1 PRODUCT NAME

ROBINUL® ***(Glycopyrronium bromide (glycopyrrolate) Injection)***

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

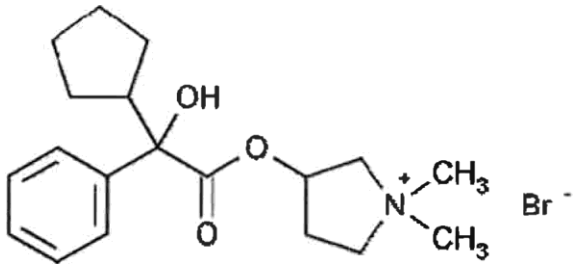
Each 1 mL ampoule contains Glycopyrronium bromide (glycopyrrolate) 0.2 mg, Water for Injections q.s., Sodium Chloride 9 mg and Sodium hydroxide/Hydrochloric acid (for pH adjustment)

Glycopyrronium bromide (glycopyrrolate) is a white, odourless, crystalline powder with a bitter taste. It is a quaternary ammonium compound. Glycopyrronium bromide (glycopyrrolate) is chemically designated as 3- (alpha-cyclopentylmandeloyloxy)-1, 1-dimethylpyrrolidinium bromide and has a molecular weight of 398.34. It is soluble in water and alcohol and practically insoluble in chloroform and ether.

ROBINUL is a clear, colourless sterile solution with a pH of 2.5 - 4.0.

The chemical name(s) for Glycopyrronium bromide (glycopyrrolate) is : Pyrrolidinium, 3-

[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl- bromide.
3-Hydroxy-1,1-dimethylpyrrolidinium bromide α-cyclopentylmandelate



Molecular formula: $C_{19}H_{28}BrNO_3$ Molecular Mass: 398.33 CAS: *[596-51-0].*

3 PHARMACEUTICAL FORM

Injection

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

In *Anaesthesia:* ROBINUL 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. ROBINUL Injectable may be used intraoperatively to counteract drug-induced or vagal traction reflexes with the associated arrhythmias. Glycopyrronium bromide (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

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.

Children (Read Contraindications) - 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.

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.

Children (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. ROBINUL may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Children (1 month to 12 years of age) - 0.01 mg/kg intravenously with 0.05 mg/kg neostigmine or the equivalent dose of pyridostigmine. ROBINUL may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

4.3 Contraindications

Known hypersensitivity to Glycopyrronium bromide (glycopyrrolate), or any of the inactive ingredients.

4.4 Special warnings and precautions for use

ROBINUL should be used with caution, if at all, in patients with glaucoma or asthma.

ROBINUL should be used with caution in patients with any of the following conditions: obstructive uropathy, obstructive disease of the gastrointestinal tract, paralytic ileus, intestinal atony, unstable cardiovascular status in acute haemorrhage, severe ulcerative colitis and toxic megacolon complicating ulcerative colitis, autonomic neuropathy and prostatic hypertrophy.

Diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy. In this instance treatment with this drug would be inappropriate and possibly harmful.

In the case of ulcerative colitis, large doses of ROBINUL may suppress intestinal motility resulting in production of paralytic ileus perhaps precipitating or aggravating toxic megacolon.

Hiatus hernia associated with reflux oesophagitis may be aggravated following administration of this medicine.

Use with caution in patients with coronary artery disease; congestive heart failure; cardiac arrhythmias; hypertensionor hyperthyroidism since an increase in heart rate may occur. Investigate any tachycardia before giving Glycopyrronium bromide (glycopyrrolate) as an increase in heart rate may occur.

In the presence of fever, as in high environmental temperature, and physical exercise, reduced sweating can occur with ROBINUL causing, heat prostration (fever and heat stroke). Use very cautiously when the ambient temperature is high and in pyrexic patients, especially children and the elderly, who have a tendency to sweat less.

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

The duration of effect of ROBINUL may be prolonged in patients with renal impairment since Glycopyrronium bromide (glycopyrrolate) is excreted mostly in urine as unchanged drug. Dosage adjustment may be needed for patients in renal failure.

The use of anticholinergic drugs in the treatment of gastric ulcer may produce a delay in gastric emptying due to antral stasis.

The closure system contains dry natural rubber that may cause hypersensitivity reactions when handled by or when the product is injected in persons with known or possible latex sensitivity.

Paediatric Use

Arrythmias associated with the use of Glycopyrronium bromide (glycopyrrolate) intravenously as a premedication or during anaesthesia appear to be more likely in paediatric patients than in adults.

Infants, patients with Down's Syndrome, and paediatric patients with spastic paralysis or brain damage may experience an increased response to anticholinergics, thus increasing the potential for side effects.

A paradoxical reaction characterised by hyperexcitability may occur in paediatric patients taking large doses of anticholinergics including Glycopyrronium bromide (glycopyrrolate). Infants and young children are especially susceptible to the toxic effects of anticholinergics.

Safety and effectiveness of long-term IV use has not been established in paediatric patients. Long-term use of ROBINUL is therefore not recommended in paediatric patients.

Use in the Elderly

Clinical studies of Glycopyrronium bromide (glycopyrrolate) did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or drug therapy.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

4.5 Interaction with other medicines and other forms of interaction

The use of Glycopyrronium bromide (glycopyrrolate), 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 ROBINUL 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.

Excessive cholinergic blockade can occur if ROBINUL is given concomitantly with belladonna alkaloids or other synthetic anticholinergic agents (such as antiparkinsonism agents), phenothiazines, tricyclic antidepressants, disopyramide, procainamide, quinidine, some antihistamines, narcotic analgesics such as pethidine, thioxanthenes, butyrophenones or amantadine.

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.

ROBINUL is compatible for mixing and injection with pethidine hydrochloride; morphine sulfate; droperidol plus fentanyl citrate; hydroxyzine; neostigmine; promethazine and pyridostigmine. ROBINUL 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.

Since the stability of Glycopyrronium bromide (glycopyrrolate) is questionable above a pH of 6.0, do not inject ROBINUL at the same intramuscular site or combine it in the same syringe with: thiopentone sodium; chloramphenicol; diazepam; dimenhydrinate; methohexitone sodium; pentazocine lactate; pentobarbitone sodium; quinalbarbitone; or sodium bicarbonate. A gas will evolve or a precipitate may form.

Mixing with dexamethasone, sodium phosphate or a buffered solution of lactated ringers solution will result in a pH higher than 6.0.

4.6 Fertility, pregnancy and lactation

Category B2.

Clinically the safe use of Glycopyrronium bromide (glycopyrrolate) has not been established. Single-dose studies in humans found that only very small amounts of Glycopyrronium bromide (glycopyrrolate) passed the placental barrier. Therefore, the drug should not be used in pregnant women, or those likely to become pregnant, unless the expected benefits outweigh any potential risk.

Reproduction studies in rats and rabbits did not reveal any teratogenic effects from Glycopyrronium bromide (glycopyrrolate). Diminished rates of conception and of survival of 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 Glycopyrronium bromide (glycopyrrolate). The significance of this for humans is not clear.

Use during Lactation

Anticholinergic agents may suppress lactation. It is not known whether Glycopyrronium bromide (glycopyrrolate) is excreted in human milk.

Therefore, it is not recommended for nursing mothers unless the expected benefits outweigh any potential risk.

4.7 Effects on ability to drive and use machines

In the ambulatory patient ROBINUL may produce drowsiness or blurred vision. In this event, the patient should be warned not to engage in activities requiring mental alertness such as operating a motor vehicle or other machinery, or performing hazardous work while taking this drug.

4.8 Undesirable effects

The following reported adverse reactions are extensions of ROBINUL's fundamental pharmacological actions:

Cardiovascular: Tachycardia, ventricular fibrillation, bradycardia, palpitation and arrhythmia, 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 hesitancy 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.

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 (glycopyrrolate). 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 drug. 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

Glycopyrronium bromide (glycopyrrolate) is a synthetic anticholinergic agent. Like other anticholinergic (antimuscarinic) 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. Doses which produce marked antisialogogue actions have little effect on heart rate, visual accommodation, or pupil size.

Glycopyrronium bromide (glycopyrrolate) antagonises muscarinic symptoms (e.g. bronchorrhoea, bronchospasm, bradycardia, and intestinal hypermotility) induced by cholinergic drugs such as anticholinesterases.

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

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

5.2 Pharmacokinetic properties

Pharmacokinetic studies in normal volunteers given a single intravenous infusion of 0.4 mg Glycopyrronium bromide (glycopyrrolate) showed that the drug undergoes a rapid distribution/elimination phase ($t_{1/2}$ = 5 min) followed by a more prolonged termination elimination phase ($t_{1/2}$ = 1.7 hr). The peak plasma concentration immediately following the end of the infusion was 26.4 mg/mL(± 7.6), and the volume of distribution was 0.158 ± 0.28 L /kg, which suggests that Glycopyrronium bromide (glycopyrrolate), is not widely distributed to the tissues.

Excretion is via the urine and bile. Radioactivity studies have shown that 85% is excreted in the urine within 48 hours, over 80% of this being unchanged drug.

5.3 Preclinical safety data

No data available

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for Injections q.s., Sodium Chloride 9 mg and Sodium hydroxide/Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

No data available

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 25°C

6.5 Nature and contents of container <and special equipment for use, administration or implantation>

1 mL single dose vials in packs of 5's

1 mL single dose ampoules in packs of 5's

Each vial /ampoule contains Glycopyrronium bromide (glycopyrrolate)0.2 mg/mLwith Sodium Chloride
9 mg/mL as preservative.
*not all presentations are commercialised

6.6 Special precautions for disposal <and other handling>

No data available

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

Pharmacy Retailing (NZ) Limited
Trading as Healthcare Logistics
58 Richard Pearce Drive
Airport Oaks
Auckland

9 DATE OF FIRST APPROVAL

8 June 1978

10 DATE OF REVISION OF THE TEXT – 7 February 2019

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information	Date Approved
All document	New document to SmPC format and update to INN Glycopyrronium bromide (glycopyrrolate)	7 February 2019