelitis since the response to neuromuscular blocking agents may be considerably altered in these patients. The magnitude and direction of this alteration may vary widely.
In patients with myastenia gravis or the myastenic (Eaton Lambert) syndrome, small doses of Pavulon may have profound effects and Pavulon should be titrated to response.

Hypothermia
In operations under hypothermia the neuromuscular blocking effect of Pavulon is increased and the duration is prolonged.

Obesity
Like other neuromuscular blocking agents, Pavulon may exhibit a prolonged duration and a prolonged spontaneous recovery in obese patients, if the administered doses are calculated on actual body weight.

Burns
Patients with burns are known to develop resistance to non-depolarizing agents. It is recommended that the dose is titrated to the response.

Conditions which may increase the effect of Pavulon are:
hypokalemia (e.g. after severe vomiting, diarrhea, and diuretic therapy), hypermagnesemia, hypocalcemia (e.g. after massive transfusions), hypoproteinemia, dehydration, acidosis, hypercapnoea, cachexia.
Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

4.5 Interaction with other medicinal products and other forms of interaction
The following drugs have been shown to influence the magnitude and/or duration of action of non-depolarizing neuromuscular blocking agents:

Effect of other drugs on Pavulon
Increased effect:
Halogenated volatile anesthetics potentiate the neuromuscular block of Pavulon. The effect only becomes apparent with maintenance dosing (see also section 4.2). Reversal of the block with anticholinesterase inhibitors could also be inhibited.
After intubation with suxamethonium (see section 4.2)
Long term concomitant use of corticosteroids and Pavulon in the ICU may result in prolonged duration of neuromuscular block or myopathy (see also section 4.4 and 4.8).
Other drugs:
- antibiotics: aminoglycoside, lincosamide and polypeptide antibiotics, acylamino-penicillin antibiotics,
- diuretics, quinidine, quinine, magnesium salts, calcium channel blocking agents, lithium salts, local anesthetics (lidocaine i.v, bupivacaine epidural) and acute administration of phenytoin or ß-blocking agents.
Recurarization has been reported after post-operative administration of: aminoglycoside, lincosamide, polypeptide and acylamino-penicillin antibiotics, quinidine, quinine and magnesium salts (see section 4.4).

Decreased effect:
- Prior chronic administration of phenytoin or carbamazepine.
- Protease inhibitors (gabexate, ulinastatin)

Variable effect:
- Administration of other non-depolarizing neuromuscular blocking agents in combination with Pavulon may produce attenuation or potentiation of the neuromuscular block, depending on the order of administration and the neuromuscular blocking agent used.
- Suxamethonium given after the administration of Pavulon may produce potentiation or attenuation of the neuromuscular blocking effect of Pavulon.

Effect of Pavulon on other drugs
Pavulon combined with lidocaine may result in a quicker onset of action of lidocaine.
The duration of action of mivacurium may be prolonged when it is administered in combination with Pavulon, as a result of a decreased plasma cholinesterase activity.

4.6 Pregnancy and lactation
There are insufficient data on the use of Pavulon during animal or human pregnancy to assess potential harm to the fetus. The drug should only be administered to a pregnant woman when the attending physician decides that the benefits outweigh the risks.
Studies with Pavulon have shown its safety for use in Cesarean section. Pavulon does not affect Apgar score, fetal muscle tone nor cardiorespiratory adaptation.
From umbilical cord sampling it

is apparent that only very limited placental transfer of Pavulon occurs, which does not lead to the observation of clinical adverse effects in the newborn. Reversal of neuromuscular block induced by Pavulon may be inhibited or unsatisfactory in patients receiving magnesium sulfate for toxemia of pregnancy because magnesium salts enhance neuromuscular blockade. Therefore, in patients receiving magnesium sulfate, the dosage of Pavulon should be reduced and be carefully titrated to twitch response.
There are no human data on the use of Pavulon during lactation. Pavulon should be given to lactating women only when the attending physician decides that the benefits outweigh the risks.

4.7 Effects on ability to drive and use machines
Since Pavulon is used as an adjunct to general anesthesia, the usual precautionary measures after a general anesthesia should be taken for ambulatory patients.

4.8 Undesirable effects
The most commonly occurring adverse drug reactions include changes in vital signs and prolonged neuromuscular block. The most frequently reported serious adverse drug reactions during post-marketing surveillance, although the overall frequency is still very rare, is 'anaphylactic and anaphylactoid reactions' and associated symptoms. See also the explanations below the table.

MedDRA SOC	Preferred term[1]	
	Uncommon/rare[2] (<1/100, >1/10 000)	Very rare (<1/10 000)
Immune system disorders		Hypersensitivity Anaphylactic reaction Anaphylactoid reaction Anaphylactic shock Anaphylactoid shock
Nervous system disorders		Flaccid paralysis
Cardiac disorders	Tachycardia	
Vascular disorders	Hypotension	Circulatory collapse and shock Flushing
Respiratory, thoracic and mediastinal disorders		Bronchospasm
Skin and subcutaneous tissue disorders		Angioneurotic edema Urticaria Rash Erythematous rash
Musculoskeletal and connective tissue disorders		Muscular weakness[3] Steroid myopathy[3]
General disorders and administration site conditions	Drug ineffective Drug effect/therapeutic response decreased Injection site pain Drug effect/therapeutic response increased	Face oedema Injection site pain Injection site reaction
Injury, poisoning and procedural complications	Prolonged neuromuscular block Delayed recovery from anesthesia	Airway complication of anaesthesia

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[1] Frequencies are estimates derived from post-marketing surveillance reports and data from the general literature.
[2] Post-marketing surveillance data cannot give precise incidence figures. For that reason, the reporting frequency was divided over two rather than five categories.
[3] After long-term use in the ICU

Anaphylaxis
Although very rare, severe anaphylactic reactions to neuromuscular blocking agents, including Pavulon, have been reported. Examples of anaphylactic / anaphylactoid reactions are: bronchospasm, cardiovascular changes (e.g. hypotension, tachycardia, circulatory collapse - shock), and cutaneous changes (e.g. angioedema, urticaria). These reactions have, in some cases, been fatal. Due to the possible severity of these reactions, one should always assume that they may occur and take the necessary precautions.
Since neuromuscular blocking agents in general are known to be capable of inducing histamine release both locally at the site of injection and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalized histaminoid (anaphylactoid) reactions should always be taken into consideration when administering these drugs. Experimental studies with intradermal injection of Pavulon have demonstrated that this drug has only a weak capacity for inducing local histamine release. Controlled studies in man failed to demonstrate any significant rise in histamine plasma levels after intravenous administration of Pavulon.

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

Myopathy
A few cases of myopathy have been reported after Pavulon was used in the ICU in combination with corticosteroids (see also section 4.4 and 4.5).

Postoperative pulmonary complications
In one published clinical study, patients treated with pancuronium bromide who had residual neuromuscular blockade had an increased incidence of postoperative pulmonary complications compared to patients without residual neuromuscular blockade. It is therefore important to prevent residual neuromuscular block (see section 4.4).

Ophthalmic
Although not reported during post-marketing surveillance, literature indicates that Pavulon can produce a significant fall in normal and elevated intraocular pressure for some minutes following administration and also to produce miosis. These changes may attenuate the rise in intraocular pressure due to laryngoscopy and tracheal intubation. Pavulon can therefore be used in ophthalmic surgery.

Cardiovascular
Pavulon causes only minor cardiovascular effects, consisting of a moderate rise in heart rate, mean arterial blood pressure and cardiac output. These effects, which are due to the slight cardioselective vagolytic action of the drug, should be taken into account in particular when doses above the recommended dose range are administered and when assessing the dosage and/or use of vagolytic drugs for premedication or at induction of anesthesia.
Through its vagolytic action, Pavulon antagonizes the cardiac depression due to the use of some inhalational anesthetics. In addition, the bradycardia induced by some potent anesthetics and analgesics is corrected by the use of Pavulon.

4.9 Overdose
In the event of overdosage and prolonged neuromuscular block, the patient should continue to receive ventilatory support and sedation. Upon start of spontaneous recovery an acetylcholinesterase inhibitor (e.g. neostigmine, edrophonium, pyridostigmine) should be administered in adequate doses. When administration of an acetylcholinesterase-inhibiting agent fails to reverse the neuromuscular effects of Pavulon, ventilation must be continued until spontaneous breathing is restored. Repeated dosage of an acetylcholinesterase inhibitor can be dangerous.

5. Pharmacological properties

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: non-depolarizing muscle relaxants, ATC code: M03A C01.
Pavulon (pancuronium bromide) is a nondepolarizing neuromuscular blocking agent chemically designated as the aminosteroid 1,1'-(3α,17β-diacetoxy-5α-androstan-2β,16β-ylene) bis (1-methylpiperidinium) dibromide. Pavulon blocks the transmission process between the motor nerve- ending and striated muscle by binding competitively with acetylcholine to the nicotinic receptors located in the motor end-plate region of striated muscle.
Unlike depolarizing neuromuscular blocking agents such as suxamethonium, Pavulon does not cause muscle fasciculations.
Pavulon has no hormonal activity.
Pavulon exerts a slight and dose-dependent vagolytic action.
Within the clinical dose range it has no ganglion blocking action.
Acetylcholinesterase inhibitors such as neostigmine, pyridostigmine or edrophonium antagonize the action of Pavulon.
The ED_{95} (dose required to produce 95% suppression of twitch height) is approximately 0.06 mg pancuronium bromide per kg bodyweight under neurolept anesthesia.
Within 90 to 120 seconds following intravenous administration of a dose of 0.1 mg pancuronium bromide per kg bodyweight clinically acceptable intubation conditions can be achieved. General muscle paralysis adequate for any type of procedure is established within 2–4 minutes. The clinical duration (the duration until spontaneous recovery to 25% of control twitch height) with this dose is approximately 100 minutes. The total duration (time until spontaneous recovery to 90% of control twitch height) is 120–180 minutes. With lower doses of pancuronium bromide onset time to maximum block is prolonged and duration of action is shortened.

5.2 Pharmacokinetic properties
Pancuronium has a(n) (apparent) volume of distribution at steady state conditions of 180–290 $ml.kg^{-1}$. Metabolism mainly occurs by de-acetylation, forming 3-OH pancuronium and to a lesser extent 17-OH and 3,17-OH pancuronium. These metabolites do not significantly contribute to the neuromuscular block occurring after the administration of Pavulon.
Renal excretion is the major route of elimination. Forty (40) to 70% of the initial dose of pancuronium is excreted in urine, mainly as unchanged pancuronium. Five (5) to 15% is excreted in the bile. Less than 5% of the dose is excreted in urine as 17-OH and 3,17-OH pancuronium and approximately 20% in urine and bile as 3-OH pancuronium.
Plasma clearance of pancuronium is 0.8–3.0 $ml.min\text{-}1.kg^{-1}$ and plasma elimination half-life is 110–190 min.
Elderly have a decreased plasma clearance of pancuronium because of an age-related decreased renal excretion.
Renal insufficiency may increase plasma elimination half-life (up to four-fold). Hepatic insufficiency mainly results in an increased plasma elimination half-life, in addition to a possible increase in distribution volume (approximately 50%). In the case of biliary tract obstruction clearance may also decrease.

5.3 Preclinical safety data
Animal studies showed no remarkable results.

6. Pharmaceutical particulars

6.1 List of excipients
Pavulon contains the following excipients:
- sodium acetate (E262)
- sodium chloride
- acetic acid (E260)
- water for injection.

6.2 Incompatibilities
As is the case for many other drugs, incompatibility has been documented for Pavulon when added to thiopental.
Except for those solutions with which Pavulon has shown to be compatible (see section 6.6), it is not recommended to mix Pavulon with solutions, or drugs in the same syringe or bag.
If Pavulon is administered via the same infusion line that is also used for other drugs, it is important that this infusion line is adequately flushed (e.g. with 0.9% NaCl) between administration of Pavulon and drugs for which incompatibility with Pavulon has been demonstrated or for which compatibility with Pavulon has not been established.

6.3 Shelf life
Pavulon has a shelf life of 3 years, provided it is stored under the prescribed conditions (see Special precautions for storage).
The date mentioned behind 'exp.:' on the label of the ampoule is the expiry date up to which the product may be used.
Since Pavulon does not contain a preservative, the solution should be used immediately after opening the ampoule.

6.4 Special precautions for storage
Pavulon must be stored at 2–8 °C in the dark.

6.5 Nature and contents of container
Type I glass ampoules containing 2 ml of pancuronium bromide solution at a concentration of 2 mg/ml.
Packaging containing 1, 10, 25, 50 or 100 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for handling and disposal
In a concentration of 2.0 mg/ml Pavulon was shown to be compatible with: 0.9% sodium chloride solution, 5% anhydrous glucose solution and lactated Ringer's solution and may be mixed in the same infusion line. Administration should begin immediately after mixing. Unused solution should be discarded.

7. Date of revision of the text

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