Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

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

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of solution contains Glycopyrronium Bromide 0.5 mg and Neostigmine Metilsulfate 2.5 mg.

Excipient with known effect: Each 1 ml contains 3 mg (0.13 mmol) sodium

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection
Colourless, sterile solution for injection, free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

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

4.2 Posology and method of administration

Posology:

Dosage:
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).

Paediatric population: 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.

Method of administration: For intravenous injection.

4.3 Contraindications

Hypersensitivity to the two active substances or to any of the excipients listed in section 6.1

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per ml Solution for Injection should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per ml Solution for Injection should not be given in conjunction with suxamethonium, as neostigmine potentiates the depolarising myoneural blocking effects of this agent.

4.4 Special warnings and precautions for use

Administer with caution to patients with bronchospasm or severe bradycardia.

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 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 Parkinson's disease.

This product should be used cautiously in pyrexial patients (especially children) due to inhibition of sweating.

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 (like glycopyronium) 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, glycopyrrolate 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, glycopyrrolate 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.

4.5 Interaction with other medicinal products and other forms of interactions

Neostigmine metilsulfate should not be administered with suxamethonium (See Contra-indications above).

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

4.6 Fertility, pregnancy and lactation

Pregnancy & Breast-feeding: The safety of neostigmine metilsulfate and glycopyrronium in pregnancy and lactation has not been established.

Fertility:Reproduction studies in rats and rabbits revealed no teratogenic effects from Glycopyrronium bromide. 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.

4.7 Effects on ability to drive and use machines

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5mg/2.5mg per ml Solution for Injection may cause the eyesight to become weak, which could interfere with the ability to drive or operate machinery safely.

4.8 Undesirable effects

Adverse events are which have been associated with Glycopyrronium Bromide -Neostigmine Metilsulfate injection are given below, listed by system organ class and frequency.
Undesirable effects are especially likely to occur at treatment onset or at dose increase.
The undesirable effects are listed below by organ class and the following frequency convention:
Very common: (≥1/10)

Common: (≥1/100, <1/10)
Uncommon: (≥1/1,000, <1/100)
Rare: (≥1/10,000, <1/1,000)
Very rare: (<1/10,000),
Not known – cannot be estimated from the available data.

Tabulated list of adverse reactions for Glycopyrronium Bromide component of Glycopyrronium Bromide and Neostigmine Metilsulfate Injection:

System Organ Class	Adverse reaction	Frequency
Nervous system disorders	Confusion** Dizziness	Not known
Eye disorders	dilatation of the pupils, photophobia, Angle closure glaucoma	Not known
Cardiac disorders	Transient bradycardia*	Not known
Respiratory, thoracic and mediastinal disorders	Bronchial secretion reduced	Not known
Gastrointestinal Disorders	Dry mouth, Constipation Nausea, vomiting	Not known
Skin and subcutaneous tissue disorders	Flushing Dry skin Sweating decreased	Not known
Renal and urinary disorders	Micturition urgency Urinary retention	Not known

* Followed by tachycardia, palpitation and arrhythmias
**Particularly in elderly

Tabulated list of adverse reactions for Neostigmine component of Glycopyrronium Bromide and Neostigmine Metilsulfate Injection:

System Organ Class	Adverse reaction	Frequency
Cardiac disorders	Bradycardia, cardiac dysrhythmias	Not known
Respiratory, thoracic and mediastinal disorders	increased oropharyngeal secretions	Not known
Gastrointestinal Disorders	increased gastrointestinal activity	Not known

Glycopyrronium -Neostigmine component of injection can give rise to hypersensitivity, angioedema and anaphylactic reaction

If severe neostigmine - induced muscarinic side effects occur (bradycardia, 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 - 0.6 mg) or atropine 400- 1200 micrograms (0.4 - 1.2mg).

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2;Tel: +353 1 6764971; Fax: +353 1 6762517;Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 Overdose

Symptoms:

Signs of neostigmine overdosage (including nausea, vomiting, diarrhoea, excessive salivation and sweating, miosis, bradycardia or tachycardia, cardiospasm, inco-ordination, muscle cramps, fasciculation and paralysis, increased oropharyngeal secretions

and bronchospasm etc.) may be treated by the administration of Glycopyrronium Bromide Injection 0.2 - 0.6mg or atropine 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 1.0mg for each 1.0mg of glycopyrronium bromide known to have been administered.

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quaternary ammonium antimuscarinic
ATC Code: A03AB02
Mechanism of action:

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 metilsulphate 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 metilsulfate than a mixture of atropine and neostigmine metilsulfate.

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/Biotransformation:
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 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:
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 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.

Elimination half-life of neostigmine 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 Summary of Product Characteristics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium phosphate dodecahydrate
Citric acid monohydrate
Sodium hydroxide (for pH adjustment)
Citric acid solution (for pH adjustment)
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

Unopened: 18 months.
Once opened, use immediately and discard any remaining contents.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the ampoules in the outer carton in order to protect from light.

6.5 Nature and contents of container

1 ml clear glass ampoules (Ph. Eur. Type 1) in pack of 10.

6.6 Special precautions for disposal and other handling

Keep this medicine out of the sight and reach of children.
Do not dilute.
If only part used, discard the remaining solution.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

MercuryPharm Ltd
4045 Kingswood Road
City West Business Park
Co. Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0857/002/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 November 1986

Date of last renewal: 07 November 2006

10 DATE OF REVISION OF THE TEXT

April 2018