NEW ZEALAND DATA SHEET

1. PRODUCT NAME
Pancuronium Bromide B.P. 2 mg/mL solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
2 mL sterile solution of pH 3.5-4.2 containing 4 mg pancuronium bromide.
Excipients with known effect: sodium chloride, sodium acetate, sodium hydroxide.
For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM
Solution for injection. Clear, colourless, particle-free solution.

4. CLINICAL PARTICULARS
4.1 THERAPEUTIC INDICATIONS
An adjunct to surgical anaesthesia to induce skeletal muscle relaxation to facilitate operative manipulations. The necessary conditions for intubation can be achieved with pancuronium alone or following suxamethonium.
Pancuronium is also indicated to promote mechanical ventilation by reducing or eliminating spontaneous breathing effort in intensive care patients.

4.2 DOSE AND METHOD OF ADMINISTRATION
The following dosage information is a guide only.
Pancuronium bromide injection BP is administered intravenously. The dosage should be individualised for each patient as there is wide variation in individual response to muscle relaxants. The potential effect of the anaesthetic or any other concomitant medicine, clinical state of the patient and the anticipated duration of the neuromuscular block must be taken into account when the dosage is determined.
It is recommended that a peripheral nerve stimulator be used to monitor response to pancuronium bromide to minimise the risk of overdosage.
Since potent inhalation agents or prior administration of suxamethonium enhance the intensity of blockade and duration of action of pancuronium bromide, these factors should be considered when selecting initial and incremental dosage.
In heavy or obese patients calculations based on mg/kg may lead to overdosage.
For use in one patient on one occasion only. Discard any unused contents of an opened ampoule.

Pancuronium Bromide Data Sheet 280818
ADJUNCT TO GENERAL ANAESTHESIA

Adults and children older than 1 month

**Initial dose:** 0.04 to 0.1 mg/kg. This usually provides rapid satisfactory muscle relaxation for ease of intubation within 2 to 3 minutes. Duration of action of the initial dose may average approximately 45 minutes but can vary widely (30 to 150 minutes or longer).

**Maintenance dose:** Additional doses of 0.01 to 0.02 mg/kg may be administered at 25 to 60 minute intervals to maintain skeletal muscle relaxation during prolonged surgery. Doses of 0.015 mg/kg may be used to maintain relaxation for controlled respiration.

**Neonates and children less than 1 month:** Dosage must be carefully individualised, since neonates are particularly sensitive to nondepolarising neuromuscular blocking agents. An initial test dose of 0.02 mg/kg has been suggested to determine responsiveness.

After suxamethonium for intubation

A reduction in the initial dose of pancuronium is recommended when it is given following administration of suxamethonium. For adults and children older than 1 month, the initial dose should be reduced by approximately a third to 0.02 to 0.06 mg/kg and the incremental doses should be 25 to 33% of the initial dose.

METHOD OF ADMINISTRATION

Do not mix pancuronium bromide with other solutions in the same syringe, since possible changes in pH may induce precipitation. Any unused contents should be discarded.

4.3 CONTRAINDICATIONS

Known hypersensitivity to pancuronium bromide or to the bromide ion.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

**General**

Pancuronium bromide should only be used in hospitals equipped with suitable equipment for anaesthesia and/or resuscitation with reversal agents immediately available and administered only by a qualified anaesthetist or a physician experienced in anaesthetics. All patients receiving pancuronium bromide should be intubated and given artificial respiration until spontaneous respiration returns.

Electrolyte imbalance, altered pH and dehydration should be corrected if possible before the administration of pancuronium bromide. Electrolyte imbalance (hypokalaemia, hyponatraemia, hypermagnesaemia, hypocalcaemia), acid/base imbalance (respiratory acidosis or metabolic alkalosis), dehydration, hypoproteinaemia and cachexia can increase the neuro-muscular blocking activity of pancuronium bromide. In burned patients, resistance to the neuromuscular blocking action of pancuronium bromide may be encountered as with other nondepolarising relaxants. In addition, pancuronium bromide should be used cautiously in patients with conditions that may lead to electrolyte imbalances such as adrenal insufficiency.

Prior administration of suxamethonium has been reported to increase the intensity and duration of neuromuscular blockade produced by pancuronium bromide and a reduction in pancuronium bromide dosage is recommended. Administration of depolarising medicines such as suxamethonium following pancuronium bromide is not recommended.
Do not mix pancuronium bromide with other solutions in the same syringe as a change in the pH may induce precipitation.

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

Pancuronium bromide is antagonised by acetylcholine, anticholinesterases and potassium ions. The action of pancuronium bromide may also be altered by concomitant administration of various medicines such as neuromuscular blocking agents, some antibiotics and certain anaesthetics (see section 4.5 Interaction with Other Medicines and Other Forms of Interaction).

**Hypersensitivity reactions**

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 would 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.

Since neuromuscular blocking agents in general are known to be capable of inducing histamine release both locally at the site of injection and systemically after intravenous injection, the possible occurrence of itching and erythematous reactions at the site of injection and/or generalised histaminoid (anaphylactoid) reactions should always be taken into consideration when administering pancuronium bromide.

**Neuromuscular syndromes**

Extreme caution should be exercised and reductions in dosage made when administering pancuronium to patients with myasthenia gravis, myasthenic syndrome associated with small cell carcinomatosis (Eaton-Lambert syndrome; originally associated with lung cancer), prior poliomyelitis or myopathies or any other neuromuscular disease (such as amyotrophic lateral sclerosis) as small doses may have profound effects.

**Obesity**

In severe obesity, pancuronium bromide should be used with extreme caution and dosed carefully since the volume of distribution for muscle relaxants is approximately equivalent to that of extracellular volume. It is important to dose obese patients based on their lean body weight to prevent intense block of long duration and possible overdose. In addition, patients with severe obesity may be predisposed to airway or ventilatory problems which require special care before, during and after treatment with pancuronium bromide (see section 4.4 Special Warnings and Precautions for Use – Respiratory Disorders).

**Cardiovascular disorders**

Pancuronium should not be used in patients with pre-existing tachycardia or in patients in whom even a minor elevation in heart rate is undesirable as pancuronium bromide increases the heart rate by direct action on the acetylcholine receptors in the heart. Pancuronium should be used with caution in patients with a tendency to hypertension including hypertension associated with phaeochromocytoma or renal disease since increases in arterial pressure may be observed with pancuronium bromide, due to vagolytic effects and secondarily by blocking the neuronal reuptake of noradrenaline.

**Prolonged Therapy**

Individual cases of prolonged paralysis, disuse atrophy and areflexia have been reported in association with prolonged use of pancuronium to assist mechanical ventilation. It is unclear whether the motor dysfunction was due to the duration of neurological blockade (usually
greater than 7 days), prolonged bedrest, underlying clinical condition, intervention of synergistic medicines or a combination of such factors. Improvement was seen after 2-5 months in some but not all cases.

Careful monitoring of motor function is therefore particularly important when prolonged pancuronium-induced neurological blockade is necessary.

**Hypothermia/Hyperthermia**

Hypothermia reduces the intensity of neuromuscular blockade and increased doses of pancuronium bromide may be required. Hyperthermia has the opposite effect. When hypothermia techniques are used during surgery, the reduction in neuromuscular blockade is reversed when the patient is rewarmed.

**Malignant hyperthermia**

Patients with a familial history of malignant hyperthermia should be treated with extreme caution. The condition can be precipitated by the use of halogenated anaesthetics because this reaction has been attributed to their use, but neuromuscular blocking agents also may be a contributory factor.

**Ophthalmic**

Pancuronium bromide has been reported to produce a significant (+/- 20%) 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 endotracheal intubation.

**Respiratory disorders**

Neuromuscular blocking agents can cause respiratory paralysis as a result of respiratory depression and should be used with extreme caution in patients with pulmonary disease such as chronic obstructive pulmonary disease (COPD).

**Carcinomas**

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

**Use in Hepatic Impairment**

Pancuronium bromide should be used with caution in patients with hepatic impairment. The elimination half-life is doubled in patients with biliary obstruction or cirrhosis and plasma clearance is decreased by <50% or about 22% respectively. In addition, patients with hepatic disease may have a 50% increase in the volume of distribution of pancuronium bromide. This usually results in the need for a higher initial dose to achieve adequate muscle relaxation and a prolonged duration of action.

**Use in Renal Impairment**

As pancuronium bromide is excreted mainly in the renal system, the elimination half-life is prolonged in patients with poor renal perfusion or renal disease, resulting in a reduction in plasma clearance and prolonged duration of action. Reduction of maintenance doses may be necessary. Pancuronium should be avoided in patients with a GFR of less than 10 mL per minute; recurarisation might occur up to 24 hours after administration.

**Use in Neonates**

Neonates are particularly sensitive to pancuronium and nondepolarising neuromuscular blocking agents in general. Dosage must be individualised (see section 4.2 Dose and Method
of Administration) and further reductions may be necessary in prematurity, acidosis, hypothermia and during antibiotic therapy. Neonates are particularly sensitive to non-depolarising neuromuscular blocking agents.

**Use in Elderly**

Plasma concentrations have been reported to decline at a decreased rate in the elderly. Dosage reduction, however, was not indicated.

However, elderly patients are more likely to have age-related renal function impairment, which may decrease the rate of clearance of pancuronium bromide and thereby prolong its effect.

**4.5 INTERACTION WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION**

**Anaesthetics**

Certain anaesthetic agents may influence the neuromuscular blocking activity of pancuronium bromide. Halothane, lether, enflurane, isoflurane, methoxyflurane, thiopentone, methohexitone, ketamine and fentanyl may increase neuromuscular blocking activity while neurolept analgesia may decrease activity.

**Other medicines**

Concomitant neomycin, streptomycin, kanamycin, gentamicin, bacitracin, polymyxins, tetracyclines, diazepam, propranolol, thiamine (high dose), IV lignocaine (high dose), magnesium sulphate, lithium carbonate, monoamine oxidase inhibitors, quinine, quindine proctamine, diuretics, phenytoin, alpha-adrenergic blocking agents, beta-adrenergic blocking agents, calcium channel blockers, imidazoles, metronidazole and magnesium salts, magnesium ions and large infusions of citrate-anticoagulated blood may potentiate the neuromuscular blocking effects of pancuronium.

Neostigmine, edrophonium, pyridostigmine, high dose corticosteroid, adrenaline, azathioprine, theophylline (high dose), potassium chloride, sodium chloride and calcium chloride may decrease the activity of pancuronium.

Prior administration of suxamethonium can increase the intensity of neuromuscular blockade due to pancuronium. (See section 4.4 Special Warnings and Precautions for Use and 4.2 Dose and Method of Administration).

Pancuronium bromide can antagonise the effects of antmyasthenics. Temporary dosage adjustment following surgery may be necessary (see section 4.4 Special Warnings and Precautions for Use – Neuromuscular Syndromes).

Calcium salts usually reverse the effects of pancuronium bromide.

Hypokalaemia potentiates neuromuscular blockade with nondepolarising neuromuscular blockers. Drugs which are associated with a significant risk of hypokalaemia (e.g. amphotericin B, cisplatin, corticosteroids, loop diuretics, thiazide diuretics) should be monitored closely when used with pancuronium bromide.

Hydrocortisone and prednisone can decrease the effect of pancuronium bromide, necessitating either increased doses of pancuronium bromide or substitution of another nondepolarising neuromuscular blocker.

The effects of botulinum toxin type A or B can be potentiated by pancuronium bromide or other medicines that interfere with neuromuscular transmission.
Pancuronium bromide increases the risk of developing arrhythmias and should be used with caution in patients receiving cardiac glycosides.

Caution is indicated when piperacillin is used perioperatively as the neuromuscular blockade produced by pancuronium bromide could be prolonged in the presence of piperacillin.

See section 6.2 - Incompatibilities

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy
The safe use of pancuronium has not been established with respect to possible adverse effects upon foetal development. Therefore, it should not be used in women in pregnancy or in those likely to become pregnant unless the potential benefits outweigh the unknown hazards.

Pancuronium may be used in operative obstetrics (Caesarian section) but reversal of medicine effects may be unsatisfactory in patients receiving magnesium sulphate for toxaemia of pregnancy. Magnesium salts enhance neuromuscular blockade; therefore a reduced dosage of pancuronium is indicated.

Pancuronium has been found to cross the placenta in small amounts.

Breast-feeding
No data available

Fertility
No data available

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 UNDESIRABLE EFFECTS

Respiratory
Complications are rare and usually associated with overdosage. This may result in prolonged apnoea or respiratory depression.

Cardiovascular
After administration approximately 10% of patients may exhibit mild to moderate increases in blood pressure and/or pulse rate. Dysrhythmias may occasionally occur and increased cardiac output is frequently noted.

Hypersensitivity
Hypersensitivity reactions occur rarely. Bradycardia, bronchospasm, hypotension and cardiovascular collapse have been reported. An occasional transient rash has been reported. Pruritus can occur, as well as rare cases of flushing, oedema and wheezing.
Skin and Appendages
A few cases of local reactions manifested by pain and burning at the site of injection have been reported.

Ocular
Pancuronium bromide decreases intraocular pressure and induces miosis.

Neuromuscular
As with all muscle relaxants, abnormal reactions may be seen in patients with neuromuscular diseases. Prolonged paralysis, disuse atrophy and areflexia have been reported with prolonged use of pancuronium bromide (see Section 4.4 Special Warnings and Precautions for Use).

Other
Hypersalivation following pancuronium bromide administration may occur, especially if no anticholinergic premedication is given.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/.

4.9 OVERDOSE

Symptoms
Symptoms of overdose are prolonged apnoea, respiratory depression and/or persistent muscle weakness, significant hypotension and shock. Death may follow acute respiratory failure.

Treatment
The patient should remain under artificial respiration with intermittent positive pressure ventilation. At the same time the neuromuscular action of pancuronium bromide may be reversed by the administration of atropine and neostigmine at incremental doses within the prescribed therapeutic range and assisted ventilation should continue until recovery is complete.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764 766).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action
Pancuronium is a non-depolarising neuromuscular blocking agent of medium duration, blocking transmission of motor nerve impulses to striated muscle receptors producing skeletal muscle paralysis. It competes with acetylcholine for cholinergic receptor sites. It has little agonist activity, having no depolarising effect at the motor endplate. Skeletal muscle relaxation starts with muscles associated with fine movements, e.g. eyes, face and neck, then followed by muscles of the limbs, chest, abdomen and finally the diaphragm. Larger doses
increase the risk of respiratory depression due to relaxation of the intercostal muscle and diaphragm. Muscle tone returns in the reverse order. Pancuronium bromide also increases heart rate by a direct blocking effect on acetylcholine receptors in the heart, but this effect is small with therapeutic doses. It produces little or no significant ganglion blockade, so hypotension and bronchospasm are not associated with its use. The muscle weight to body weight ratio, the volume of extracellular fluid and renal function also contribute to response.

Despite its steroid structure, pancuronium bromide exhibits no hormonal activity. Cholinesterase inhibitors such as pyridostigmine and neostigmine reverse the action of pancuronium.

Clinical Efficacy and Safety
No data available.

5.2 PHARMACOKINETIC PROPERTIES
With an initial dose of pancuronium of 0.06 mg/kg IV, muscle relaxation reaches a level suitable for endotracheal intubation within 2 to 3 minutes, and the effects of the medicine begin to subside in about 35 to 45 minutes (these data are approximations since muscle relaxant response may be variable).

Onset and duration of action of pancuronium is dose dependent. Supplemental incremental doses, following the initial dose, slightly increase the magnitude of blockade, and significantly increase the duration of blockade alone or following suxamethonium.

Distribution
Following intravenous injection pancuronium bromide is rapidly distributed into body tissues. Figures of 30 - 87% protein binding have been reported. Small amounts of pancuronium bromide cross the placenta.

Metabolism
Metabolism occurs via hepatic pathways to at least 3 metabolites, a 3-hydroxy metabolite, a 17-hydroxy metabolite and a 3,17-hydroxy metabolite. These metabolites are significantly less potent than pancuronium.

Excretion
Plasma concentrations appear to fall in a triphasic manner, the last phase having a half-life of about 2 hours. Most of the drug and its metabolites are excreted in the urine. About 80% is excreted in the urine and 10% in the faeces as unchanged pancuronium. A small amount is excreted in the bile.

Since a large fraction of pancuronium bromide is excreted in the urine, the duration of neuromuscular blockade is prolonged in patients with renal failure and the dose should be reduced. In patients with impaired hepatic function, prolonged distribution and elimination half-lives result in a higher initial dose to be given and longer duration of action respectively.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity
No data available.

Carcinogenicity
No data available.

Pancuronium Bromide Data Sheet 280818
6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS
Sodium chloride, sodium acetate, water for injections, acetic acid and sodium hydroxide for pH adjustment.

6.2 INCOMPATIBILITIES
Do not mix other solutions in the same syringe as a change in pH may cause precipitation. A precipitate may form if pancuronium is mixed with barbiturates in the same syringe.

6.3 SHELF-LIFE
24 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE
Should be refrigerated at 2-8°C until use. DO NOT FREEZE.

Pancuronium need not be refrigerated during normal periods of use in operating theatres.

Pancuronium bromide is stable for up to 48 hours in the following solutions: 5% dextrose, 0.9% sodium chloride, lactated Ringer’s or 5% dextrose and 0.45 or 0.9% sodium chloride.

6.5 NATURE AND CONTENTS OF CONTAINER
2 mL polyethylene ampoules (Polyamp Duo Fit) in packs of 50.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL
Return unused and expired medicines to your local pharmacy for disposal.

7. MEDICINE SCHEDULE
Prescription Medicine.

8. SPONSOR
AstraZeneca Limited
P299 Private Bag 92175
Auckland 1142
Telephone: (09) 306 5650

9. DATE OF FIRST APPROVAL
25 July 1991
10 DATE OF REVISION OF THE TEXT

28 August 2018

(Aust PI 170818)

SUMMARY TABLE OF CHANGES

<table>
<thead>
<tr>
<th>Section changed</th>
<th>Summary of new information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Various</td>
<td>Conversion to SPC format.</td>
</tr>
<tr>
<td>4.4</td>
<td>Neonates section – additional sentence</td>
</tr>
<tr>
<td>4.5</td>
<td>Additional medicines added.</td>
</tr>
<tr>
<td>4.8</td>
<td>“Neuromuscular” and “Other” sections added.</td>
</tr>
</tbody>
</table>