Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL

**Presentation**

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for injection is a clear, colourless sterile, solution for injection intended for parenteral administration presented in 1 mL clear, type 1 Ph. Eur. glass ampoule.

Each 1 mL of solution contains 500 micrograms (0.5 mg) of glycopyrronium bromide and 2.5 mg of neostigmine metilsulfate.

**Indications**

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

**Dosage and Administration**

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for injection is for intravenous administration.

**Adults and older patients**

1 – 2 mL intravenously over a period of 10 - 30 seconds [equivalent to neostigmine metilsulfate 2500 micrograms (2.5 mg) with glycopyrronium bromide 500 micrograms (0.5 mg) to neostigmine metilsulfate 5000 micrograms (5 mg) with glycopyrronium bromide 1000 micrograms (1 mg)].

Alternatively 0.02 mL/kg intravenously over a period of 10 - 30 seconds may be used [equivalent to neostigmine metilsulfate 50 micrograms/kg (0.05mg/kg) with glycopyrronium bromide 10 micrograms/kg (0.01mg/kg)].

**Children**

0.02 mL/kg intravenously over a period of 10 - 30 seconds [equivalent to neostigmine metilsulfate 50 micrograms/kg (0.05mg/kg) with glycopyrronium bromide 10 micrograms/kg (0.01mg/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.
**Contraindications**

Patients with known hypersensitivity to either of the two active ingredients or any of the excipients

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, or severe bradycardia. Administration of anticholinesterase agents to patients with intestinal anastomosis may produce rupture of the anastomosis or leakage of intestinal contents. Although Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for 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, thyrotoxicosis and cardiac insufficiency.

Use with caution in patients with epilepsy or Parkinsonism.

As glycopyrronium bromide inhibits sweating, patients with increased temperature (especially children) should be observed closely.

In common with other antimuscarinic drugs caution is advised in patients with prostatic hypertrophy, paralytic ileus, pyloric stenosis and closed angle glaucoma.

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

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.

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.

Neostigmine metilsulfate: Glycopyrronium or alternatively atropine, given before or with neostigmine, prevents bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

**Use in pregnancy**

Animal studies are of very limited relevance. Use in human pregnancy has not been systematically evaluated.

**Use in lactation**

May reach breast milk but in amounts probably too small to be harmful.
**Effects on ability to drive or operate machinery**

Not applicable

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**Adverse Effects**

The glycopyrronium bromide component of Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for injection can give rise to dry mouth, constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils, photophobia, flushing and dryness of the skin. Side-effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting, and giddiness; very rarely, angle-closure glaucoma may occur.

The neostigmine component of Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for injection can give rise to bradycardia, increased oropharyngeal secretions, cardiac dysrhythmias and increased gastrointestinal activity.

If severe neostigmine-induced muscarinic side effects occur (bradycardia, increased oropharyngeal secretions, decreased cardiac conduction rate, increased sweating, 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).

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**Interactions**

Neostigmine potentiates the depolarising myoneural blocking effects of suxamethonium (see Contraindications above).

There is increased risk of antimuscarinic side effects in patients taking drugs with antimuscarinic effects such as MAOIs, amantadine, clozapine, tricyclic antidepressants and nefopam.

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**Overdose**

The treatment of overdosage depends upon whether signs of anticholinesterase or anticholinergic overdosage are predominant presenting features.

Signs of neostigmine overdosage include increased oropharyngeal secretions, bronchospasm, nausea, vomiting, diarrhoea, excessive salivation and sweating, miosis, bradycardia or tachycardia, cardiospasm, incoordination, muscle cramps, fasciculation and paralysis.

This may be treated by the administration of glycopyrronium bromide injection 200 - 600 micrograms (0.2 - 0.6mg) or atropine 400 - 1200 micrograms (0.4 - 1.2mg). In severe cases, respiratory depression may occur and artificial ventilation may be necessary in such patients.

Signs of glycopyrronium bromide overdosage (tachycardia, ventricular irritability etc) may be treated by the administration of neostigmine metilsulfate 1000 micrograms (1.0mg) for each 1000 micrograms (1.0mg) 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.

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 0.5mg/2.5mg per mL solution for injection is associated with less initial tachycardia and better protection against the subsequent cholinergic effects of neostigmine than a mixture of atropine and neostigmine. 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 is associated with greater cardiostability than administration of glycopyrronium bromide and neostigmine metilsulfate separately.

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per mL solution for injection can be used when atropine has been used as a pre-operative anticholinergic.

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. A number or pertinent clinical studies were included in the Product Licence application for glycopyrronium bromide injection, approved in UK in March 1981.

In the Product Licence Application for glycopyrronium bromide injection it was demonstrated that over 90% of the glycopyrronium bromide disappeared from serum within 5 minutes following intravenous administration. The drug was 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 85% of product was excreted within 48 hours. It has subsequently been confirmed in a single dose pharmacokinetic study using radioimmunological 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.

The pharmacokinetics of neostigmine metilsulfate are described in Martindale. 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.
Other

Glycopyrronium bromide

3-hydroxy-1, 1-dimethylpyrrolidinium bromide-alpha-cyclopentyl mandelate Pyrrolidinium, 3-[Cyclopentylhydroxyphenylacetyl) oxy]-1,1-dimethyl-, bromide

\[ C_{19}H_{28}BrNO_{3} \]

Molecular Weight: 398.34
CAS Registry number: 596-51-0

Neostigmine metilsulfate

3-[(Dimethylcarbamoyl)oxy]-N,N,N-trimethylanilinium methyl sulphate

\[ C_{13}H_{22}N_{2}O_{6}S \]

Molecular Weight: 334.39
CAS Registry number: 51-60-5

Excipients
Disodium Hydrogen Phosphate Dodecahydrate
Citric Acid
Sodium Hydroxide
Citric Acid Solution
Water for Injections
Pharmaceutical Precautions

Incompatibilities
Do not mix Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5 mg/2.5 mg per mL solution for injection with any other product.

Shelf life
24 months

Special precautions for storage
Store below 25ºC.
Keep in outer carton.
If only part of an ampoule is used, discard the remaining solution.

Package Quantities
Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5 mg/2.5 mg per mL solution for injection is presented in clear glass ampoules packed in cardboard cartons to contain 10 ampoules.

Medicine Schedule
Prescription Medicine

Sponsor Details
Boucher & Muir (NZ) Ltd, trading as Mercury Pharma (NZ)
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27 August 2015