1 PRODUCT NAME

Glycopyrronium Bromide 0.5 mg/mL and Neostigmine Metilsulphate 2.5 mg/mL Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains Glycopyrronium Bromide (Glycopyrrolate) 0.5 mg and Neostigmine Metilsulfate 2.5 mg.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

A clear and colourless sterile solution for Injection.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Reversal of residual non-depolarising (competitive) Neuromuscular block.

4.2 Dose and method of administration

For intravenous injection.

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).

Paediatric0.02 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.

4.3 Contraindications

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

Glycopyrronium Bromide and Neostigmine Metilsulfate Injection should not be given to patients with known hypersensitivity to either of the two active ingredients or given to patients with mechanical obstruction of the gastrointestinal or urinary tracts. In addition, this product 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

Administer with caution to patients with bronchospasm (extreme caution), bradycardia, 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'.

4.5 Interaction with other medicines and other forms of interaction

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis.

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

Aminoglycosides -Effects of Neostigmine antagonised by aminoglycosides.

Chloroquine and Hydroxychloroquine - effects of Neostigmine may be diminished because of potential for Chloroquine and Hydroxychloroquine to increase symptoms of myasthenia gravis.

Many drugs have antimuscarinic effects; 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.

Clindamycin - Effects of Neostigmine antagonised by Clindamycin

Lithium - Effects of Neostigmine antagonised by lithium

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

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

4.6 Fertility, pregnancy and lactation

Pregnancy
Category B2.

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.

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

Breast-feeding:
May reach breast milk but in amounts probably too small to be harmful.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The Glycopyrronium Bromide component of Glycopyrrolate - Neostigmine Metilsulfate Injection can give rise to a dry mouth, difficulty in micturition, cardiac dysrhythmias, and disturbances of visual accommodation and inhibition of sweating.

The Neostigmine component of Glycopyrronium Bromide and Neostigmine Metilsulfate Injection can give rise to nausea, vomiting, increased salivation, diarrhoea, abdominal cramps (more marked with higher doses); signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, bradycardia, photophobia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.

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://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

The treatment of overdosage depends on whether signs of anticholinesterase or anticholinergic overdose is the predominant presenting feature.

Signs of Neostigmine overdosage include those of muscarinic effects (nausea, vomiting, increased salivation, diarrhoea, abdominal cramps (more marked with higher doses); signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, 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 or atropine 0.4 – 1.2 mg. In severe cases, respiratory depression may occur, artificial ventilation may be necessary in such patients.

Signs of Glycopyrronium Bromide overdose (tachycardia, ventricular irritability etc.) may be treated by intravenous administration of Neostigmine Metilsulfate 1.0 mg for each 1.0 mg of Glycopyrronium Bromide 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 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: Anticholinesterases ATC code: N07AA51

Glycopyrronium Bromide is a quaternary ammonium anticholinergic agent. The quaternary ammonium moiety renders Glycopyrronium Bromide highly ionised at physiological pH and it thus penetrates the blood brain and placental barriers poorly. Glycopyrronium Bromide has a more gradual onset and longer duration of action than atropine.
Neostigmine Metilsulfate is a quaternary ammonium anticholinesterase. Glycopyrronium Bromide and Neostigmine Metilsulfate Injection is associated with less initial tachycardia and better protection against the subsequent cholinergic effects of Neostigmine Metilsulfate than a mixture of Atropine and Neostigmine Metilsulfate.

Neostigmine is used mainly for its effects on skeletal muscle in myasthenia gravis and in anaesthesia for termination of the effects of competitive neuromuscular blocking drugs.

In addition, residual central anticholinergic effects are minimised due to the limited penetration of Glycopyrronium Bromide into the central nervous system. Administration of Glycopyrronium Bromide with Neostigmine Metilsulfate is associated with greater cardiostability than administration of Glycopyrronium Bromide and Neostigmine Metilsulfate separately.

5.2 Pharmacokinetic properties

Absorption
Glycopyrronium Bromide and Neostigmine Metilsulfate are routinely administered simultaneously to reverse residual non-depolarising (competitive) neuromuscular block. Numerous clinical studies, which demonstrate this to be a safe and effective combination, have been published.

Over 90% of the Glycopyrronium Bromide disappears from serum within 5 minutes following intravenous administration. The drug is rapidly excreted into bile with highest concentrations being

found 30 to 60 minutes after dosing with some product being detected up to 48 hours after administration.

Distribution
Glycopyrronium Bromide is also rapidly excreted into urine with the highest concentrations being found within 3 hours of administration. Over 85% of product is excreted within 48 hours. It has subsequently been confirmed in a single dose pharmacokinetic study using radio immunological assay procedures that Glycopyrronium Bromide was rapidly distributed and/or excreted after intravenous administration. The terminal elimination phase was relatively slow with quantifiable plasma levels remaining up to 8 hours after administration. The elimination half-life was 1.7 hours.

Neostigmine Metilsulfate is extensively hydrolysed in the blood. In one study, following intravenous administration, the plasma concentration declined to about 8% of its initial value after 5 minutes with a distribution half-life of less than one minute.

Elimination
Elimination half-life ranged from about 15-30 minutes. Trace amounts of Neostigmine Metilsulfate could be detected in the plasma after one hour. In a study in non-myasthenic patients, the plasma half-life was 0.89 hours.

5.3 Preclinical safety data

No further relevant information other than that, which is included in other sections of the Data Sheet.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Citric Acid
Sodium Hydroxide
Citric Acid Solution
Water for Injections
Sodium Phosphate

6.2 Incompatibilities

Do not mix Glycopyrronium Bromide and Neostigmine Metilsulfate Injection with any other preparation.

6.3 Shelf life

12 months.

6.4 Special precautions for storage

Do not store above 25˚C.
Keep the container in the outer carton to protect from light.

6.5 Nature and contents of container

Glycopyrronium Bromide 0.5 mg/mL and Neostigmine Metilsulfate 2.5 mg/mL Solution for Injection is presented in clear Type I ampoules of neutral glass containing 10 x 1mL ampoules packed in a cardboard carton.

6.6 Special precautions for disposal

Do not dilute.
If only part of an ampoule is used, discard the remaining solution.
Keep out of the sight and reach of children.

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

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Max Health Ltd
P O Box 65 231
Mairangi Bay
Auckland 0754
Ph:(09) 815 2664.

9 DATE OF FIRST APPROVAL

28 August 2016

10 DATE OF REVISION OF THE TEXT

17 October 2017

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.