# Summary of Product Characteristics

## 1 NAME OF THE MEDICINAL PRODUCT

Pancuronium Bromide 2 mg/ml Solution for 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.

Excipients with known effect:
For the full list of excipients, see section 6.1.

## 3 PHARMACEUTICAL FORM

Solution for injection.
A clear, colourless solution with a pH of 3.8 – 4.2.

## 4 CLINICAL PARTICULARS

### 4.1 Therapeutic Indications

Pancuronium bromide is a neuromuscular blocking agent with a long duration of action. It is used as an adjuvant in surgical anaesthesia to obtain relaxation of the skeletal muscles in a wide range of surgical procedures. It is also used as relaxant in orthopaedic manipulations. Used in intensive care therapy for a variety of pathologies e.g. intractable status asthmaticus and tetanus.

### 4.2 Posology and method of administration

**Posology**

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

The following may be used as a guideline:

ADULT: Initial dose: 50-80 micrograms/kg (intubation within 150 to 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:

Initial dose: 30-40 micrograms/kg

Incremental doses: As neonates are sensitive this dose should be adjusted according to the initial response but generally incremental doses lie in the range 10 to 20 micrograms/kg.

Ifsuxamethonium is used for intubation, the administration of pancuronium bromide should be delayed until the patient has clinically recovered from the neuromuscular block induced by suxamethonium.

Following the administration of suxamethonium, the dose of pancuronium bromide 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 bromide is prolonged in the elderly and lower doses may be necessary.

**OBESITY:**
In obese patients, doses of pancuronium bromide based on a mg/kg basis, may lead to overdose. The dose must be adjusted according to response.

**INTENSIVE CARE:**
Pancuronium bromide 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. See section 4.4.

Hyperdiuresis may result in a decreased neuromuscular blocking effect.

In the control of tetanus, the duration of pancuronium bromide 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 bromide 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.

**Method of administration**

Pancuronium Bromide Solution for Injection is administered intravenously. It is not recommended to be given by infusion. The dosage should be individualised for each patient as there is a wide variation in individual response to muscle relaxants.

**4.3 Contraindications**

Hypersensitivity to pancuronium or the bromide ion or to any of the excipients listed in section 6.1.
Concurrent use of a depolarising neuromuscular blocking drug e.g. Suxamethonium.

**4.4 Special warnings and precautions for use**

**<u>Warnings</u>**

Anaphylactic reactions can occur following the administration of neuromuscular blocking agents. Precautions for treating such reactions should always be taken. (See 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 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 the 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 recovery time in these patients.
As with other non-depolarising muscle relaxants pancuronium bromide should be used with care in patients with pre-existing pulmonary, hepatic or renal disease and with particular care in patients with muscular dystrophy, myasthenia gravis and myasthenic syndrome, unless it is intended to administer prolonged post-operative respiratory assistance.

Before administration of pancuronium bromide conditions such as electrolyte disturbance, altered pH and dehydration should, if possible, be corrected.

Pancuronium bromide should be used cautiously in patients with a tendency for hypertension.

Pancuronium bromide can cause a reduction in the partial prothromboplastin time and prothrombin time. Conditions associated with slower circulation times, e.g. cardiovascular disease, oedema, and old age, result in an increased volume of distribution, which may lead to an increased onset time.

Pancuronium bromide should be used with particular care in neo-nates, in ill or cachectic 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 hypothermic techniques, the neuromuscular blocking effect of non-depolarising drugs is decreased and increased by warming the patient.

*Neuromuscular disease:* As is the case with other curariform agents, in cases of neuromuscular disease or after poliomyelitis, pancuronium bromide 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. In patients with myasthenia gravis or the myasthenic (Eaton Lambert) syndrome, small doses of pancuronium bromide may have profound effects and only very small doses of pancuronium bromide should be used initially.

Since pancuronium bromide 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 blockage achieved with Pancuronium bromide 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 bromide are:hypokalaemia (e.g. after severe vomiting, diarrhoea, digitalisation and diuretic therapy), hypermagnesaemia, hypocalcaemia (after massive transfusions), hypoproteinaemia, dehydration, acidosis, hypercapnia and cachexia. Severe electrolyte disturbances, altered blood pH or dehydration should therefore be corrected when possible.

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

In man, pancuronium bromide has been shown to cross the blood brain barrier.

Excipient information
This medicine contains less than 1 mmol sodium (23 mg) per ampoule, that is to say essentially 'sodium- free'.

**Precautions:**
Pancuronium bromide 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 or endotracheal intubation are available for immediate use.

**4.5 Interaction with other medicinal products and other forms of interactions**

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

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

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

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

Variable effect: Noradrenaline, adrenaline, depolarising muscle relaxants given after the administration of pancuronium bromide 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 bromide, due to the reduction of plasma cholinesterase activity by the pancuronium bromide.

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

Several studies have attributed the occurrence of acute myopathy in Intensive Care Unit patients to the combination of corticosteroids and neuromuscular blocking agents.

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 Fertility, pregnancy and lactation**

The safe use of pancuronium bromide in pregnant and breast-feeding women with respect to safety has not been established. Therefore the drug should only be administered to pregnant women when the attending physician decides that the potential benefits outweigh the risks. Therefore it should not be used in women likely to become pregnant or breast-feeding mothers and particularly during the first twelve weeks of pregnancy unless, in the opinion of the physician, the potential benefits outweigh the unknown hazards.

Pancuronium bromide may be used for caesarean section. Pancuronium bromide does not affect Apgar score, foetal muscle tonus or cardiorespiratory adaptation of the new-born. From assays of pancuronium bromide 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 bromide may be unsatisfactory in patients receiving magnesium sulfate for toxaemia of pregnancy because magnesium salts enhance the neuromuscular blockade. The dose 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 bromide.

**4.8 Undesirable effects**

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

*Cardiac disorders and vascular disorders:* After pancuronium bromide administration, a slight to moderate rise in arterial pressure may occur. Increased pulse rate and cardiac output are frequently reported, showing pancuronium bromide to have weak vagolytic activity. In general this is considered to be a favourable effect. Arrhythmias may occur occasionally.

*Eye disorders*: Pancuronium bromide decreases intra-ocular pressure and induces miosis, both effects being favourable in ophthalmic surgery.

*Gastrointestinal disorders:* Salivation is sometimes noted during anaesthesia.
*Skin and subcutaneous tissue disorders:* Rash
*Immune disorders:* Hypersensitivity
Anaphylactic reactions to neuromuscular blocking agents in general have been reported. Although these are very rarely seen with pancuronium bromide, precautions for treating such reactions if they occur, should always be taken. Particularly in the case of known former anaphylactic reactions to neuromuscular blocking agents, special caution should be taken since allergic cross reactivity between neuromuscular blocking agents has been reported (see section 4.4).
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.

Experimental studies with intradermal injection of pancuronium bromide 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 pancuronium bromide.

*General disorders and administration site conditions:* Injection Site Reactions: Pain or local skin reactions have been noted at the site of injection.
*Respiratory disorders:* Bronchospasm has rarely been reported.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance.
Website: www.hpra.ie.

**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 (2.5 mg) administered with atropine (1.2 mg) or glycopyrrolate, can be used to reverse the neuromuscular block while ventilation is continued. When administration of a cholinesterase inhibiting agent fails to reverse the neuromuscular blocking effects of pancuronium bromide, ventilation must continue until spontaneous breathing is restored. Repeated doses of cholinesterase inhibitors can be dangerous.

**5 PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**

Pharmacotherapeutic group: ATC code: M03AC01
Mechanism of action
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 bromide 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**

Absorption
Following I/V administration of pancuronium bromide 0.06 mg/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 0.06 mg/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.

Distribution
Protein binding of pancuronium bromide 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 bromide crosses the placenta in small amounts.

Elimination
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 Preclinical safety data**

None.

**6 PHARMACEUTICAL PARTICULARS**

**6.1 List of excipients**

Sodium chloride
Sodium acetate trihydrate
Glacial acetic acid
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 in a refrigerator (2-8 °C). Do not freeze. Keep ampoule in the outer carton in order to protect from light.

**6.5 Nature and contents of container**

2 ml Type I clear glass ampoules.
Pack sizes of 5, 10 and 50.
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

For single use only. Discard any unused contents.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**7 MARKETING AUTHORISATION HOLDER**

Pfizer Healthcare Ireland
9 Riverwalk
National Digital Park
Citywest Business Campus
Dublin 24
Ireland

**8 MARKETING AUTHORISATION NUMBER**

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