1. NAME OF THE MEDICINAL PRODUCT
   Pancuronium Bromide 2mg/ml Injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
   Each 1 ml contains 2 mg of pancuronium bromide.
   Each 2 ml ampoule contains 4 mg of pancuronium bromide.
   For excipients, see 6.1.

3. PHARMACEUTICAL FORM
   Solution for injection.

4. CLINICAL PARTICULARS
   4.1. Therapeutic Indications
   The active substance of pancuronium bromide is an amino steroid which effectively blocks transmission of motor nerve impulses to the striated muscle receptors. It is a non-depolarising neuromuscular blocking agent with a long duration of action and is used in the following indications:

   1. As an adjuvant in surgical anaesthesia to obtain relaxation of skeletal muscles in a wide range of surgical procedures.
   2. Use in intensive care as a non-depolarising neuromuscular blocker for the treatment of various pathologies e.g. intractable status asthmaticus and tetanus.

   4.2. Posology and Method of Administration
   Pancuronium should be administered intravenously.

   It is not recommended to be given by infusion.
The dosage should be individualised as there is a wide variation in individual response to muscle relaxants. When determining the dose, the method of anaesthesia, expected duration of surgery, potential interaction with other drugs that are administered before and during anaesthesia and the condition of the patient should be taken into account.

The use of a peripheral nerve stimulator is recommended for monitoring the neuromuscular block and recovery.

**ADULT:**

Initial dose: 50-80 micrograms/kg (intubation accomplished within 150-120 seconds) or 80-100 micrograms/kg (intubation accomplished within 120-90 seconds).

Incremental doses: 10-20 micrograms/kg

**PAEDIATRIC:**

Initial dose: 60-100 micrograms/kg

Incremental doses: 10-20 micrograms/kg

**NEONATES:**

Doses of pancuronium in neonates up to one month of age must be carefully individualised since neonates are particularly sensitive to non-depolarising neuromuscular blocking agents.

Dosage 30-40 micrograms/kg initially I/V followed by 10-20 micrograms/kg thereafter.

If succinylcholine is used for intubation the administration of pancuronium should be delayed until the patient has clinically recovered from the neuromuscular block induced by succinylcholine.

Following the administration of suxamethonium the dosage of pancuronium may be considerably reduced:

**Adults:**
Initial dose: 20-60 micrograms/kg
Incremental doses 10-20 micrograms/kg

**Children:**
Initial dose: 20-60 micrograms/kg
Incremental doses 10-20 micrograms/kg

**ELDERLY:**
The neuromuscular blocking activity of pancuronium is prolonged in the elderly and lower doses may be necessary.

**OBESITY:**

In obese patients doses of pancuronium based on a mg/kg basis may lead to overdosage. Dosage must be adjusted according to response.

**INTENSIVE CARE:**

Pancuronium is longer acting in the intensive care patient, and an intravenous dose of 60 micrograms/kg every one to one and a half hours, or even less frequently is usually adequate.

**IMPAIRED LIVER AND RENAL FUNCTION:**

Care must be exercised in patients with impaired liver or renal function as mentioned in the special warnings and precautions section.

Hyperdiuresis may result in a decreased neuromuscular blocking effect.

In the control of tetanus, duration of pancuronium relaxation probably depends upon the severity of the spasm, therefore duration of effect can be variable.

The duration of action depends upon the clinical condition of the patient and the dose administered, but in normal subjects receiving perioperative muscle relaxant doses the duration of action is usually 45-60 minutes.

Pancuronium should not be mixed with other agents in the same syringe, or with solutions for intravenous infusions as a change in pH may cause precipitation.

Discard any unused solution.

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**4.3. Contraindications**

Patients with a known hypersensitivity to pancuronium or the bromide ion. Concurrent use of a depolarising neuromuscular blocking agent e.g. suxamethonium.

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**4.4. Special Warnings and Special Precautions for Use**

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. (See also Section 4.8).
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 (see also Section 4.8).

**Renal Failure**

As pancuronium bromide is excreted mainly in the renal system, the elimination half-life is prolonged in renal failure, resulting in a reduction in plasma clearance and prolonged duration of action.

The prolongation of half-life in patients with renal failure is often but not always associated with an extended duration of neuromuscular blockage. In these patients, the recovery from neuromuscular block may also be prolonged.

**Impaired Hepatic/Biliary Tract Disease.**

The duration of action may be prolonged in these conditions and resistance to neuromuscular blocking action of pancuronium bromide may occur because of the increased volume of distribution of the drug.

In such conditions, the drug has a slower onset and coupled with the increased total dosage requirements, there may be a prolongation of blockade and recovering time in these patients.

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.

As with other non-depolarising muscle relaxants pancuronium should be used with care in patients with pre-existing pulmonary, hepatic or renal disease and with particular care in patients with muscular dystrophies, myasthenia gravis and myasthenic syndrome unless it is intended to administer prolonged post-operative respiratory assistance. As is the case with other curariform agents, in cases of neuromuscular disease or after poliomyelitis, pancuronium should be used with extreme caution since the response to neuromuscular blocking agents may be considerably altered in these patients. The magnitude and direction of this alteration may vary widely.

Before administration of pancuronium conditions such as electrolyte disturbance, altered pH, and dehydration should be corrected if possible. Pancuronium should be used cautiously in patients with a tendency to hypertension.

Pancuronium can cause a reduction in the partial prothromboplastin time and prothrombin time. Conditions associated with slower circulation times e.g. cardiovascular disease, oedema, old age result in an increased volume of distribution which may lead to an increased onset time.
Pancuronium should be used with particular care in neonates, in ill or cachetic patients, in the presence of liver disease or obstructive jaundice (resistant to the effects of drugs) in states with altered plasma protein levels or when there is diminished renal blood flow or renal disease. In operations employing the hypothermic techniques the neuromuscular blocking effect of non-depolarising drugs is decreased and increased by warming the patient.

Pancuronium should be administered in carefully adjusted dosage or under the supervision of a qualified anaesthetist and only when facilities for controlled ventilation, insufflation with oxygen and endotracheal intubation are available for immediate use.

Since pancuronium causes relaxation of the respiratory muscles, respiration must be assisted in all patients. It is essential to ensure that the patient is breathing spontaneously, deeply and regularly before leaving the theatre after anaesthesia. The neuromuscular blockade achieved with pancuronium can be reversed with a cholinesterase inhibiting agent (e.g. neostigmine) in an adequate dose, together with atropine as an anticholinergic agent.

Care should be exercised if there is a danger of regurgitation when intubating the patient, for example during crash induction.

Other conditions which may increase the effect of pancuronium are: hypokalaemia (e.g. after severe vomiting, diarrhoea, digitalisation and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnoea and cachexia.

4.5. Interaction with other Medicinal Products and other Forms of Interaction

1. Suxamethonium. Used prior to pancuronium (for endotracheal intubation) enhances the relaxation effect of the pancuronium and the duration of action. Therefore administration of pancuronium should be delayed until suxamethonium shows signs of wearing off.

2. Anaesthetics. The following anaesthetics may potentiate the neuromuscular blocking activity of pancuronium: halothane, ether, enflurane, isoflurane, methoxyflurane, cyclopropane, thiopentone, methohexitone, ketamine, fentanyl, gammahydroxybutyrate, etomidate.

3. The following drugs may influence the duration of action of pancuronium and the intensity of neuromuscular block.

Potentiation: Other non-depolarising muscle relaxants, prior administration of succinylcholine, antibiotics of the polypeptide and aminoglycoside groups, diazepam, propranolol, thiamine (high dose), MAO inhibiting agents, quinidine, magnesium sulphate, protamine, nitroglycerin, narcotic analgesics,
diuretics, phenytoin, alpha and beta adrenergic blocking agents, imidazoles, metronidazole, noradrenaline and adrenaline.

**Decreased effect:** Neostigmine, edrophonium, corticosteroids (high dose), noradrenaline, adrenaline, potassium chloride, calcium chloride, sodium chloride, heparin (temporary decrease), azathioprine, theophylline, pyridostigmine, neurolept analgesia and propanidid.

**Variable effect:** Depolarising muscle relaxants given after the administration of pancuronium may produce potentiation or attenuation of the neuromuscular blocking effect.

The non-depolarising drug increases resistance towards the neuromuscular blocking effect of the depolarising drug. Therefore high doses of a depolarising drug are necessary before muscular relaxation can be obtained. These high doses of a depolarising drug may cause endplate desensitisation and prolong post-operative apnoea.

Unlike a non-depolarising block, a depolarising block cannot be overcome by, and may even be worsened by an anticholinesterase agent.

The duration of action of mivacurium has been found to be significantly increased when given after pancuronium, due to the reduction of plasma cholinesterase activity by pancuronium.

**Influence on the cardiovascular system:** Pancuronium does not intensify the hypotension induced by halothane; in addition the cardiac depression is partly restored. The excessive bradycardia induced by neurolept analgesia and some of the cholinergic effects of morphine derivatives are counteracted by pancuronium.

Pancuronium should be given with caution to patients receiving chronic tricyclic antidepressant therapy who are anaesthetised with halothane or any inhalation anaesthetic since this enhances the predisposition to the development of cardiac arrhythmias associated with tricyclic antidepressants.

Recent evidence suggests that alkylating drugs (nitrogen mustards) should be considered a possible hazard when given to patients during anaesthesia involving the use of muscle relaxants.

### 4.6. Pregnancy and Lactation

The use of pancuronium in pregnant or breast feeding women with respect to safety has not been established. Therefore the drug should only be administered to pregnant women or lactating women when the attending physician decides that the potential benefits outweigh the risks.
Pancuronium may be used for caesarean section. Pancuronium does not affect Apgar score, fetal muscle tonus nor cardiorespiratory adaptation of the newborn. From assays of pancuronium concentration in umbilical blood samples it is apparent that only very limited placental transfer of pancuronium occurs.

The reversal of neuromuscular block induced by pancuronium may be unsatisfactory in patients receiving magnesium sulphate for toxaemia of pregnancy because magnesium salts enhance neuromuscular blockade. Dosages should be reduced in such cases.

4.7. Effects on Ability to Drive and Use Machines

It is not recommended to use potentially dangerous machinery or drive a car within 24 hours after full recovery from the neuromuscular blocking action of pancuronium.

4.8. Undesirable Effects

High doses of a depolarising drug may cause end-plate desensitisation and prolong post-operative apnoea.

Cardiovascular: Increased pulse rate and cardiac output. Blood pressure may rise. Arrhythmias may occur occasionally.

Gastrointestinal: Salivation is sometimes noted during anaesthesia.

Hypersensitivity: Occasional transient rash has been noted.

Injection Site Reactions: Pain or local skin reactions noted at the site of injection.

Respiratory: Bronchospasm has rarely been reported.

Serious or life threatening reactions: Severe anaphylactoid reactions have been reported uncommonly. In the case of previous anaphylactic reactions to neuromuscular blocking agents, special precautions should be taken since allergic cross reactivity between neuromuscular blocking agents has been reported.

Since neuromuscular blocking agents in general are known to be capable of inducing histamine release both locally and systemically, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions such as bronchospasm and cardiovascular changes should always be taken into consideration when administering these drugs.
Ocular: Pancuronium decreases intra-ocular pressure and induces miosis, both effects being favourable in ophthalmic surgery.

4.9. Overdose

Clinical features: The symptoms are those of prolonged apnoea, respiratory depression and/or muscle weakness. Death may follow acute respiratory failure.

Management: Neostigmine at a dose of 2.5mg and Atropine at a dose of 1.2mg can be administered to reverse the neuromuscular block whilst ventilation is continued. When administration of the cholinesterase inhibiting agent fails to reverse the neuromuscular blocking effects of pancuronium ventilation must continue until spontaneous breathing is restored. Repeated dosage of cholinesterase inhibitor can be dangerous.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic Properties

Pharmacotherapeutic group: Muscle relaxants, peripherally acting agents, other quaternary ammonium compounds, M03AC01

ATC code: M03AC01

Pancuronium bromide produces pharmacologic effects similar to those of other non-depolarising neuromuscular blocking agents. The drug may produce an increase in heart rate which appears to result from a direct blocking effect on the acetylcholine receptors of the heart. The increase in heart rate appears to be dose related and is minimal with usual doses. Pancuronium causes little or no histamine release and no ganglionic blockade and therefore does not cause hypotension or bronchospasm. Despite its steroidal structure, the drug exhibits no hormonal activity.

5.2. Pharmacokinetic Properties

Following I/V administration of pancuronium bromide 60micrograms /kg, muscle relaxation reaches a level suitable for endotracheal intubation within 2-3 minutes, slightly more rapidly than with tubocurarine. The onset and duration of paralysis are dose related. After a dose of 60micrograms/kg, the effects of the drug begin to subside in about 35-45 minutes. Supplemental doses may increase the magnitude and duration of the neuromuscular blockade. The duration of action depends upon the clinical condition of the
patient and the dose administered, but in normal subjects receiving perioperative muscle relaxant doses the duration of action is usually 45-60 minutes.

Protein binding of pancuronium does not appear to be substantial. The activity of the drug is not greatly affected by plasma carbon dioxide concentrations or pH. Redistribution is responsible for the termination of activity following single doses. Pancuronium crosses the placenta in small amounts.

Plasma concentrations appear to decline in a triphasic manner. In adults with normal renal and hepatic function, the half-life in the terminal phase is about 2 hours. The elimination half-life may be prolonged in patients with impaired renal and/or hepatic function. The drug is eliminated mainly unchanged by the kidneys, although small amounts may be metabolised and some of the drug may be eliminated in the bile.

5.3. Pre-clinical Safety Data

There is no pre-clinical data of relevance to the prescriber which are additional to that already included in other sections of the SPC.

6. PHARMACEUTICAL PARTICULARS

6.1. List of Excipients

Sodium chloride, sodium acetate, acetic acid, sodium hydroxide, nitrogen and Water for Injections

6.2. Incompatibilities

Do not mix other solutions in the same syringe as a change in pH can cause precipitation.

6.3. Shelf Life

2 years

6.4. Special Precautions for Storage
Store at 2°C -8°C.
Keep the container in the outer carton.
Do not freeze.

6.5. Nature and Contents of Container

2ml Type I clear glass ampoules.
Pack sizes of 5, 10 and 50.

6.6. Instructions for Use/Handling

For single use only. Any unused solution should be discarded.

7 MARKETING AUTHORISATION HOLDER

Hospira UK Limited
Horizon
Honey Lane
Hurley
Maidenhead
SL6 6RJ
UK

8. MARKETING AUTHORISATION NUMBER

PL 04515/0062.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORIZATION

07/02/1997.

10 DATE OF REVISION OF THE TEXT