Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 200 micrograms/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains:
Glycopyrronium bromide 200 micrograms (0.2 mg)

Each 3 ml contains:
Glycopyrronium bromide 600 micrograms (0.6 mg)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.
Clear, colourless aqueous solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

1. To protect against the peripheral muscarinic actions of anticholinesterases such as neostigmine and pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.
2. As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.
3. As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of suxamethonium or due to cardiac vagal reflexes.

4.2 Posology and method of administration

Posology
Premedication:

Adults and Elderly:
200 to 400 micrograms (0.2mg to 0.4mg) intravenously or intramuscularly before the induction of anaesthesia.

Alternatively, a dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. Larger doses may result in a profound and prolonged antisialagogue effect which may be unpleasant for the patient.

Paediatric population
4 to 8 micrograms/kg (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) intravenously or intramuscularly before the induction of anaesthesia.
Larger doses may result in a profound and prolonged antisialagogue effect which may be unpleasant for the patient.

Intraoperative use:
Adults and Elderly:
A single dose of 200 to 400 micrograms (0.2 to 0.4mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. This dose may be repeated if necessary.

Paediatric population:
A single dose of 200 micrograms (0.2mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 8 micrograms/kg (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block:
Adults and Elderly:
200 micrograms (0.2mg) intravenously per 1000 micrograms (1mg) neostigmine or the equivalent dose of pyridostigmine. Alternatively, a dose of 10 to 15 micrograms/kg (0.01 to 0.015mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) neostigmine or equivalent dose of pyridostigmine. Glycopyrronium Bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Paediatric population
10 micrograms/kg (0.01mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) neostigmine or the equivalent dose of pyridostigmine. Glycopyrronium Bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Renal impairment
Dose reduction should be considered in patients with renal impairment (see sections 4.4 and 5.2).

Method of administration
For intravenous or intramuscular injection

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In common with other antimuscarinics: angle-closure glaucoma; myasthenia gravis (large doses of quaternary ammonium compounds have been shown to block end plate nicotinic receptors); paralytic ileus; pyloric stenosis; prostatic enlargement.

Anticholinesterase-antimuscarinic combinations such as neostigmine plus glycopyrronium should be avoided in patients with a prolonged QT interval.

4.4 Special warnings and precautions for use

Antimuscarinics should be used with caution (due to increased risk of side effects) in Down's syndrome, in children and in the elderly.
They should be used with caution in gastro-esophageal reflux diseases, diarrhoea, ulcerative colitis and acute myocardial infarction, thyrotoxicosis, hypertension, congestive heart failure, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) because of the increase in heart rate produced by the administration of anticholinergics, use with caution in patients with coronary artery disease, cardiac arrhythmias, pregnancy and breast feeding.

This product should be used very cautiously in pyrexial patients (especially children) due to inhibition of sweating.

Because of prolongation of renal elimination, repeated or large doses of glycopyrronium should be avoided in patients with uraemia. It is known that the administration of anticholinergic agents during inhalation anaesthesia can result in ventricular arrhythmias especially in association with the halogenated hydrocarbons.

Unlikeatropine, glycopyrrolate is a quaternary ammonium compound and does not cross the blood-brain barrier. It is therefore less likely to cause postoperative confusion which is a particular concern in the elderly patients. Compared to atropine, glycopyrrolate has reduced cardiovascular and ocular effects.
The duration of effect of Glycopyrronium Bromide 200 micrograms /ml Solution for Injection may be prolonged in patients with renal impairment since glycopyrrolate is excreted mostly in urine as unchanged drug. Dosage adjustment may be needed for patients with renal impairment.
The injection can increase the tachycardia effect of sympathomimetic medicinal products.
This medicine contains less than 1mmol sodium (23mg) per 2 ml, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Many drugs have antimuscarinic effects; concomitant use of two or more of such drugs can increase side-effects such as dry mouth, urine retention and constipation. Concomitant use can also lead to confusion in the elderly.

Anticholinergic agents may delay absorption of other medication given concomitantly.

Concurrent administration of anticholinergics and corticosteroids may result in increased intraocular pressure.

Concurrent use of anticholinergic agents with slow-dissolving tablets of digoxin may cause increased serum digoxin levels.

Ritodrine: tachycardia

There is an increased risk of antimuscarinic side effects in patients taking drugs with antimuscarinic effects such as antihistamines, disopyramaide, MAOIs, pethidine, phenothiazines (increase antimuscarinic side-effects of phenothiazines but reduced plasma concentration), amantadine, clozapine, tricyclic antidepressants and nefopam.

Domperidone/Metoclopramide: antagonism of effect on gastro-intestinal activity Ketoconazole: reduced absorption of ketoconazole

Levodopa: absorption of levodopa possibly reduced

Memantine: effects possibly enhanced by memantine

Nitrates: possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)

Parasympathomimetics: antagonism of effect.

4.6 Fertility, pregnancy and lactation

Pregnancy
For use as indicated, animal studies (see section 5.3) are of very limited relevance. Use in human pregnancy has not been systematically evaluated. This product should only be used in pregnancy if considered essential.
Breast-feeding
May reach breast milk but in amounts probably too small to be harmful. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Glycopyrronium Bromide 200 micrograms /ml Solution for Injection therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman
Fertility
There are no data on the effects of glycopyrronium bromide on male or female fertility. For non-clinical studies please refer to section 5.3

4.7 Effects on ability to drive and use machines

Glycopyrrolate has moderate influence on the ability to drive and use machines. It is not anticipated that patients will be driving or operating machinery under its influence. However, systemic administration of antimuscarinics may cause blurred vision, dizziness and other effects that may impair a patient's ability to perform skilled tasks such as driving. Do not drive or operate heavy machinery unless the drug has been shown not to interfere with mental or physical ability.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: Very common: (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very rare (<1/10,000); not known: cannot be estimated from the available data.
Tabulated list of adverse reactions:

Table 1

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity, Angioedema	Not known
Nervous system disorders	Drowsiness Confusion* Dizziness	Not known
Eye disorders	Angle closure glaucoma Visual disturbances Accommodation disorder Photophobia	Very rare Not known

Cardiac disorders	Tachycardia, Transient Bradycardia**, Palpitations and arrhythmias	Not known
Respiratory, thoracic and mediastinal disorders	Bronchial secretion retention	Not known
Gastrointestinal disorders	Dry mouth Constipation Nausea Vomiting	Not known
Skin and subcutaneous tissue disorders	Anhidrosis Flushing Dry skin	Not known
Renal and urinary disorders	Micturition disorder Micturition urgency Urinary retention	Not known

* Particularly in elderly
** Followed by tachycardia, palpitation and arrhythmias

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

Symptoms
Since glycopyrrolate is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature.

Management
To combat peripheral anticholinergic effects a quaternary ammonium anticholinesterase such as neostigmine metilsulfate may be given in a dose of 1.0mg for each 1.0mg of glycopyrrolate known to have been administered by the parenteral route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Glycopyrrolate is a synthetic quaternary ammonium antimuscarinic.

ATC Code: A03AB02

Mechanism of action
Like other anticholinergic agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and to a limited degree in the autonomic ganglia. Thus it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions. Glycopyrrolate antagonises muscarinic symptoms (e.g., bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

The highly polar quaternary ammonium group of glycopyrrolate limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to atropine sulphate and scopolamine hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily.

Glycopyrronium Bromide Injection has been used successfully as an adjunct to reversal by neostigmine when atropine has been used as the preoperative anticholinergic. The use of Glycopyrronium Bromide Injection as an adjunct to reversal by neostigmine of non-depolarising muscle relaxants is associated with less initial tachycardia and better protection against the cholinergic effects of neostigmine compared to reversal with a mixture of neostigmine and atropine.

5.2 Pharmacokinetic properties

Absorption
With intravenous injection, the onset of action is generally evident within one minute. Peak effects occur approximately 30 to 45 minutes after intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine.

Distribution
Glycopyrrolate is rapidly distributed and/or excreted after intravenous administration.

Elimination
Following either intravenous or intramuscular administration, 50% of Glycopyrronium Bromide is excreted in the urine in 3 hours in non-uraemic individuals; renal elimination is considerably prolonged in patients with uraemia. Appreciable amounts are excreted in bile. In 48 hours, 85% has been excreted into the urine. About 80% of the excreted amount is as unchanged Glycopyrronium Bromide or active metabolites. The terminal elimination phase is relatively slow with quantifiable plasma levels remaining up to 8 hours after administration.

5.3 Preclinical safety data

Safety Pharmacology
Acute toxicity of glycopyrrolate was studied in mice and rats. Following intraperitoneal administration, the LD50 was estimated to be 107 mg/kg in mice and 196 mg/kg in rats. Following oral dosing, the LD50 was estimated to be 1150 mg/kg in rats. Chronic oral administration doses of 4, 16, and 64 mg/kg for up to 27 weeks in dogs produced mydriasis, cycloplegia, xerostomia, emesis, occasional lacrimation, injection of sclera and rhinorrhea. There were no changes in organ weight and histopathology showed no drug-related changes.

Teratogenicity

Although reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate.

Toxicity to reproduction and development

Safety in human pregnancy and lactation has not been established.

Diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate. The significance of this for man is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment)
Sodium chloride
Water for injection

6.2 Incompatibilities

Glycopyrronium Bromide Injection has been shown to be physically incompatible with the following agents commonly used in anaesthetic practice: Diazepam, Dimenhydrinate, Methohexital Sodium, Pentazocine, Pentobarbital Sodium and Thiopental Sodium.

The medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened: 18 months.
Once opened, use immediately and discard any remaining contents.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.
Do not store above 25°C.

6.5 Nature and contents of container

1 ml and 3 ml clear glass one-point-cut (OPC) ampoules (Ph. Eur. Type 1) in packs of 10 x 1 ml, 3 x 3 ml or 10 x 3 ml

Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any remaining contents after use.
Glycopyrronium Bromide Injection has been shown to be physically compatible with the following agents commonly used in anaesthetic practice: Butorphanol, Lorazepam, Droperidol and Fentanyl Citrate, Levorphanol Tartrate, Pethidine Hydrochloride, Morphine Sulphate, Neostigmine, Promethazine and Pyridostigmine.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MercuryPharm Ltd
4045 Kingswood Road
City West Business Park
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0857/001/001

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