

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Glycopyrronium Bromide 200 micrograms / ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of injection contains 200 micrograms (0.2 mg) of Glycopyrronium Bromide.
For full list of excipients, see 6.1.

3 PHARMACEUTICAL FORM

A clear and colourless sterile solution for Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In anaesthesia

Glycopyrrolate is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions, and to block cardiac vagal inhibitory reflexes during induction of anaesthesia and intubation when indicated. Glycopyrronium Bromide 200 micrograms/ml Solution for Injection may be used intraoperatively to counteract drug-induced or vagal traction reflexes with the associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g. bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarising muscle relaxants.

In peptic ulcer

For use in adults as adjunctive therapy for the treatment of peptic ulcer when rapid anticholinergic effect is desired or when oral medication is not tolerated.

4.2 Dose and method of administration

Glycopyrronium bromide is a sterile solution for intramuscular or intravenous administration.

Pre-Anaesthetic Use

Adults

0.2 mg to 0.4 mg intravenously or intramuscularly before the induction of anaesthesia.

Alternatively, a dose of 0.004 to 0.005 mg/kg up to a maximum of 0.4 mg may be used. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Paediatric population (see section 4.3)

1 month to 12 years of age: 0.004 to 0.008 mg/kg up to a maximum of 0.2 mg intravenously or intramuscularly before the induction of anaesthesia. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Intraoperative use

When used to treat arrhythmias associated with traction reflexes, the usual attempts should be made to determine the aetiology of the arrhythmia, and the surgical or anaesthetic manipulations necessary to correct parasympathetic imbalance should be performed.

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Adults

In those situations where intraoperative use is indicated, a single dose of 0.2 to 0.4 mg (or 0.004 to 0.005 mg/kg up to a maximum of 0.4 mg) by intravenous injection should be used. This dose may be repeated if necessary.

Paediatric population (1 month to 12 years of age)

In those situations where intraoperative use is indicated, a single dose of 0.004 to 0.008 mg/kg or up to a maximum of 0.2 mg by intravenous injection should be used. This dose may be repeated if necessary.

Reversal of neuromuscular blockade

Adults

0.2 mg intravenously per 1 mg neostigmine or the equivalent dose of pyridostigmine. Alternatively, a dose of 0.01-0.015 mg intravenously with 0.05 mg/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 (1 month to 12 years of age)

0.01 mg/kg intravenously with 0.05 mg/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

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 also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, 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 their administration, coronary artery disease and cardiac arrhythmias, pyrexia (due to inhibition of sweating), pregnancy and breast feeding. As Glycopyrronium Bromide inhibits sweating, patients with increased temperature (especially children) should be observed closely.

Because of prolongation of renal elimination, repeated or large doses of Glycopyrronium Bromide should be avoided in patients with uraemia.

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Anticholinergic drugs can cause ventricular arrhythmias when administered during inhalation anaesthesia especially in association with the halogenated hydrocarbons.

Unlike atropine, Glycopyrronium Bromide 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, Glycopyrronium Bromide has reduced cardiovascular and ocular effects.

This medicinal product contains less than 1 mmol sodium (23mg) per dose, i.e. essentially 'sodium free'.

4.5 Interaction with other medicines 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.

The use of Glycopyrronium Bromide, like atropine, with or within several hours of ritodrine hydrochloride administration may result in a drug interaction causing tachycardia.

The intravenous administration of any anticholinergic in the presence of cyclopropane anaesthesia can result in ventricular arrhythmias; therefore, caution should be observed if Glycopyrronium Bromide is used during cyclopropane anaesthesia. If the drug is given in small incremental doses of 0.1 mg or less, the likelihood of producing ventricular arrhythmias is reduced.

Anticholinergic agents may delay absorption of other medications given concomitantly.

Increased antimuscarinic side-effects: amantadine; tricyclic antidepressants; antihistamines; clozapine; disopyramide; MAOIs; nefopam; pethidine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations)

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

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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2.

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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. Caution is advised when considering administration to a nursing mother.

Fertility

No information available.

Long-term studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential of glycopyrrolate.

4.7 Effects on ability to drive and use machines

Glycopyrronium Bromide 200 micrograms/ml Injection is used in anaesthesia. 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. These activities should not be undertaken until any disturbance of visual accommodation or balance has resolved.

4.8 Undesirable effects

The following reported adverse reactions are extensions of Glycopyrronium Bromide 200 micrograms/mL Injection fundamental pharmacological actions.

Cardiovascular

ventricular fibrillation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), hypertension, hypotension, cardiac arrest, heart block, prolonged QTc interval.

Dermatological

Flushing and inhibition of sweating. Severe allergic reactions or drug idiosyncrasies including urticaria and other dermal manifestations, pruritus, dry skin.

Gastrointestinal

Nausea, vomiting, dry mouth, constipation, taste alterations, including loss of taste.

Genitourinary

Urinary urgency and retention, impotence.

Ocular

Blurred vision due to mydriasis, cycloplegia, photophobia, increased ocular tension.

Nervous system

Inhibition of transmission at neuromuscular junction, headache, nervousness, drowsiness, dizziness, seizure, insomnia, some degree of mental confusion especially in the elderly, hyperexcitability in children.

Pregnancy and perinatal

Suppression of lactation.

Respiratory system

Respiratory arrest.

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General

Hyperpyrexia, bloated feeling, anaphylaxis/anaphylactoid reaction, hypersensitivity.

Injection site reactions including pruritus, oedema, erythema, pain have been reported rarely.

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 <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

The signs and symptoms of overdosage reflect the pharmacological effects of Glycopyrronium Bromide. These may include hypotension, respiratory failure and a curare-like action, i.e., neuromuscular blockade leading to muscular weakness and possibly paralysis.

Treatment should be symptomatic.

Dialysis is of no value because of low plasma concentrations of the medicine.

To combat peripheral anticholinergic effects a quaternary ammonium anticholinesterase such as neostigmine methylsulfate may be given intravenously in increments of 0.25 mg in adults.

This dosage may be repeated every five to ten minutes until anticholinergic over-activity is reversed or up to a maximum of 2.5 mg. Proportionately smaller doses should be used in children. Indication for repetitive doses of neostigmine should be based on close monitoring of the decrease in heart rate and the return of bowel sounds.

In the unlikely event that CNS symptoms (excitement, restlessness, convulsions, psychotic behaviour) occur, physostigmine (which does cross the blood-brain barrier) should be used. Physostigmine 0.5 to 2.0 mg should be slowly administered intravenously and repeated as necessary up to a total of 5 mg in adults. Proportionately smaller doses should be used in children.

Fever should be treated symptomatically. In the event of a curare-like effect on respiratory muscles, artificial respiration should be instituted and maintained until effective respiratory action returns.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Synthetic anticholinergics, quaternary ammonium compounds, ATC Code: A03AB02

Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. It is used similarly to atropine in anaesthetic practice. Given as a premedicant before general anaesthesia, it diminishes the risk of vagal inhibition of the heart and reduces salivary and bronchial secretions. Intra-operatively, it may be given to reduce bradycardia and hypotension induced by drugs such as suxamethonium, halothane or propofol. Glycopyrronium bromide may be used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects.

Antimuscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic)

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nerves, as well as being inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilatation of the pupils (mydriasis) and paralysis of accommodation (cyclopegia); increased heart rate; inhibition of micturition and reduction in gastrointestinal tone; inhibition of gastric acid secretion.

Quaternary ammonium compounds are sparingly lipid soluble and do not readily pass lipid membranes such as the blood-brain barrier. Central effects are negligible.

5.2 Pharmacokinetic properties

Absorption

Following intravenous administration, onset of action occurs within one minute, with peak activity at around 5 minutes.

Following intramuscular injection, maximum plasma concentration and onset of action of Glycopyrronium Bromide is achieved within 30 minutes. Peak effects occur after approximately 30 - 45 minutes; vagal blocking effects last for 2 – 3 hours and antisialagogue effects persist for 7 - 8 hours. There is a faster absorption rate when Glycopyrronium Bromide is injected into the deltoid muscle rather than into the gluteal or vastus lateralis muscles.

Distribution

Cerebrospinal fluid levels of Glycopyrronium Bromide remain below detection level up to one hour after therapeutic dosing.

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. Although the elimination half-life of Glycopyrronium Bromide from plasma is within 75 minutes, quantifiable levels may remain up to 8 hours after administration.

5.3 Preclinical safety data

Long-term studies in animals have not been performed to evaluate the carcinogenic or mutagenic potential of glycopyrrolate.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride

Water for injections.

Solution is adjusted to pH 2.5 with hydrochloric acid.

6.2 Incompatibilities

Glycopyrronium Bromide Injection has been shown to be physically compatible with the following agents commonly used in anaesthetic practice: Butorphanol, Lorazepam, Droperical and Fentanyl Citrate, Levorphanol Tartrate, Pethidine Hydrochloride, Morphine Sulphate Sulfate, Neostigmine, Promethazine and Pyridostigmine.

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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.

6.3 Shelf life

2 years

Unopened

Store at or below 25°C.

Opened

For single use only. Store the neat or diluted solution between 2 to 8°C. Do not use if more than 24 hours has elapsed since the solution was opened and/or diluted. Do not use if visible particles are present.

6.4 Special precautions for storage

For storage conditions after dilution and first opening of the medicine, see section 6.3.

6.5 Nature and contents of container

Type I glass colourless with one point cut 1ml and 3ml

0.2 mg in 1 ml

Type I glass colourless ampoules with one cut point and double colour coded red, red ring.
Packs of 10 ampoules.

0.6 mg in 3 ml

Type I glass colourless ampoules with one cut point and triple colour coded red, blue and black ring.
Packs of 10 ampoules.

6.6 Special precautions for disposal

Compatible medicines and diluents

Glycopyrronium Bromide 200 micrograms/ml Solution for Injection is compatible for mixing and injection with pethidine hydrochloride; morphine sulfate; droperidol plus fentanyl citrate; hydroxyzine; neostigmine; promethazine and pyridostigmine. Glycopyrronium Bromide 200 micrograms/ml Solution for Injection may be mixed with 4%-10% glucose in water or saline, or it may be administered via the tubing of a running infusion of physiological saline, glucose, or lactated Ringers solution.

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

7 MEDICINE SCHEDULE

Prescription Medicine.

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8 SPONSOR

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Ph: (09) 815 2664

9 DATE OF FIRST APPROVAL

13 June 2013

10 DATE OF REVISION OF THE TEXT

25 March 2019

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
All	Reformatting to new template
4.3	Information from Warnings and Precautions moved to Contraindications for clarity and alignment with SPC.
4.4	Duplication of information and accordingly moved to Contraindications
5.2	Adoption of Martindale approved SPC
25 March 2019: 1, 4.1, 6.6	Name amended from: "Glycopyrronium Bromide 200 micrograms per ml Solution for Injection", to "Glycopyrronium Bromide 200 micrograms/ml Solution for Injection"