UKPAR

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LAY SUMMARY

The MHRA today granted Martindale Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal products Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection (PL 00156/0116). This is a prescription-only medicine (POM) used to reverse the muscle relaxing effects produced by non-polarising muscle relaxants.

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection contains the active ingredients glycopyrronium bromide, which belongs to a group of medicines called anticholinergic drugs, and neostigmine, which belongs to a group of medicines called non-depolarising muscle relaxants.

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection (PL 00156/0116) on 7th September 2007. The product is a prescription-only medicine.

This was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, referring to the original product Robinul-Neostigmine Injection (PL 00100/0099), which was originally authorised to A H Robins Company Limited in 1987 and is now authorised to Anpharm Limited (following a Change of Ownership application in July 1997).

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.

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. Neostigmine Metilsulfate is extensively hydrolyzed in the blood. Elimination half-life ranged from about 15-30 minutes.

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection is indicated for the reversal of residual non-depolarising (competitive) neuromuscular block.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE Glycopyrronium Bromide

rINN: Glycopyrronium Bromide CAS Number: 596-51-0

Structure:

Chemical names: 3-hydroxy-1, 1-dimethylpyrrolidinium bromide-alpha-cyclopentyl

mandelate Pyrrolidinium, 3-[Cyclopentylhydroxyphenylacetyl) oxy]-

1,1-dimethyl-, bromide

MW: 398.34

Glycopyrrolate (glycopyrronium bromide) is a white, crystalline powder. Soluble in 1 in 4.2 of water, 1 in 30 of alcohol, 1 in 260 of chloroform, and 1 in 35,000 of ether.

The active substance manufacturer has provided an active substance file for glycopyrronium bromide.

An appropriate method of manufacture has been provided, with suitable in-process controls. Certificates of analysis for all starting materials have been provided and it has been confirmed that no materials of animal or human origin are used in the production of the active substance.

An appropriate specification is provided for the active substance glycopyrronium bromide. This complies with the USP monograph, with additional tests for residual solvents, endotoxins and organic volatile impurities (which are in-line with current requirements). On receipt of each batch of active substance, the finished product manufacturer tests for total viable count (which are in-line with current requirements). Batch analysis data are provided that comply with the proposed specification.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. All reference standards used are appropriate and satisfactory.

The active glycopyrronium bromide is stored in polyethylene bags, which are placed inside kraft-board drums with metal closure lids. The specifications and typical analytical test reports are provided and appear to be satisfactory.

Appropriate stability data have been generated supporting a retest period of 1 year when stored in the packaging proposed for marketing. Suitable commitments have been provided about continued testing of production batches of active substance.

Neostigmine Metilsulfate

rINN: Neostigmine Metilsulfate CAS Number: 51-60-5

Structure:

Chemical names: 3-[(Dimethylcarbamoyl)oxy]-N,N,N-trimethylanilinium methyl

sulphate

MW: 334.39

Neostigmine metilsulfate Ph Eur is hygroscopic, colourless crystals or a white crystalline powder, very soluble in water; freely soluble in alcohol, practically insoluble in ether.

The active substance manufacturer has provided a Certificate of Suitability for the manufacture of neostigmine metilsulfate. A declaration has been provided that none of the materials used in the manufacture of neostigmine metilsulfate are of animal or human origin.

An appropriate specification is provided for the active substance neostigmine metilsulfate. Batch analysis data are provided that comply with the proposed specification. All reference standards used are appropriate and satisfactory.

The active neostigmine metilsulfate is stored and shipped in 1000 ml square amber glass bottles with twist-off caps. The bottles are made of amber glass of hydrolytic class 3 (DIN ISO 719) and are manufactured according DIN 52339-T0180 (container class 3). The specifications and typical analytical test reports are provided and appear to be satisfactory. Furthermore the glass meets the Ph Eur requirements for glass type III. The closure consists of Moplen HP501H (Polypropylene homopolymer).

Appropriate stability data have been generated supporting a retest period of 36 months when stored in the proposed packaging. Suitable commitments have been provided about continued testing of production batches of active substance.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium hydroxide solution 10%, sodium phosphate, citric acid monohydrate, citric acid solution 10% and water for injections.

All excipients are controlled to British Pharmacopoeial standards. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain material of animal or human origin.

Pharmaceutical development

A suitable pharmaceutical development section has been provided. Comparable impurity profiles have been provided for both the proposed product and the reference product.

Manufacture

A description and flow-chart of the manufacturing method has been provided. A satisfactory batch formula has been provided for manufacture of the maximum batch size.

In-process controls are satisfactory based on process validation data and controls on the finished product. Process validation has been carried out and the results appear satisfactory.

Finished product specification

The proposed product complies with the general requirements of the Ph Eur for solutions for injection. The finished product specification provided is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of analysis have been provided for any working standards used.

Container Closure System

The finished product is packaged in Type I neutral glass ampoules of 1ml size. The ampoules are sealed by fusion and packed into cardboard cartons in packs of 10. Specifications and Certificates of Analysis for all packaging types used have been provided. These are satisfactory. Break force testing has been carried out in accordance with British Standard BS795.

Stability

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 12 months has been set, which is satisfactory, with the storage conditions "Do not store above 25 degrees" and "Keep container in the outer carton"...

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for essential similarity of the proposed and reference products have been met with respect to qualitative and quantitative content of the active substance, and the similar impurity profiles.

PRECLINICAL ASSESSMENT

This application for a generic product refers to Robinul-Neostigmine Injection (A H Robins Company Limited), which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

1. INDICATIONS

The applicant has submitted the following therapeutic indications:

Reversal of residual non-depolarising (competitive) neuromuscular block

These are consistent with the indications licensed for the UK reference product and are satisfactory.

2. DOSE & DOSE SCHEDULE

The applicant has submitted the following:

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), 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.

These are consistent with the indications licensed for the UK reference product and are satisfactory.

3. TOXICOLOGY

No new pre-clinical data have been provided.

4. CLINICAL PHARMACOLOGY

Both the proposed product and reference product are indicated for parenteral use and as such will be readily available via the intravenous route of administration.

Bioavailability and/or bioequivalence are not relevant to the intended use of the product. No comparative bioavailability or bioequivalence study data are required or included with the application.

5. EFFICACY

No new data are submitted and none are required for this type of application.

6. SAFETY

No new data are submitted and none are required for this type of application.

7. EXPERT REPORTS

A satisfactory expert report has been written by an appropriately qualified Doctor.

8. PATIENT INFORMATION LEAFLET (PIL)

A full-size colour mock-up of the PIL is supplied. It is consistent with the SPC, complies with current guidelines and is satisfactory.

9. LABELLING

Full colour mock-ups of the labelling are supplied. These comply with the current guidelines for a product of this type and are satisfactory.

10. APPLICATION FORM (MAA)

The MAA is medically satisfactory.

11. SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

The SPC is consistent to that licensed for the reference product and is satisfactory.

12. DISCUSSION

As the active ingredient, proposed route of administration and dosage are well-established, no new clinical data have been generated for the purpose of this application and none are required. Bibliographic references have been supplied as supporting data.

Bioequivalence to the claimed essentially similar product has been adequately demonstrated.

The requested indications, SPC, PIL and labelling are satisfactory.

The MAA form is satisfactory.

13. MEDICAL CONCLUSION

Marketing authorisation may be granted for this product.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

As the product is a simple aqueous solution for injection, with an essentially identical quantitative and qualitative composition to those for the reference product, no bioequivalence data were required. The applicant has demonstrated that Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml Solution for Injection is a generic product of the reference product Robinul-Neostigmine Injection.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Robinul-Neostigmine Injection.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The data supplied supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with glycopyrronium bromide and neostigmine metilsulfate is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 8 th November 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 13 th January 2006.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 13 th December 2006 and further information relating to the quality dossiers on 22 nd March 2006, 24 th January 2007, 23 rd February 2007 and 27 th March 2007
4	The applicant responded to the MHRA's requests, providing further information on 30 th January 2007 for the clinical sections, and again on 13 th October 2006, 6 th February 2007, 27 th March 2007 and 28 th March 2007 for the quality sections.
5	The applications were determined on 7 th September 2007

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

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

2 OUALITATIVE AND QUANTITATIVE COMPOSITION

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

3 PHARMACEUTICAL FORM

Sterile Solution for Injection A clear and colourless, sterile solution.

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), 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.

4.3 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.

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.

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 medicinal products 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 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.

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 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).

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 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 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

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.

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 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.

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 Hydrogen Phosphate Dodecahydrate

Citric Acid

Sodium Hydroxide

Citric Acid Solution

Water for Injections

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 $10 \times 1 ml$ 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.

7 MARKETING AUTHORISATION HOLDER

Martindale Pharmaceuticals

Bampton Road

Harold Hill

Romford

Essex

RM3 8UG

UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 00156/0116

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION 07/09/2007

10 DATE OF REVISION OF THE TEXT

07/09/2007

PACKAGE LEAFLET: INFORMATION FOR THE USER

C91182

GLYCOPYRRONIUM BROMIDE 0.5MG/ML AND NEOSTIGMINE METILSULFATE 2.5 MG/ML SOLUTION FOR INJECTION

Read all of this leaflet carefully before you start taking this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your Doctor or Pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your Doctor or Pharmacist.
- 1. What is Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection and what is it used for?
- Before you use Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection.
- How to use Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection.
- Possible side effects.
- How to store Glycopyrronium Bromide 0,5mg/ml and Neostigmine Metilsulfate 2,5 mg/ml Solution for Injection.
- Further information.

1. WHAT IS GLYCOPYRRONIUM BROMIDE 0,5MG/ML AND NEOSTIGMINE METILSULFATE 2.5 MG/ML SOLUTION FOR INJECTION?

Neostigmine belongs to a group of medicines called cholinesterase inhibitors. It can be used to reverse the effects of a group of muscle-relaxing drugs called nondepolarising muscle relaxants.

Glycopyrronium Bromide belongs to a group of medicines called anticholinergic drugs. It is used to counteract some unwanted effects that may occur with Neostigmine.

Glycopyrronium Bromide 0,5mg/ml and Neostigmine Metilsulfate 2,5 mg/ml Solution for Injection is used to reverse the muscle relaxation produced by non-depolarising muscle relaxants.

2. BEFORE YOU USE GLYCOPYRRONIUM BROMIDE 0.5MG/ML AND NEOSTIGMINE METILSULFATE 2.5 MG/ML SOLUTION FOR INJECTION.

Do not use Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection.

- If you are allergic to Glycopyrronium Bromide or Neostigmine Metilsulfate.
- If you think you may have a blockage in the intestine or urinary passage.

Take special care with Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection.

- If you are pregnant or breast feeding.
 If you suffer from glaucoma (increased pressure in the eye).
- · If you have had a recent operation on the intestines.
- If you suffer from attacks of asthma or wheezing.
- If you have a very slow heart beat (less than 60 beats per minute) or you are suffering from coronary artery disease, heart failure, irregular heart beats or high blood pressure.
- If you have an overactive thyroid gland.
- If you are suffering from epilepsy or Parkinsonism.
- If you have a fever.

Taking other medicines.

Please tell your Doctor or Pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and Breast feeding.

Ask your Doctor or Pharmacist for advice before taking any medicine.

Driving and using machines.

Do not drive or operate machinery unless you have been advised that it is safe to do so.

Important information about some of the ingredients of Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection. This medicinal product contains less than 1mmol Sodium (23mg) per dose, i.e.

essentially 'Sodium-free'.

3. HOW TO USE GLYCOPYRRONIUM BROMIDE 0,5MG/ML AND NEOSTIGMINE METILSULFATE 2.5 MG/ML SOLUTION FOR INJECTION.

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection is administered by injection into a vein.

Adults and elderly patients:

1-2ml injected into a vein over a period of 10 to 30 seconds.

Alternatively, a dose of 0.02ml per kg body weight may be injected into a vein over a period of 10 to 30 seconds.

Children:

0.02ml per kg body weight may be injected into a vein over a period of 10 to 30 seconds.

The dose may be repeated up to a maximum of 2ml

If you use more Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for injection.

In case of an overdose or a suspected overdose, the Doctor should be informed. immediately.

If you forget to use Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection.

Do not use a double dose to make up for a forgotten dose.

If you have any further questions on the use of this product, ask your Doctor or Pharmacist.

4. POSSIBLE SIDE EFFECTS.

Along with its needed effects, a medicine may cause unwanted effects. Tell your doctor if you notice any of the following symptoms:

- A dry mouth, difficulty in passing water, blurred vision or absence of sweating (these could be related to Glycopyrronium Bromide).
- A very slow heart beat, too much saliva, wheeziness, tummy cramps, vomiting or diarrhoea (these could be related to Neostigmine Metilsulfate).
- Palpitations or irregular heart beats (could be related to either Glycopyrronium Bromide or Neostigmine Metilsulfate).

If you notice any unwanted effects that are not mentioned here, tell your doctor.

5. HOW TO STORE GLYCOPYRRONIUM BROMIDE 0.5MG/ML AND NEOSTIGMINE METILSULFATE 2.5 MG/ML SOLUTION FOR INJECTION.

Keep out of the reach and sight of children.

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

You should not be given this medicine if the expiry date on the label has passed or if it shows signs of deterioration. The doctor or nurse will check that the expiry date on the label has not passed and that the product does not show signs of deterioration. If only part of an ampoule is used, discard the remaining solution.

6. FURTHER INFORMATION.

What Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection contains.

The active substance are; Glycopyrronium Bromide and Neostigmine Metilsulfate The other ingredients are; Sodium phosphate, Citric Acid Monohydrate, Diluted Citric Acid Solution, diluted Sodium Hydroxide and Water for Injections.

What Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection looks like and contents of the pack.

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection is a clear, colourless, sterile solution for injection. Each 1ml of solution contains the two active ingredients 0.5 mg of Glycopyrronium Bromide and 2.5 mg Neostigmine Metilsulfate. The product also contains Sodium phosphate, Citric Acid Monohydrate, Diluted Citric Acid Solution, dilute Sodium Hydroxide and Water for Injections.

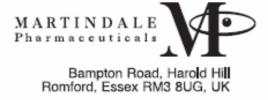
Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5 mg/ml Solution for Injection is presented in glass ampoules containing 1ml of solution. They are supplied in cartons each containing 10 x 1 ml.

Marketing Authorisation Holder and Manufacturer

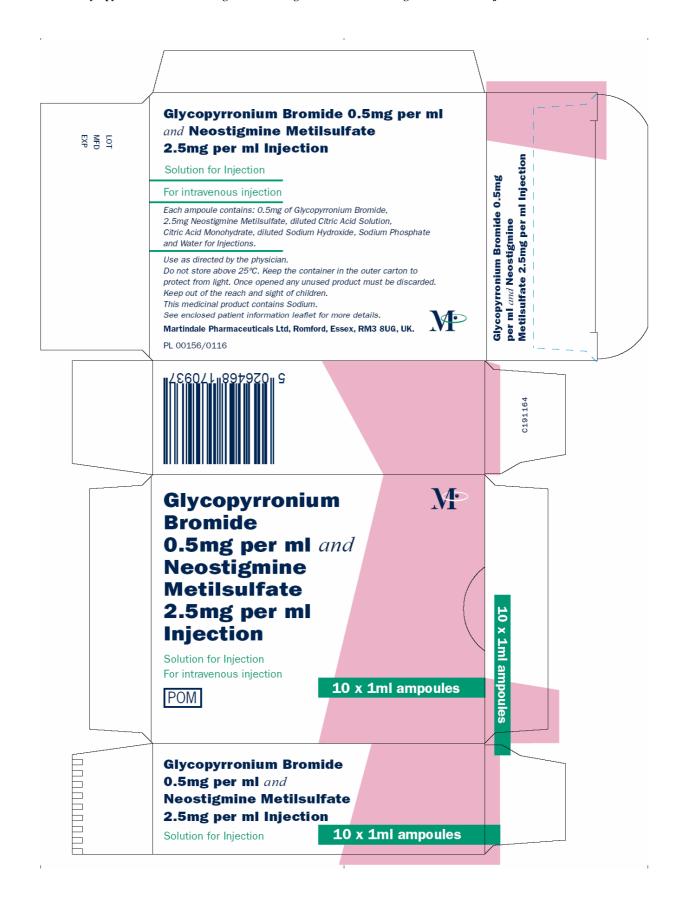
Martindale Pharmaceuticals, Bampton Road, Harold Hill, Romford, Essex, RM3 8UG, UK,

Date of Preparation: January 2007

Product Licence Number: PL 00156/0116



C91182



MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use

PL00156/0116 Lat xxxxxx Exp xx/xx/xx

POM

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate

2.5mg/ml Solution for injection. For intravenous use only.

PL00156/0116 1ml Lot xxxxxx POM Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use

PL00156/0116 Imi Lot xxxxxx POM Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 Lot xxxxx POM Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml Neostigmine Metilsulfate

2.5mg/ml Solution for injection. For intravenous use only

PL00156/0116 Lot xxxxxx Exp xx/xx/xx

Iml

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 Lot xxxxxx Exp xx/xx/xx

1 ml POM

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 l ml Lot xxxxxx POM Exp xx/xx/xx A 1349

MARITNDALE

Glycopyrronium Bromide 0.5mg/ml Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 1ml Lot xxxxxx POM Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 Iml Lot xxxxxx Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 Iml POM Lot xxxxx Exp xx/xx/xx

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 I ml POM Lot xxxxx Exp xx/xx/xx A 1345

MARTINDALE

Glycopyrronium Bromide 0.5mg/ml and Neostigmine Metilsulfate 2.5mg/ml

Solution for injection. For intravenous use only.

PL00156/0116 POM Lot xxxxxx Exp xx/xx/xx