

## 1. NAME OF THE MEDICINAL PRODUCT

Pancuronium Injection BP 4mg in 2ml.

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 2ml contains 4mg of pancuronium bromide (0.2% w/v).

## 3. PHARMACEUTICAL FORM

Colourless, sterile solution intended for parenteral administration to human beings.

## 4. CLINICAL PARTICULARS

### 4.1. Therapeutic Indications

Pancuronium bromide a non-depolarising neuromuscular blocking agent with a medium duration of action. It is used as an adjuvant in surgical anaesthesia to obtain relaxation of the skeletal muscle in a wide range of surgical procedures.

Pancuronium is also employed for neuromuscular blockade during intensive care therapy for a variety of pathologies, including intractable status asthmaticus and tetanus.

### 4.2. Posology and Method of Administration

Pancuronium Injection BP 4mg in 2ml is for intravenous administration.

When determining the dose, the method of administration, expected duration of surgery, potential interaction with other drugs that are administered before or during anaesthesia and the condition of the patient should be taken into account. The use of a peripheral nerve stimulator is recommended for monitoring neuromuscular block and recovery.

The following may be used as a general guide to dosage :

**Adult Surgery :** Initial dose 50 - 80 micrograms/kg (intubation accomplished within 120 - 150 seconds) or 80 - 100 micrograms/kg (intubation accomplished within 90 - 120 seconds).  
Incremental doses : 10 - 20 micrograms/kg.

**Child Surgery :** Initial dose : 60 - 100 micrograms/kg.  
Incremental doses : 10 - 20 micrograms/kg.

**Neonatal Surgery :** 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 - 20 micrograms/kg body weight.

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.

In obese patients, all of these doses should be reduced.

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 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.

The neuromuscular blocking activity of pancuronium is prolonged in the elderly.

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

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

Any unused solution should be discarded.

### **4.3. Contraindications**

Patients with a known hypersensitivity to pancuronium injection. Pancuronium should not be used before or concurrently with a depolarising neuromuscular blocking drug e.g. suxamethonium (See also Section 4.5).

### **4.4 Special warnings and precautions for use**

Pancuronium should be administered only by anaesthetists familiar with its use, 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. The neuromuscular blockade achieved with pancuronium can be reversed with a cholinesterase inhibiting agent such as neostigmine in an adequate dose.

It is essential to ensure that the patient is breathing spontaneously, before leaving the theatre after anaesthesia.

**Anaphylactic reactions:**

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).

**Myopathies and Neuromuscular disease:**

As with other non-depolarising muscle relaxants pancuronium should be used with 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, pancuronium should be used with extreme caution in cases of 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 myasthenia gravis or the myasthenic (Eaton Lambert) syndrome, small doses of pancuronium may have profound effects and only very small doses of pancuronium should be used initially.

**Renal impairment:** 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. Pancuronium should be used with caution in patients with severe renal impairment as the duration of action can be prolonged.

Prolongation of half-life and prolonged recovery of the neuromuscular blockade in patients with renal failure is often (but not always) associated with an extended duration of neuromuscular blockade. Hyperdiuresis may result in a decreased neuromuscular blocking effect.

**Hepatic and/or biliary tract disease:** In hepatic disease (including obstructive jaundice) slower onset, higher total dosage requirements and prolongation of neuromuscular blockade and recovery time may occur with pancuronium because of

- significant increases (up to 50%) in its volume of distribution
- prolonged elimination half life

**Respiratory disease:**

Caution in patients with pre-existing respiratory disease

**Hypertension:**

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

**Altered circulation time :**

Conditions associated with slower 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.

**Carcinomatosis:**

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

**Other circumstances where particular care is needed:**

Possible increased effect of pancuronium in

- neonates (see below Hypothermia)
- ill or cachetic patients
- hypoproteinaemia
- electrolyte disturbances (eg hypokalaemia, hypermagnesaemia, acidosis, dehydration, hypercapnoea). These should be corrected, if possible, prior to pancuronium use.

**Halothane anaesthesia:**

Pancuronium can enhance dysrhythmias during halothane anaesthesia.

Bleeding/clotting time:

Pancuronium (like d-tubocurarine) causes a reduction in the partial thromboplastin time and the prothrombin time.

Hypothermia:

In operations requiring hypothermia, the neuromuscular blockade of non-depolarising drugs is decreased and increases when re-warming the patient. Hypothermia in neonates therefore, requires a reduced dosage of pancuronium

Malignant hyperpyrexia:

Malignant hyperpyrexia may occur in conjunction with the use of pancuronium.

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

The following drugs have been shown to influence the intensity of effect and/or duration of action of non-depolarising neuromuscular blocking agents:

Increased effect:

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.

Anaesthetics: Halothane, ether, enflurane, isoflurane, methoxyflurane, cyclopropane, thiopental, methohexital, ketamine, fentanyl, gammahydroxybutyrate, etomidate.

Other drugs: Other non-depolarising muscle relaxants, prior administration of succinylcholine, aminoglycoside and polypeptide antibiotics, diuretics, beta-adrenergic blocking agents, propranolol, clindamycin, piperacillin, polymixins, calcium channel blockers, verapamil thiamine (high dose), M.A.O. inhibiting agents, quinidine, protamine, phenytoin, alpha-adrenergic blocking agents, imidazoles, metronidazole, nitroglycerin, diazepam, magnesium sulphate, narcotic analgesics, noradrenaline and adrenaline.

Decreased effect:

Anaesthetics: Neurolept analgesia, propanidid.

Other drugs : Neostigmine, edrophonium, pyridostigmine, prior chronic administration of corticosteroids (high dose), noradrenaline, adrenaline, azathioprine, theophylline, potassium chloride, calcium chloride, sodium chloride, heparin (temporary decrease).

Donepezil may antagonise the effects of pancuronium.

Variable effect:

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

Carbamazepine may result in accelerated recovery from neuromuscular blockade.

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, 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.

Effect within the cardiovascular system:

Pancuronium should be given with caution to a patient receiving chronic tricyclic antidepressant therapy who is 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 due to synergic effects over the QT prolongation.

#### **4.6. Pregnancy and Lactation**

There are insufficient data on the use of pancuronium during animal or human pregnancy to assess potential harm to the foetus. The drug should only be administered to a pregnant woman when the attending physician decides that the benefits outweigh the risks.

Caesarean section : Studies with pancuronium have shown its safety for use in caesarean section. Pancuronium does not affect Apgar score, foetal muscle tone nor cardiorespiratory adaptation of the newborn. From assays of the pancuronium concentration in umbilical blood samples, it is apparent that only very limited placental transfer of pancuronium occurs.

Reversal of neuromuscular block induced by pancuronium may be unsatisfactory in patients receiving magnesium sulphate for toxemia 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**

Not applicable as the patient would be too ill.

#### **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.

#### **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 a cholinesterase inhibiting agent fails to reverse the blocking effects of pancuronium, ventilation must be continued until spontaneous breathing is restored. It is important that attempts at reversal of pancuronium should not be carried out without prior assessment of the adequacy of neuromuscular transmission e.g. with a peripheral nerve stimulator as repeated dosage of a 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 is a quaternary ammonium steroid and is a non-depolarising (competitive) neuromuscular blocking agent. It prevents depolarisation of the motor end plate, thus blocking the transmission of motor nerve impulses to striated muscle receptors. 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.

Histamine mediated effects are relatively rare but have been reported (see section 4.8)

Following intravenous administration of pancuronium, muscle relaxation generally commences within about one to three minutes and lasts for about forty five minutes.

### **5.2. Pharmacokinetic Properties**

Following intravenous administration, pancuronium is rapidly distributed into body tissues. It is partially metabolised in the liver and is excreted in urine as unchanged drug and metabolites. Some pancuronium is also excreted in bile. Only very limited placental transfer of pancuronium occurs. The half-life of pancuronium is about 2.3 hours.

### **5.3. Pre-clinical Safety Data**

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1. List of Excipients**

Sodium Acetate B.P.  
Sodium Chloride B.P.  
Glacial Acetic Acid B.P.  
Water for Injections B.P.  
Nitrogen

### **6.2. Incompatibilities**

Pancuronium Injection should not be mixed with other agents in the same syringe, or with solutions for intravenous infusion, as a change in pH may induce precipitation. Any unused solution should be discarded.

### **6.3. Shelf-Life**

2 years (24 months).  
If only part used, discard the remaining solution.

### **6.4. Special Precautions for Storage**

Protect from light.  
Store at 2° to 8°C.  
Do not freeze.

### **6.5. Nature and Content of Container**

2ml, clear glass ampoules, glass type 1 Ph. Eur. packed in cardboard cartons to contain 10 x 2ml ampoules.

### **6.6. Instructions for Use, Handling and Disposal**

For I.V. injection.  
Use as directed by the physician.  
Do not mix or dilute with other solutions.  
Keep out of reach of children.

**7. MARKETING AUTHORISATION HOLDER**

Antigen International Ltd.,  
Roscrea,  
Co. Tipperary,  
Ireland.

**8. MARKETING AUTHORISATION NUMBER(S)**

PL 2848/0166.

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**

Date of first authorization : 11 February 1992.

**10. DATE OF REVISION OF THE TEXT**

16/03/2011