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

Each 1mL contains Glycopyrrolate USP 0.5mg (Glycopyrronium Bromide) and Neostigmine Metilsulfate Ph. Eur. 2.5mg.

Presentation

Clear Type I ampoule of neutral glass, colour coded double yellow ring, containing a clear and colourless sterile solution for injection containing Glycopyrrolate 0.5mg (Glycopyrronium Bromide) and Neostigmine Metilsulfate 2.5mg in 1mL.

Indications

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

Dosage and Administration

For intravenous injection.

Adults and elderly patients

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

Children

0.02ml/kg intravenously over a period of 10 to 30 seconds (equivalent to Neostigmine Metilsulfate 0.05mg/kg with Glycopyrronium Bromide 0.01mg/kg).

These doses may be repeated if adequate reversal of neuromuscular blockade is not achieved. Total doses in excess of 2ml are not recommended as this dose of Neostigmine may produce depolarising neuromuscular block.

Contraindications

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.

**Warnings and Precautions**

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.

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’.

**Use in Pregnancy and Lactation**

Reproductive studies in rats and rabbits revealed no teratogenic effects from Glycopyrronium Bromide. Safety in human pregnancy and lactation has not been established. However, 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 Glycopyrronium bromide. The significance of this for man is not clear.

The safety of Neostigmine Metilsulfate in pregnancy and lactation has not been established. Neostigmine is unlikely to be excreted in breast milk in significant amounts, given its hydrophilicity. Neostigmine can cross the placenta.

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

**Adverse 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 defaecation and micturition, miosis, nystagmus, bradycardia, 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 oropharyngeal 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 – 0.6mg) or atropine 400 – 1200 micrograms (0.4 – 1.2mg).

Interactions

**Drug Interactions**
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.
Overdosage

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

Signs of Neostigmine overdose 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 defaecation 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 – 0.6mg or atropine 0.4 – 1.2mg. 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 1.0mg for each 1.0mg of Glycopyrronium Bromide known to have been administered. As Glycopyrronium Bromide is a quaternary ammonium agent, symptoms of overdose are peripheral rather than central in nature. Centrally acting anticholinesterase drugs such as physostigmine are therefore unnecessary to treat Glycopyrronium Bromide overdose.

Further Information

Pharmacodynamics

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 anesthesia 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.
Pharmacokinetics

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.

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 hydrolyzed 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 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.

List of Excipients

Disodium Hydrogen Phosphate Dodecahydrate
Citric Acid
Sodium Hydroxide
Citric Acid Solution
Water for Injections.

This medicine has been granted provisional consent under Section 23 of the Medicines Act 1981

Pharmaceutical Precautions

Incompatibilities

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

Shelf life

12 month.
Special Precautions for Storage

Do not store above 25˚C.

Keep the container in the outer carton to protect from light.

Package Quantities

10 x 1ml ampoules

Medicine Schedule

Prescription Medicine

Sponsor Details

Max Health Limited
PO Box 65 231
Mairangi Bay
Auckland 0754
09 476 9469

Date of Preparation

21 July 2012