

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)

Also contains 3.5mg (0.15mmol) sodium per ml

For a 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

As an anti-muscarinic agent.

4.2 Posology and method of administration

Route of Administration: For intravenous or intramuscular injection.

Dosage:

Premedication:

Adults and Elderly Patients:

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.

Children:

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 patients :

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.

Children:

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:**Adults and Elderly Patients:**

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.

Children:

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.

4.3 Contraindications

Apart from established hypersensitivity to glycopyrrolate, and any one of the excipients, there are no absolute contraindications to Glycopyrronium Bromide .

Antimuscarinics are contra-indicated in angle-closure glaucoma, myasthenia gravis, paralytic ileus, pyloric stenosis, and prostatic enlargement.

4.4 Special warnings and precautions for use

Because of the increase in heart rate produced by the administration of anticholinergics, use with caution in patients with coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertension; thyrotoxicosis.

Antimuscarinics should be used with caution in Down's syndrome. They should be used with caution in gastro-oesophageal reflux diseases, diarrhoea, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterized by tachycardia including (hyperthyroidism, cardiac insufficiency, and cardiac surgery), and pyrexia.

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

It is known that the administration of anticholinergic agents during inhalation anaesthesia can result in ventricular arrhythmias.

Large doses of quaternary ammonium anticholinergic compounds have been shown to block end plate nicotinic receptors. This should be considered before using glycopyrrolate in patients with myasthenia gravis.

4.5 Interaction with other medicinal products and other forms of interaction

Anticholinergic agents may delay absorption of other medicaments given concomitantly.

Excessive cholinergic blockade can occur if Glycopyrronium Bromide Injection is given concomitantly with belladonna alkaloids or other synthetic anticholinergic agents (such as antiparkinsonism agents), phenothiazines, tricyclic antidepressants, disopyramide, procainamide, quinidine, antihistamines, or narcotic analgesics such as meperidine.

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.

Amantadine, clozapine, MAOIs, and nefopam increase the risk of antimuscarinic side effects.

Antimuscarinics antagonize the effects of domperidone, metoclopramide on gastro-intestinal activity. They also antagonize the effects of parasympathomimetics.

Antimuscarinics reduce the absorption of ketoconazole, while their activities are enhanced by memantine.

4.6 Fertility, pregnancy and lactation

Although reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate, 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. This product should not be used during pregnancy unless considered essential by the physician.

4.7 Effects on ability to drive and use machines

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

Glycopyrronium Bromide may produce the following effects which are extensions of its fundamental pharmacological actions: dry mouth, difficulty in micturition, disturbances in visual accommodation, tachycardia, palpitation, inhibition of sweating.

4.9 Overdose

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

Glycopyrrolate is a quaternary ammonium antimuscarinic agent and, 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

Glycopyrrolate is rapidly distributed and/or excreted after intravenous administration. The terminal elimination phase is relatively slow with quantifiable plasma levels remaining up to 8 hours after administration. 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. With intravenous injection, the onset of action is generally evident within one minute.

5.3 Preclinical safety data

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

6.2 Incompatibilities

Glycopyrrolate 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.

6.3 Shelf life

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

6.4 Special precautions for storage

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.

Glycopyrrolate 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.

7 MARKETING AUTHORISATION HOLDER

Anpharm Limited,
Roscrea,
County Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER

PA0857/001/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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