GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION (PL 00156/0115)

UKPAR

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GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION (PL 00156/0115)

LAY SUMMARY

The MHRA today granted Martindale Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicinal products Glycopyrronium Bromide 0.2mg/ml Solution for Injection (PL 00156/0115). This is a prescription-only medicine (POM) used to (i) protect against some of the unwanted effects of drugs such as Neostigmine or Pyridostigmine (which reverse the effects of certain muscle-relaxing drugs); (ii) to reduce saliva and other secretions, and to reduce acidity in stomach contents before an operation; and (iii) to prevent slowness of the heartbeat during surgery.

Glycopyrronium Bromide 0.2mg/ml Solution for Injection contains the active ingredient glycopyrronium bromide, which belongs to a group of medicines called anticholinergic drugs

No new or unexpected safety concerns arose from these applications and it was, therefore, judged that the benefits of taking Glycopyrronium Bromide 0.2mg/ml Solution for Injection outweigh the risks, hence a Marketing Authorisation has been granted.

GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION (PL 00156/0115)

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 0.2mg/ml Solution for Injection (PL 00156/0115) 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 Injection (PL 00100/0054), which was originally authorised to A H Robins Company Limited in 1981 and is now authorised to Anpharm Limited (following a Change of Ownership application in July 1997).

The product contains the active ingredient glycopyrronium bromide, a quaternary ammonium antimuscarinic agent. Like other anticholinergic agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and to a limited degree in the autonomic ganglia. Thus, it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions. Glycopyrronium Bromide antagonises muscarinic symptoms (e.g. bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

The highly polar quaternary ammonium group of Glycopyrronium Bromide limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to Atropine Sulphate and Scopolamine Hydrobromide (which are non-polar tertiary amines that penetrate lipid barriers easily).

Glycopyrronium Bromide is rapidly diminished and/or excreted after intravenous administration. The terminal elimination phase is relatively slow with quantifiable levels remaining up to 8 hours after administration. Peak effects occur approximately 30 to 45 minutes after intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine. With, intravenous injection, the onset of action is generally evident within 1 minute.

Glycopyrronium Bromide 0.2mg/ml Solution for Injection is indicated for the following:

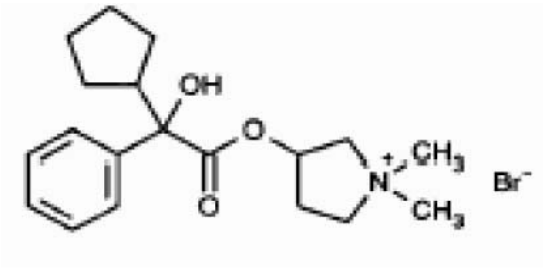
To protect against the peripheral muscarinic actions of anticholinesterases such as Neostigmine and Pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.

As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.

As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of Suxamethonium or due to cardiac vagal reflexes.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE
Glycopyrronium Bromide
rINN: Glycopyrronium Bromide CAS Number: 596-51-0
Structure:



$C_{19}H_{28}BrNO_3$

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.

DRUG PRODUCT

Other ingredients

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, hydrochloric acid and water for injections.

All ingredients comply with their relevant BP/Ph Eur monographs. Satisfactory certificates of analysis have been provided for all excipients.

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

Impurity profiles

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 on small-scale batches of product and the results appear satisfactory. The applicant has committed to providing validation data for the first three production-scale batches produced.

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 either 1ml (for the 1ml pack size) or 5ml (for the 3ml pack 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 24 months has been set, which is satisfactory, with no storage conditions.

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 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:

To protect against the peripheral muscarinic actions of anticholinesterases such as Neostigmine and Pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.

As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.

As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of Suxamethonium or due to cardiac vagal reflexes.

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:

Glycopyronium Bromide Injection is a sterile solution for intravenous or intramuscular administration.

Premedication
Adults and older patients:
200 to 400 micrograms (0.2mg to 0.4mg) intravenously or intramuscularly before the induction of anaesthesia. Alternatively, a dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Children:
4 to 8 micrograms/kg (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) intravenously or intramuscularly before the induction of anaesthesia. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Intra-operative use
Adults and older patients:
A single dose of 200 to 400 micrograms (0.2 to 0.4mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. This dose may be repeated if necessary.
Children:
A single dose of 200 micrograms (0.2mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 8 micrograms/kg by intravenous injection (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block
Adults and older patients:
200 micrograms (0.2mg) intravenously per 1000 micrograms (1mg) of Neostigmine or the equivalent dose of Pyridostigmine. Alternatively, a dose of 10 to 15 micrograms/kg (0.01 to 0.015mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) Neostigmine or equivalent dose of pyridostigmine. Glycopyrronium Bromide Injection may be administered simultaneously from the same syringe with the anticholinesterase; as there are greater cardiovascular stability results from this method of administration.

Children:
10 micrograms/kg (0.01mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) Neostigmine or equivalent dose of pyridostigmine. Glycopyrronium Bromide Injection may be administered simultaneously from the same syringe with the anticholinesterase; as there are greater cardiovascular stability results from this method of administration.

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 and intramuscular route of administration.

Published pharmacokinetic data indicate that, although the onset may be delayed, other parenteral routes are equally bioavailable. 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 0.2mg/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 0.2mg/ml Solution for Injection is a generic product of the reference product Robinul Injection.

No new or unexpected safety concerns arise from these applications.

The SPC, PIL and labelling are satisfactory and consistent with that for Robinul 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 is considered to have demonstrated the therapeutic value of the compound.

The risk benefit is, therefore, considered to be positive.

GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION (PL 00156/0115)

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 8th November 2005
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21st November 2005.
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 13th December 2006 and further information relating to the quality dossiers on 22nd March 2006, 8th January 2007 and 23rd February 2007
4	The applicant responded to the MHRA's requests, providing further information on 26th January 2007 for the clinical sections, and again on 13th October 2006, 21st February 2007 and 27th March 2007 for the quality sections.
5	The applications were determined on 7th September 2007

GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION (PL 00156/0115)

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 0.2mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of injection contains 200 micrograms (0.2mg) of Glycopyrronium Bromide.

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

To protect against the peripheral muscarinic actions of anticholinesterases such as Neostigmine and Pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.

As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.

As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia associated with the use of Suxamethonium or due to cardiac vagal reflexes.

4.2 Posology and method of administration

Glycopyronium Bromide Injection is a sterile solution for intravenous or intramuscular administration.

Premedication
Adults and older patients:
200 to 400 micrograms (0.2mg to 0.4mg) intravenously or intramuscularly before the induction of anaesthesia. Alternatively, a dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Children:
4 to 8 micrograms/kg (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) intravenously or intramuscularly before the induction of anaesthesia. Larger doses may result in profound and prolonged antisialogogue effect which may be unpleasant for the patient.

Intra-operative use
Adults and older patients:
A single dose of 200 to 400 micrograms (0.2 to 0.4mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 5 micrograms/kg (0.004 to 0.005mg/kg) up to a maximum of 400 micrograms (0.4mg) may be used. This dose may be repeated if necessary.
Children:
A single dose of 200 micrograms (0.2mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 8 micrograms/kg by intravenous injection (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block
Adults and older patients:
200 micrograms (0.2mg) intravenously per 1000 micrograms (1mg) of Neostigmine or the equivalent dose of Pyridostigmine. Alternatively, a dose of 10 to 15 micrograms/kg (0.01 to 0.015mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) Neostigmine or equivalent dose of pyridostigmine. Glycopyrronium Bromide Injection may be administered simultaneously from the same syringe with the anticholinesterase; as there are greater cardiovascular stability results from this method of administration.

Children:
10 micrograms/kg (0.01mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) Neostigmine or equivalent dose of pyridostigmine. Glycopyrronium Bromide Injection may be administered

simultaneously from the same syringe with the anticholinesterase; as there are greater cardiovascular stability results from this method of administration.

4.3 Contraindications

Apart from established hypersensitivity to Glycopyrronium Bromide, there are no absolute contra-indications to Glycopyrronium Bromide.

4.4 Special warnings and precautions for use

Because of the increase of heart rate produced by the administration of anticholinergics, use with caution in patients with coronary artery disease; congestive heart failure; cardiac arrhythmias, hypertension and thyrotoxicosis. This product should be used very cautiously in pyrexial patients due to inhibition of sweating.

Large doses of quaternary ammonium anticholinergic compounds have been shown to block end plate nicotinic receptors. This should be considered before using Glycopyrronium Bromide in patients with myasthenia gravis.

It is known that the administration of anticholinergic agents during inhalation anaesthesia can result in ventricular arrhythmias.
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

Anticholinergic agents may delay absorption of other medicaments given concomitantly.

Excessive cholinergic blockade can occur if Glycopyrronium Bromide 0.2mg/ml Solution for Injection is given concomitantly with belladonna alkaloids or other synthetic anticholinergic agents (such as antiparkinsonism agents), phenothiazines, tricyclic antidepressants, disopyramide, procainamide, quinidine, antihistamines, or narcotic analgesics such as meperidine.

Concurrent administration of anticholinergics and corticosteroids may result in increased intraocular pressure.

Concurrent use of anticholinergic agents with slow-dissolving tablets of digoxin may cause increased serum digoxin levels.

4.6 Pregnancy and lactation

Although reproduction studies in rats and rabbits revealed no teratogenic effects from Glycopyrronium Bromide, safety in human pregnancy and lactation has not been established. 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

Do not operate or drive heavy machinery until instructed by a physician.

4.8 Undesirable effects

Glycopyrronium Bromide Injection may produce the following effects which are extensions of its fundamental pharmacological actions: dry mouth, difficulty in micturition, disturbances in visual accommodation, tachycardia, palpitations and inhibition of sweating.

However, the use of Glycopyrronium Bromide Injection as a preoperative anticholinergic is associated with less effect on the cardiovascular system compared to Atropine.

4.9 Overdose

Symptoms

Since Glycopyrronium Bromide is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature.

Treatment
To combat the peripheral anticolinergic effects of Glycopyrronium Bromide anticholinergic effects, a quaternary ammonium anticholinesterase such as Neostigmine methylsulphate may be given in a dose of 1000 micrograms (1.0mg) for each 1000 micrograms (1.0mg) of glycopyrrolate known to have been administered by the parenteral route.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Glycopyrronium Bromide is a quaternary ammonium antimuscarinic agent and like other anticholinergic agents, it inhibits the action of acetylcholine on structures innervated by postganglionic cholinergic nerves and on smooth muscles that respond to acetylcholine but lack cholinergic innervation. These peripheral cholinergic receptors are present in the autonomic effector cells of smooth muscle, cardiac muscle, the sinoatrial node, the atrioventricular node, exocrine glands and to a limited degree in the autonomic ganglia. Thus it diminishes the volume and free acidity of gastric secretions and controls excessive pharyngeal, tracheal and bronchial secretions. Glycopyrronium Bromide antagonises muscarinic symptoms (e.g. bronchorrhea, bronchospasm, bradycardia and intestinal hypermotility) induced by cholinergic drugs such as the anticholinesterases.

The highly polar quaternary ammonium group of Glycopyrronium Bromide limits its passage across lipid membranes, such as the blood-brain barrier, in contrast to Atropine Sulphate and Scopolamine Hydrobromide, which are non-polar tertiary amines which penetrate lipid barriers easily.

Glycopyrronium Bromide Injection has been used successfully as an adjunct to reversal by Neostigmine when Atropine has been used as the preoperative anticholinergic. The use of Glycopyrronium Bromide Injection as an adjunct to reversal by Neostigmine of non-depolarising muscle relaxants is associated with less initial tachycardia and better protection against the cholinergic effects of Neostigmine compared to reversal with a mixture of Neostigmine and Atropine.

5.2 Pharmacokinetic properties

Glycopyrronium Bromide is rapidly diminished and/or excreted after intravenous administration. The terminal elimination phase is relatively slow with quantifiable levels remaining up to 8 hours after administration. Peak effects occur approximately 30 to 45 minutes after intramuscular administration. The vagal blocking effects persist for 2 to 3 hours and the antisialagogue effects persist up to 7 hours, periods longer than for atropine. With, intravenous injection, the onset of action is generally evident within one minute.

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

Sodium Chloride
Dilute Hydrochloric Acid
Water for Injections

6.2 Incompatibilities

Glycopyrronium Bromide Injection has been shown to be physically compatible with the following agents commonly used in anaesthetic practice: Butorphanol, Lorazepam, Droperical and Fentanyl Citrate, Levorphanol Tartrate, Pethidine Hydrochloride, Morphine Sulphate, Neostigmine, Promethazine and Pyridostigmine.

Glycopyrronium Bromide Injection has been shown to be physically incompatible with the following agents commonly used in anaesthetic practice: Diazepam, Dimenhydrinate, Methohexital Sodium, Pentazocine, Pentobarbital Sodium and Thiopental Sodium.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Glycopyrronium Bromide Injection is presented in clear Type I ampoules of neutral glass containing 10 x 1ml ampoules or 10 x 3ml ampoules packed in a cardboard carton.

6.6 Special precautions for disposal

Keep out of the reach and sight of children.
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 00156/0115

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

07/09/2007

10 DATE OF REVISION OF THE TEXT

07/09/2007

11 DOSIMETRY (IF APPLICABLE)

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS (IF APPLICABLE)

PACKAGE LEAFLET: INFORMATION FOR THE USER. C91181

Glycopyrronium Bromide 0.2mg/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.

In this leaflet

1. WHAT IS GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION AND WHAT IS IT USED FOR?

Glycopyrronium Bromide belongs to a group of medicines called anticholinergic drugs.

Glycopyrronium Bromide 0.2 mg/ml Solution for Injection may be used:
- To protect against some of the unwanted effects of drugs such as Neostigmine or Pyridostigmine, which are used to reverse the effects of certain types of muscle-relaxing drugs (called non-depolarising muscle relaxants).
- Before an operation, to reduce saliva and other secretions and to reduce acidity in the stomach contents.
- Before or during an operation, to reduce or prevent slowness of the heartbeat during surgery.

2. BEFORE YOU USE GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION.

Do not use Glycopyrronium Bromide 0.2mg/ml Solution for Injection.
- If you are allergic to Glycopyrronium Bromide.

Take special care with Glycopyrronium Bromide 0.2mg/ml Solution for Injection.
- If you are pregnant or breast feeding.
- If you suffer from myasthenia gravis (a disease resulting in severe muscle weakness and fatigue).
- If you have an abnormally high heart rate associated with an over-active thyroid gland, poor heart function, heart failure or have had cardiac surgery.
- If have a history of high blood pressure, coronary artery disease or irregular heart beats.
- If you have a fever.

Please tell your Doctor or Pharmacist if you are taking or have recently taken:
- Other anticholinergic drugs (such as ones used to treat Parkinson's disease, spasm of the intestine or a 'weak bladder', or some inhalers to relieve wheeziness).
- Tricyclic antidepressants (drugs used to treat depression).
- Phenothiazines (drugs used to stabilise your mood, nausea, vomiting or vertigo).
- Digoxin tablets (a drug used to treat heart condition).
- Disopyramide (a drug used to treat heart disorders).
- Procainamide and Quinidine (used to treat irregular heart beats).
- Antihistamines (for allergic conditions).
- Corticosteroids (e.g. to reduce inflammation or to relieve asthma).
- Pethidine (a strong pain reliever).

If you 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 this 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 0.2mg/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 0.2MG/ML SOLUTION FOR INJECTION.
Glycopyrronium Bromide 0.2 mg/ml Solution for Injection is administered by injection into a muscle or into a vein.

Dosage when used before an operation:

Adults and older patients:
200 to 400 micrograms (0.2 to 0.4mg) may be injected into a vein or into a muscle before the anaesthetic is given. Alternatively, a dose of 4 to 5 micrograms per kilogram of body weight (0.004 to 0.005mg per kg) may be used, up to a maximum dose of 400 micrograms (0.4mg).

Children:
4 to 8 micrograms per kilogram of body weight (0.004 to 0.008mg per kg) may be injected into a vein or into a muscle before the anaesthetic is given, up to a maximum of 200 micrograms (0.2mg) may be used.

Dosage when used during an operation:

Adults and older patients:
A single dose of 200 to 400 micrograms (0.2 to 0.4mg) should be given by injection into a vein. Alternatively, a single dose of 4 to 5 micrograms per kilogram of body weight (0.004 to 0.005mg per kg) may be used, up to a maximum of 400 micrograms (0.4mg). This dose may be repeated if necessary.

Children:
A single dose of 200 micrograms (0.2mg) should be given by injection into a vein. Alternatively a single dose of 4 to 8 micrograms per kilogram of body weight (0.004 to 0.008mg per kg) should be given by injection into a vein, up to a maximum of 200 micrograms (0.2mg). This dose may be repeated if necessary.

Dosage when reversing the effects of non-depolarising muscle relaxants:

Adults and older patients:
200 micrograms (0.2mg) per 1,000 micrograms (1mg) of Neostigmine or the equivalent dose of Pyridostigmine, by injection into a vein. Alternatively, a dose of 10 to 15 micrograms per

kilogram of body weight (0.01 to 0.015 mg per kg) may be injected into a vein with 50 micrograms per kg (0.05 mg per kg) of Neostigmine or equivalent dose of Pyridostigmine. Glycopyrronium Bromide 0.2 mg/ml Solution for Injection may be administered at the same time and from the same syringe with the Neostigmine or Pyridostigmine.

Children:
10 micrograms per kg of body weight (0.01mg per kg) may be injected into a vein with 50 micrograms per kg (0.05mg per kg) of Neostigmine or the equivalent dose of Pyridostigmine. Glycopyrronium Bromide 0.2 mg/ml Solution for Injection may be administered at the same time and from the same syringe with the Neostigmine or Pyridostigmine.

If you use more Glycopyrronium Bromide 0.2mg/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 0.2mg/ml Solution for Injection.
Please seek medical help.

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

4. POSSIBLE SIDE EFFECTS.
Like all medicines Glycopyrronium Bromide 0.2mg/ml Solution for Injection can cause side effects, although not everybody gets them. If you notice any of the following symptoms, tell your Doctor:

A dry mouth or you have difficulty in passing urine, blurred vision, or absence of sweating, palpitations or a fast heart beat.

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.

5. HOW TO STORE GLYCOPYRRONIUM BROMIDE 0.2MG/ML SOLUTION FOR INJECTION.
Keep out of the reach and sight of children.
This medicinal product does not require any special storage conditions.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 0.2mg/ml Solution for Injection contains.
The active substance is; Glycopyrronium Bromide.
The other ingredients are; Sodium Chloride, dilute Hydrochloric Acid and Water for Injections.

What Glycopyrronium Bromide 0.2mg/ml Solution for Injection looks like and contents of the pack.
Glycopyrronium Bromide 0.2mg/ml Solution for Injection is an isotonic aqueous solution for injection. Each ml of solution contains 0.2mg of Glycopyrronium Bromide. It also contains Sodium Chloride, dilute Hydrochloric Acid and Water for Injections.

Glycopyrronium Bromide 0.2mg/ml Solution for Injection is presented in glass ampoules containing 1ml or 3ml of solution. They are supplied in cartons each containing 10 x 1 ml or 10 x 3 ml.

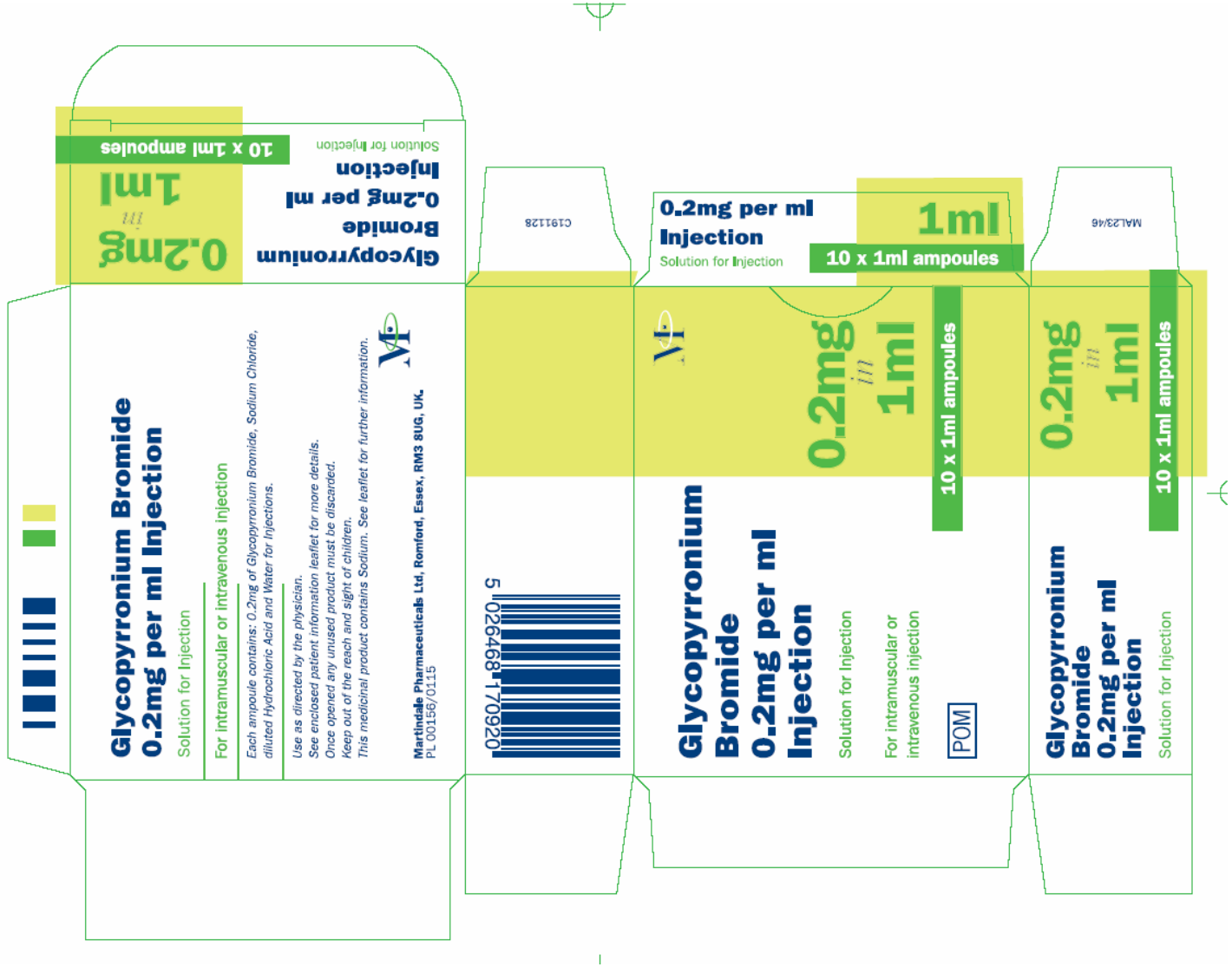
Marketing Authorisation Holder and Manufacturer
Martindale Pharmaceuticals, Bampton Road,
Harold Hill, Romford, Essex, RM3 8UG, UK.

This leaflet was last approved in:
Date of Preparation: January 2007
Product Licence Number: PL 00156/0115

MARTINDALE
Pharmaceuticals

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

C91181


Glycopyrronium Bromide 0.2mg per ml Injection
Solution for Injection
For intramuscular or intravenous Injection
Each ampoule contains: 0.2mg of Glycopyrronium Bromide, Sodium Chloride, diluted Hydrochloric Acid and Water for Injections.
Use as directed by the physician.
See enclosed patient information leaflet for more details.
Once opened any unused product must be discarded.
Keep out of the reach and sight of children.
This medicinal product contains Sodium. See leaflet for further information.
Martindale Pharmaceuticals Ltd, Romford, Essex, RM3 8UG, UK.
PL 00156/0115
5 026468 170920
0.2mg in 1ml
10 x 1ml ampoules
Glycopyrronium Bromide 0.2mg per ml Injection
Solution for Injection
For intramuscular or intravenous injection
POM
0.2mg per ml Injection
Solution for Injection
1ml
10 x 1ml ampoules
C19112B
MAL23/46


MARTINDALE
Glycopyrronium Bromide 0.2mg/ml Injection
Solution for injection.
For IV or IM use only.
PL00156/0115
Lot xxxxxx
Exp xx/xx/xx
1ml
POM
A1350


Glycopyrronium Bromide 0.2mg per ml Injection
Solution for Injection
For intramuscular or intravenous injection
Each ampoule contains: 0.6mg of Glycopyrronium Bromide, Sodium Chloride, diluted Hydrochloric Acid and Water for Injections.
Use as directed by the physician.
See enclosed patient information leaflet for more details.
Once opened any unused product must be discarded.
Keep out of the reach and sight of children.
This medicinal product contains Sodium. See leaflet for further information.
Martindale Pharmaceuticals Ltd, Romford, Essex, RM3 8UG, UK.
PL 00156/0115
5 026268 709713
C191163
0.2mg per ml Injection
Solution for Injection
3ml
10 x 3ml ampoules
0.6mg in 3ml
10 x 3ml ampoules
POM
MAL104/8


MARTINDALE
Glycopyrronium Bromide 0.2mg/ml Injection
Solution for injection.
For IV or IM use only.
PL00156/0115
3ml
Lot xxxxxx
Exp xx/xx/xx
POM
A1351