1 PRODUCT NAME

GlycoNeo 0.5/2.5 glycopyrronium bromide (glycopyrrolate) 0.5 mg/neostigmine methylsulfate 2.5 mg in 1 mL solution for injection ampoule

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution for injection contains 500 micrograms (0.5 mg) of glycopyrronium bromide (glycopyrrolate) and 2.5 mg of neostigmine methylsulfate.

Excipients with known effect:

For the full list of excipients, see Section 6.1 List of excipients.

The solution is preservative free and sulfite free.

3 PHARMACEUTICAL FORM

Clear, colourless sterile solution for injection free of any visible particles or fibres intended for parenteral intravenous administration

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reversal of residual non-depolarising (competitive) neuromuscular block

4.2 Dose and method of administration

Dosage

This fixed-dose combination product contains a 0.5 mg:2.5 mg/1 mL of glycopyrronium bromide (glycopyrrolate): neostigmine in a fixed 1:5 ratio. If other ratios of these agents are required, these should be prepared using available monotherapy products.

Adults and elderly patients: 1-2mL intravenously over a period of 10 to 30 seconds (equivalent to Neostigmine Metilsulfate 2.5 mg with Glycopyrronium Bromide 0.5 mg to Neostigmine Metilsulfate 5 mg with Glycopyrronium Bromide 1 mg). Alternatively, 0.02 mL/kg intravenously over a period of 10 to 30 seconds may be used, (equivalent to Neostigmine Metilsulfate 0.05 mg/kg with Glycopyrronium Bromide 0.01 mg/kg), dose may be repeated (total maximum 2 mL).

Paediatric: 0.02 mL/kg intravenously over a period of 10 to 30 seconds (equivalent to Neostigmine Metilsulfate 0.05 mg/kg with Glycopyrronium Bromide 0.01 mg/kg).
These doses may be repeated if adequate reversal of neuromuscular blockade is not achieved.

Total doses in excess of 2 mL are not recommended as this dose of neostigmine may produce depolarising neuromuscular block.

Method of administration

This medicine is for intravenous administration.

It contains no antimicrobial preservative and is for use in one patient on one occasion only. Discard any residue.

GlycoNeo 0.5 /2.5 should be administered when the first twitch response is substantially greater than 10 % of baseline, or when a second twitch is present.

Adequacy of the reversal of the neuromuscular block needs to be based on a clinical assessment of the patient and not train-of-four responses alone, unless quantitative (numeric) assessment is made of neuromuscular function.

Patients should be monitored for clinical signs of residual blockade (e.g. difficulty maintaining a patent airway, generalised weakness, inadequate ventilatory effort) following cessation of the anaesthetic and extubation.

GlycoNeo 0.5 /2.5 should be used as is and should not be further diluted prior to use (see also Section 6.2 Incompatibilities).

Dosage adjustment

Renal impairment: The duration of effect may be prolonged in patients with renal impairment since glycopyrronium bromide (glycopyrrolate) and neostigmine are excreted mostly in the urine. Dosage adjustment may be needed for patients in renal failure.

Elderly: 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.

4.3 Contraindications

- Hypersensitivity to the two active substances, or to any of the excipients listed in Section 6.1 List of excipients.
- Mechanical obstruction of intestinal or urinary tract.
- This medicine should not be given in conjunction with suxamethonium as neostigmine potentiates the depolarising myoneural blocking effects of this agent.
- 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

Neuromuscular function monitoring must be available for every patient in whom neuromuscular blockade has been induced and should be used whenever the anaesthetist is considering extubation following the use of non-depolarising neuromuscular blockade.

Antagonism of the neuromuscular block with a cholinesterase inhibitor should not be initiated before at least two to four responses to train-of-four stimulation are observed.

Re-administration of muscle relaxant shortly after use of GlycoNeo 0.5 /2.5 should be done with caution: competing at the neuro-muscular junction there may be increased levels of acetyl choline and neostigmine has some direct postsynaptic cholinomimetic effects, thus resistance to muscle relaxation may be seen. There will still be some previously administered relaxant in the patient, thus prolonged recovery may also be seen.

The administration of sugammadex after neostigmine reversal may increase muscle relaxation as all muscle relaxant is removed and the neuro muscular inhibition by neostigmine is revealed.

Neostigmine may prolong the depolarising neuromuscular blocking action of depolarising muscle relaxants such as suxamethonium and prolonged apnoea may result (see Section 4.5 Interactions with other medicines and other forms of interaction).

Administer with caution to patients with bronchospasm (extreme caution). Neostigmine alone induces significant bronchoconstriction, whereas neostigmine combined with glycopyrrolate causes bronchodilation. Secretions may be thickened with neostigmine (see also Section 5.1 Pharmacodynamic properties).

Administer with caution to patients with severe bradycardia. Further falls in heart rate may occur.

Administer with caution to patients with arrhythmias, recent myocardial infarction, epilepsy, hypotension, parkinsonism, vagotonia, peptic ulceration, hyperthyroidism, renal impairment or glaucoma.

Administration of anticholinesterase agents to patients with intestinal anastomoses may produce rupture of the anastomosis or leakage of intestinal contents.

Although Glycopyrronium Bromide and Neostigmine Metilsulfate Injection has been shown to have less impact on the cardiovascular system than Atropine with Neostigmine Metilsulfate, use with caution in patients with coronary artery disease, congestive heart failure, cardiac dysrhythmias, hypertension or thyrotoxicosis.

Quaternary ammonium compounds in large dose have been shown to block the nicotinic muscle end plate receptors. This must be evaluated prior to its administration in patients with myasthenia gravis.

Use with caution in patients with epilepsy or Parkinson's disease.

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

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

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

Earlier literature reports of a high incidence (5 – 15 %) in fit patients of arrhythmia associated with reversal after halothane are not supported by more recent studies (since 2008) where the reported incidence of reversal after sevoflurane or propofol was ~ 1 %.

Glycopyrronium bromide (glycopyrrolate) is a quaternary ammonium compound and thus does not readily cross the blood-brain barrier. It is therefore less likely to cause postoperative confusion which is a particular concern in elderly patients.

Glycopyrrolate/neostigmine should be used with caution, if at all, in patients with glaucoma; increases in intraocular pressure have been reported.

Administration of anticholinesterase agents to patients with intestinal anastomosis may produce rupture of the anastomosis or leakage of intestinal contents.

GlycoNeo 0.5 /2.5 should be used with caution in patients with mechanical urinary tract obstruction such as obstructive uropathy, and prostatic hypertrophy, and in patients who have undergone recent bladder surgery.

GlycoNeo 0.5 /2.5 should be used with caution in patients:

• with mechanical gastrointestinal tract obstruction such as paralytic ileus, intestinal atony. Diarrhoea may be an early symptom of incomplete intestinal obstruction, especially in patients with ileostomy or colostomy.
• who have undergone recent intestinal surgery.
• with severe ulcerative colitis and toxic megacolon complicating ulcerative colitis.

GlycoNeo 0.5 /2.5 should be used with caution in patients with unstable cardiovascular status:

- autonomic neuropathy
- arrhythmias
- coronary artery disease
- congestive heart failure
- cardiac arrhythmias
- hypertension or hyperthyroidism since an increase in heart may occur
- recent myocardial infarction or coronary occlusion
- hypotension.

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

Large doses of quaternary ammonium anticholinergic compounds have been shown to block end-plate nicotinic receptors. This should be considered before using GlycoNeo 0.5 /2.5 in patients with myasthenia gravis.

Glycopyrronium bromide (glycopyrrolate)
In the presence of fever and in high environmental temperature, reduced sweating can occur with glycopyrronium bromide (glycopyrrolate), 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.

Neostigmine
Use neostigmine with caution in patients with epilepsy, vagotonia, parkinsonism or Addison's disease.

Use in renal impairment
Use GlycoNeo 0.5 /2.5 with caution in patients with renal impairment. Glycopyrronium bromide (glycopyrrolate) and neostigmine are excreted mostly in the urine. Please also refer to Section 4.2 Dose and method of administration.

Use in the elderly
In a study of 59 patients over 65 years of age (32 with cardiovascular disease) receiving neostigmine 50 µg/kg with glycopyrronium 10 µg/kg, compared to previous studies in healthy adults, the initial increase in heart rate is higher, the subsequent falls in heart rate are less in elderly patients and the incidence of cardiac dysrhythmias was higher. 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.

Paediatric use
A paradoxical reaction characterised by hyperexcitability may occur in paediatric patients taking large doses of anticholinergics including glycopyrronium bromide (glycopyrrolate).

Infants and young children, 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.

Effects on laboratory tests
No data available.

4.5 Interaction with other medicines and other forms of interactions

Glycopyrronium bromide (glycopyrrolate)

There is increased risk of antimuscarinic side effects in patients taking drugs with antimuscarinic effects such as MAOIs, amantadine, clozapine, tricyclic antidepressants and nefopam. concomitant use of two or more such drugs can increase side- effects such as dry mouth, urine retention, and constipation; concomitant use can also lead to confusion in the elderly.

Excessive cholinergic blockade can occur if glycopyrronium bromide (glycopyrrolate) is given in patients taking 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.

Neostigmine

Corticosteroids
Corticosteroids may decrease the anticholinesterase effects of neostigmine.
Conversely anticholinesterase effects may increase after stopping corticosteroids.

Depolarising muscle relaxants
Neostigmine may prolong the Phase I block of depolarising muscle relaxants such as suxamethonium (see Section 4.3 Contraindications). Prolonged muscle paralysis with extended periods of apnoea may occur unless IPPV (intermittent positive pressure ventilation) is maintained.

Muscle Relaxants, non-depolarising - Neostigmine antagonises effects of non-depolarising muscle relaxants

Aminoglycosides, local/general anaesthetics, antiarrhythmic agents
Anticholinesterase agents can be effective in reversing neuromuscular block induced by aminoglycoside antibiotics. Aminoglycoside antibiotics, local and some general anaesthetics, and antiarrhythmic agents may interfere with neuromuscular transmission and should be used cautiously,

particularly in patients with myasthenia gravis. The dose of neostigmine may need to be increased accordingly.

Quinine, chloroquine, hydroxychloroquine, beta-blockers and lithium may reduce the effectiveness of treatment with neostigmine because of potential for Chloroquine and Hydroxychloroquine to increase symptoms of myasthenia gravis.

Clindamycin - Effects of Neostigmine antagonised by Clindamycin

Non-depolarizing neuromuscular block induced by the muscle relaxants used in anesthesia; neuromuscular block induced by aminoglycoside antibiotics and antiarrhythmic agents.

Polymyxins - Effects of Neostigmine antagonised by polymyxins

Procainamide - Effects of Neostigmine antagonised by Procainamide

Propafenone -Effects of Neostigmine possibly antagonised by Propafenone

Propranolol -Effects of Neostigmine antagonised by Propranolol

Quinidine -Effects of Neostigmine antagonised by Quinidine

Suxamethonium -Neostigmine enhances effects of Suxamethonium

Antimuscarinics - Effects of parasympathomimetics antagonised by antimuscarinics

QT interval
In 10 healthy adults anaesthetised with propofol and no muscle relaxants, 30 min after neostigmine 50 µg/kg plus glycopyrronium bromide (glycopyrrolate) 10 µg/kg mean QTcB prolongations was 5.3 ms.
Please see Section 6.2 Incompatibilities.

4.6 Fertility, pregnancy and lactation

Effects on fertility
No data available.

Use in pregnancy – Pregnancy Category B2
Glycopyrronium bromide (glycopyrrolate)

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.

Neostigmine

Cholinergic effects in the neonate are rare.

The safety of neostigmine in pregnancy has not been established with respect to possible adverse effects on foetal development. Anticholinesterase agents may cause uterine irritability and induce premature labour when given IV to pregnant women near term. Therefore, neostigmine should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh any potential risk.

For use as indicated, animal studies (see section 5.3) are of very limited relevance. Use in human pregnancy has not been systematically evaluated.

The use of Neostigmine in pregnant patients with myasthenia gravis has revealed no untoward effect of the drug on the course of pregnancy.

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

Evidence indicates that only negligible amounts of neostigmine enter the breast milk; nevertheless, the possibility of adverse effects on the breast-feeding infant should be considered.

Therefore, this product 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 glycopyrronium bromide (glycopyrrolate) may produce drowsiness or blurred vision. 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.

4.8 Undesirable effects

Inadequate reversal

Studies have shown ~ 31 % to 50 % of patients have clinically significant residual neuromuscular blockade with train-of-four ratios less than 0.90 following surgery. Patients with train-of-four ratios less than 0.90 are at increased risk for hypoxemic events, impaired control of breathing during hypoxia, airway obstruction, postoperative pulmonary complications (there is an increase in the risk of aspiration) and symptoms of muscle weakness.

Clinical signs include:

• weakness (head lift, hand grip, eye opening, or tongue protrusion)
• inability to smile, swallow, speak, cough, track objects with eyes; or inability to perform a deep or vital capacity breath.

Symptoms also include blurry vision, diplopia, facial weakness, facial numbness, and general weakness.

Adverse reactions
Adverse reactions in a study in 14 healthy volunteers receiving neostigmine 2.5 mg with glycopyrronium bromide (glycopyrrolate) 450 µg repeated after ¼ h in 9 of the volunteers included: muscle weakness 14 (100 %), blurred vision 13 (93 %), abdominal cramping 13 (93 %), dry mouth 11 (79 %), nausea 11 (79 %), vomiting 1 (7 %); none of these were seen in the 7 subjects receiving saline placebo.

Across 5 trials in the literature among 225 patients receiving glycopyrronium bromide (glycopyrrolate) and neostigmine to reverse effect of the muscle relaxant, the following adverse reactions were reported.

TABLE 1:

Adverse reaction	**N**	**%**
Nausea	17	7.6
Dry mouth	7	3.1
Abdominal pain	2	0.9
Vomiting	2	0.9
Dyspepsia	1	0.4
Increased/decreased heart rate	7	3.1
Heart rate increased	1	0.4
Bradycardia	1	0.4
Supraventricular extrasystole	2	0.9
Ventricular extrasystoles	1	0.4
Procedural hypertension	1	0.4
Hypertension	1	0.4
Chest discomfort	1	0.4
Dizziness	1	0.4
Restlessness	1	0.4
Somnolence	1	0.4
Sleep disorder	1	0.4
Involuntary muscle contractions	1	0.4
Visual accommodation disorder	1	0.4
Neuromuscular blockade prolonged	2	0.9
Muscle weakness	3	1.3
Productive cough	1	0.4
Pyrexia	1	0.4
Erythema	1	0.4
Hyperhidrosis	1	0.4
Pruritus	1	0.4
Increased urine β2 microglobulin	1	0.4
Albuminuria	2	0.9
Glutamyltransferase increased	1	0.4

Decreased blood total protein	1	0.4
Incision-site complication	1	0.4

Reported adverse reactions

Glycopyrronium bromide (glycopyrrolate) and neostigmine

Immune system disorders: Hypersensitivity, angioedema and anaphylactic reaction.

Glycopyrronium bromide (glycopyrrolate)

The following reported adverse reactions are extensions of glycopyrronium bromide (glycopyrrolate)'s fundamental pharmacological actions:

Cardiovascular: Tachycardia, ventricular fibrillation, bradycardia, palpitation and arrhythmia, hypertension, hypotension, cardiac arrest, heart block, prolonged QTc interval, cardiac dysrhythmias.

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, micturition urgency.

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, disturbances of visual accommodation.

Pregnancy and perinatal: Suppression of lactation.

Respiratory system: Respiratory arrest, bronchial secretion reduced.

General: Hyperpyrexia, bloated feeling, anaphylaxis/anaphylactoid reaction, hypersensitivity.
Injection site reactions including pruritus, oedema, erythema, pain have been reported rarely.

Neostigmine

Adverse reactions generally associated with neostigmine overdosage are:

Cardiovascular: Cardiac arrhythmias (especially bradycardia), hypotension, syncope, cardiac arrest, heart block, arrhythmias, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.

Dermatological: Rash and urticaria.

Central nervous system: Headache, dizziness, convulsions, loss of consciousness, coma, drowsiness, restlessness, ataxia, slurred speech, agitation and fear, photophobia.

Gastrointestinal: Nausea, vomiting, diarrhoea, abdominal cramps, flatulence, increased peristalsis and involuntary defaecation and micturition.

Genitourinary: Involuntary urination or desire to urinate.

Musculoskeletal: Muscle cramps, fasciculation, general weakness and paralysis.

Respiratory: Increased oral, pharyngeal and bronchial secretions, dyspnoea, bronchospasm, respiratory depression, respiratory arrest, tight chest and wheezing.

Allergic: Allergic reactions including anaphylaxis.

Other: Increased sweating and salivation, miosis, vision changes, nystagmus and lacrimation.

Glycopyrronium-Neostigmine component of injection can give rise to hypersensitivity, angioedema and anaphylactic reaction. Their frequency is not known.

Hypersensitivity:
If severe Neostigmine induced muscarinic side effects occur (bradycardia, hypotension, increased or pharyngeal secretions, decreased cardiac conduction rate, bronchospasm or increased gastrointestinal activity etc), these may be treated by the intravenous administration of Glycopyrronium Bromide Injection 200 – 600 micrograms (0.2 – 0.6 mg) or atropine 400 – 1200 micrograms (0.4 – 1.2 mg).

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://pophealth.my.site.com/carmreportnz/s/}

4.9 Overdose

The mainstay of overdose treatment is supportive and symptomatic care. The treatment of overdosage depends upon whether signs of anticholinesterase or anticholinergic overdosage are predominant presenting features.

Neostigmine overdosage can cause cholinergic crisis, which is characterised by increasing muscle weakness. Cholinergic crisis can lead to respiratory paralysis, which may result in death. Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretion, salivation, diaphoresis and miosis. signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, involuntary defecation and micturition, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.) may be treated by administration of Glycopyrronium Bromide Injection 0.2 – 0.6 mg (200 – 600 micrograms) or atropine 0.4 – 1.2 mg (400 – 1200 micrograms). In severe cases, respiratory depression may occur, artificial ventilation may be necessary in such patients. Nicotinic effects consist of muscular cramps, fasciculations and general weakness. Bradycardia and hypotension may also occur.

Glycopyrronium bromide (glycopyrrolate) signs and symptoms of overdosage: these may include tachycardia, ventricular irritability, hypotension, respiratory failure and neuromuscular blockade leading to muscular weakness and possibly paralysis, may be treated by intravenous administration of

Neostigmine Metilsulfate 1.0 mg (1000 micrograms) for each 1.0 mg of Glycopyrronium Bromide (1000 micrograms) known to have been administered. As Glycopyrronium Bromide is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature. Centrally acting anticholinesterase drugs such as physostigmine are therefore unnecessary to treat Glycopyrronium Bromide overdosage.

For risk assessment and 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) and neostigmine

The following are from the literature:

In healthy volunteers glycopyrronium bromide (glycopyrrolate)/neostigmine in combination produces muscle weakness in a dose related fashion, affecting hand grip strength, single twitch height, dysphagia and to some extent diplopia.
Neostigmine-induced weakness with characteristics of phase-1 depolarising neuromuscular blockade was evidenced by fasciculations of multiple muscle groups, depression of the single twitch height, no fade in train-of-four and increased neuromuscular blockade after the second dose of anticholinesterase agent and muscle weakness.

Thus residual post-operative weakness may be both inadequate reversal and neostigmine induced weakness (especially with large doses).

Respiratory muscle weakness produces decreased volumes (FEV1 and FVC).

In spinal injured patients the net effect of the glycopyrronium bromide (glycopyrrolate)/ neostigmine combination is bronchodilation (as assessed by resistance to flow).

In healthy volunteers, there were no significant differences in heart rate, however, there were significant differences over time in mean arterial pressure (p = 0.003), with a maximal change from baseline of mean (SD) +10 (8.7) mmHg, +11 (9.2) % in the neostigmine group at 10 min, compared with +0.34 (5.6) mmHg, +0.37 (6.1) % in the placebo group at 10 min (p = 0.009).

When used to reverse neuromuscular blockade in post-operative patients, the cardiac effects vary with the anaesthetic agents used including the muscle relaxant.

Geometric mean recovery time after neostigmine/glycopyrronium bromide (glycopyrrolate) from second twitch (T2) to train-of four ratio (TOFR) > 0.9 was after rocuronium 17.0 min (95 % CI 11.6 – 24.8), after vecuronium 17.9 min (13.1 – 24.3), and after rocuronium in Korean subjects 14.8 min (12.4 - 17.6).

Mechanism of action

<u>Neostigmine</u>

Neostigmine is an anticholinesterase agent which inhibits reversibly the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase. As a result, acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Neostigmine is therefore capable of producing a generalised cholinergic response, including miosis, increased tonus of intestinal and skeletal musculature, constriction of bronchi and ureters, bradycardia and stimulation of salivary and sweat glands.

Extremely high doses produce CNS stimulation followed by CNS depression.

Glycopyrronium bromide (glycopyrrolate)

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 vagal blocking effects persist for 2 to 3 hours and the antisialogogue effects persist up to 7 hours. With intravenous injection, the onset of action is generally evident within one minute.

Clinical trials
No data available.

5.2 Pharmacokinetic properties

Distribution
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 (t1/2 = 5 min). The peak plasma concentration immediately following the end of the infusion was 26.4 ± 7.6 mg/mL, 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.

The highly polar quaternary ammonium group of glycopyrronium bromide (glycopyrrolate) limits its passage across lipid membranes, such as the blood-brain barrier.

The major site of uptake of neostigmine is the liver. Because of its quaternary ammonium structure, in moderate doses, neostigmine does not cross the blood-brain barrier to produce CNS effects.

Metabolism
For glycopyrronium bromide (glycopyrrolate), over 80 % of the drug is excreted unchanged in urine in 48 hours.

Neostigmine is excreted in urine as unchanged drug (50 %) and metabolites. It is metabolised partly by the hydrolysis of the ester linkage and partly by microsomal enzymes in the liver.

Excretion

Excretion of glycopyrronium bromide (glycopyrrolate) is via the urine and bile, with a terminal elimination phase half-life of 1.7 hours. Radioactivity studies have shown that 85 % is excreted in the urine within 48 hours.

Following IV administration the elimination half-life of neostigmine ranges from 47 to 60 minutes. Approximately 80 % of a single IM dose of neostigmine is excreted in the urine in 24 hours.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

GlycoNeo 0.5 /2.5 contains dibasic sodium phosphate dodecahydrate, citric acid, sodium hydroxide and water for injections.

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 25 °C. Keep the ampoules in the outer carton to protect from light.

6.5 Nature and contents of container

Glycopyrronium bromide (0.5 mg/1 mL) and Neostigmine methylsulfate (2.5 mg/ 1 mL) solution for injection is proposed to be marketed in 1 mL flint OPC (One Point Cut) clear glass Type I ampoules with blue colour dot. 10 x 1 mL ampoules packaged in clear PVC trays within a carton and including a package insert.

6.6 Special precautions for disposal

Use in one patient on one occasion only. Contains no antimicrobial preservative. If only part of an ampoule is used, discard the remaining solution.
Any unused medicine or waste material should be disposed of in accordance with local requirements.

Do not dilute this product.

7 MEDICINE SCHEDULE

Schedule 4 - Prescription Only Medicine

8 SPONSOR

KSJ Pharmatech
24 Treestump Road
Takanini
Auckland 2112
Distributed in New Zealand by:
Healthcare Logistics
58 Richard Pearse Drive Airport Oaks, Mangere 2022
Ph: 64-9-9185100

9 DATE OF FIRST APPROVAL

12 DEC 2024

10 DATE OF REVISION OF THE TEXT

N/A

SUMMARY TABLE OF CHANGES