

Irish Medicines Board

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide and Neostigmine Metilsulfate 0.5 / 2.5 mg 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.

Excipients: Each 1 ml contains 3 mg (0.13 mmol) sodium.

For 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

Route of administration: For intravenous injection.

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).

Children: 0.02ml/kg intravenously over a period of 10 to 30 seconds (equivalent to neostigmine metilsulfate 0.05mg/kg 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.

4.3 Contraindications

Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1 ml Solution for Injection should not be given to patients with known hypersensitivity to either of the two active ingredients.

Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml Solution for Injection should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.

Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml 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, severe bradycardia 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 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml 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 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.

4.5 Interaction with other medicinal products and other forms of interaction

Neostigmine metilsulfate should not be administered with suxamethonium (See Contraindications above).

4.6 Pregnancy and lactation

Reproduction 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.

4.7 Effects on ability to drive and use machines

Not applicable.

4.8 Undesirable effects

The glycopyrronium bromide component of Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml Solution for Injection can give rise to dry mouth, difficulty in micturition, cardiac dysrhythmias, disturbances of visual accommodation and inhibition of sweating. The neostigmine component of Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml 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, bronchospasm or increased gastrointestinal activity etc.), these may be treated by the intravenous administration of

Glycopyrronium Bromide Injection 200 - 600 micrograms (0.2 - 0.61mg) or atropine 400- 1200 micrograms (0.4 - 1.2mg).

4.9 Overdose

The treatment of overdose depends on whether signs of anticholinesterase or anticholinergic overdose is the predominant presenting feature. Signs of neostigmine overdose (bradycardia, increased oropharyngeal secretions, 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, artificial ventilation may be necessary in such patients.

Signs of glycopyrronium bromide overdose (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.

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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml 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

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

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.

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

Do not mix with any other preparation.

6.3 Shelf Life

Unopened: 2 years.
Once opened, use immediately and discard any remaining contents.

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

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

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

Do not dilute.
If only part used, discard the remaining solution.

7 MARKETING AUTHORISATION HOLDER

Anpharm Limited
River Lane
Roscrea
County Tipperary

8 MARKETING AUTHORISATION NUMBER

PA 857/2/1

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

20 January 2012