

**GLYCOPYRRONIUM BROMIDE 200 MCG/ML INJECTION
(GLYCOPYRRONIUM BROMIDE)**

PL 20910/0003

UK Public Assessment Report

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PL 20910/0003

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Taro Pharmaceuticals (Ireland) Limited a Marketing Authorisation (licence) for the medicinal product Glycopyrronium Bromide 200mcg/ml injection (PL 20910/0003) on 1st April 2008. This is a prescription-only medicine used before and during inhalation anaesthesia to dry the bronchial and salivary secretions.

The injection contains the active ingredient glycopyrronium bromide, which belongs to a group of medicines called anti-muscarinic agents. Glycopyrronium Bromide injection is administered either into a vein or into a muscle.

The approved product was considered to be a generic version of the reference product Robinul injection 0.2mg / ampoule (PL 15372/0004, Anpharm Limited) based on data submitted by Taro Pharmaceuticals (Ireland) Limited.

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Glycopyrronium Bromide 200mcg/ml injection outweigh the risk; hence a Marketing Authorisation (MA) has been granted.

**GLYCOPYRRONIUM BROMIDE 200 MCG/ML INJECTION
(GLYCOPYRRONIUM BROMIDE)**

PL 20910/0003

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the MHRA granted Taro Pharmaceuticals (Ireland) Limited a Marketing Authorisation for the medicinal product Glycopyrronium Bromide 200mcg/ml injection (PL 20910/0003) on 1st April 2008. The product is a prescription-only medicine (POM).

The application was submitted as a national abridged application, according to Article 10.1 of Directive 2001/83/EC, as amended. The application refers to the reference product, Robinul injection 0.2mg / ampoule (PL 15372/0004, Anpharm Limited) that was granted a licence on 1st July 1997, as a Change of Ownership application (CoA) from PL 00100/0054, authorised to A H Robins Company Limited on 17/03/1981.

The drug product is an injection containing 200mcg/ml of the active ingredient glycopyrronium bromide (available as 200mcg in 1ml and 600mcg in 3ml). Glycopyrronium bromide is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. It is used similarly to atropine in anaesthetic practice. Glycopyrronium bromide may be used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects in the reversal of non-depolarising neuromuscular block.

Antimuscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves, as well as being inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilation of the pupils (mydriasis) and paralysis of accommodation (cycloplegia); increased heart rate; inhibition of micturition, reduction in gastrointestinal tone; and inhibition of gastric acid secretion.

Glycopyrronium Bromide 200 micrograms/ml Injection is indicated: 1. To protect against the peripheral muscarinic actions of anticholinesterases; 2. As a pre-operative antimuscarinic agent to reduce salivary, tracheobronchial and pharyngeal secretions and to reduce the acidity of gastric contents; 3. As a pre-operative or intra-operative antimuscarinic.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

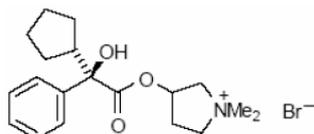
Glycopyrronium bromide

Nomenclature:

INN: Glycopyrronium bromide

Chemical name: Pyrrolidinium, 3-[cyclopentylhydroxyphenylacetyl]oxy]-1,1-dimethyl-, bromide

Structure:



Molecular formula: $C_{19}H_{28}NO_3 \cdot Br$

Molecular weight: 398.3

CAS number: 58493-54-2

Physical form: A white crystalline powder with a melting point of 193-198°C

Solubility: Soluble in water and methanol

The active substance, glycopyrronium bromide, is not described in the British Pharmacopeia (BP) or European Pharmacopeia (EP).

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis. Confirmation has been provided that the raw materials, intermediates and auxiliary agents used in synthesis of the active are not of animal, biological or genetically modified origin, and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided which was set by the ASMF (Active Substance Master File) holder. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for primary and working reference standards used by the active substance manufacturer during validation studies.

Active glycopyrronium bromide is stored in appropriate packaging. It is packed into polyethylene bags, which are then placed inside drums with metal closure lids. Specifications and Certificates of Analysis have been provided for the packaging materials used. The polyethylene bags in direct contact with the active substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 1 year, and a shelf life of 3 years.

DRUG PRODUCT

Description and Composition

The drug product is presented as a clear, colourless solution for injection.

Other ingredients consist of pharmaceutical excipients, namely sodium chloride, hydrochloric acid, and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeia monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Impurity profiles for the drug product were found to be similar to those for the reference product, and all the impurities were within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation studies have been conducted and are satisfactory.

Finished product specification

The finished product specification at release and for the product shelf life is supplied, and provides an assurance of the quality and consistency of the finished product. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. 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 primary and working reference standards used.

Container Closure System

The drug product is presented in 1ml and 3ml capacity clear, colourless Type I glass ampoules containing 1ml or 3ml of solution. The ampoules are packaged with the Patient Information Leaflet (PIL) into cardboard outer cartons, as packs of 10. The ampoules satisfy Directive 2002/72/EC (as amended), and are suitable for contact with parenteral preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 24 months has been set for the 1ml ampoules, and a shelf-life of 18 months has been set for the 3ml ampoules. The storage instructions for both ampoule sizes are 'Do not store above 25°C' and 'Keep the ampoules in the outer carton in order to protect from light'. This is satisfactory.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

Expert Report

The quality overview is written by an appropriately qualified expert and is adequate. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

Product Information

The approved SmPC, leaflet, and labelling are satisfactory.

Conclusion

The proposed product, Glycopyrronium Bromide 200mcg/ml injection, has been shown to be a generic version of the reference product, Robinul injection 0.2mg / ampoule, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

All pharmaceutical issues have been resolved and the quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged application, according to Article 10.1 of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical overview has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

BACKGROUND

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.

INDICATIONS

Glycopyrronium Bromide 200mcg/ml injection is indicated-

- 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.

The indications for this product are consistent with those for the reference product.

POSODOLOGY AND METHOD OF ADMINISTRATION

The posology is consistent with that for the reference product.

TOXICOLOGY

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

CLINICAL PHARMACOLOGY

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

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report.

Glycopyrronium Bromide 200mcg/ml injection is to be administered as an intravenous or intramuscular solution and contains the same active substance, in the same concentration, as the currently authorised reference product Robinul. Thus, in accordance with the "Note for Guidance on the Investigation of Bioavailability and Bioequivalence", (CPMP/EWP/QWP/1401/98), the applicant is not required to submit a bioequivalence study.

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical overview. The safety profile of amiodarone is very well defined.

Expert Report

A satisfactory clinical overview is provided, and has been prepared by an appropriately qualified expert. An appropriate CV for the expert has been supplied.

PRODUCT INFORMATION:**Summary of Product Characteristics (SmPC)**

The approved SmPC is consistent with that for the reference product and is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SmPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Robinul injection 0.2mg / ampoule (PL 15372/0004), are considered adequate. The product literature is approved.

All issues have been adequately addressed by the applicant and sufficient clinical information has been submitted to support this application. When used as indicated, Glycopyrronium Bromide 200mcg/ml injection has a favourable benefit-to-risk ratio. A Marketing Authorisation may be granted on medical grounds.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Glycopyrronium Bromide 200mcg/ml 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

The applicant's Glycopyrronium Bromide 200mcg/ml injection has been demonstrated to be a generic version of the reference product, Robinul injection 0.2mg / ampoule (PL 15372/0004, Anpharm Limited).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SmPC, PIL, and labelling are satisfactory and consistent with that for the reference product.

The Marketing Authorisation Holder has provided a commitment to update the Marketing Authorisation with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups, no later than 1st July 2008.

The approved labelling artwork complies with statutory requirements.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's product and the reference product are interchangeable. Extensive clinical experience with glycopyrronium bromide is considered to have demonstrated the therapeutic value of the active substance. The risk: benefit is, therefore, considered to be positive.

**GLYCOPYRRONIUM BROMIDE 200 MCG/ML INJECTION
(GLYCOPYRRONIUM BROMIDE)**

PL 20910/0003

STEPS TAKEN FOR ASSESSMENT

- 1 The MHRA received the marketing authorisation application on 7th October 2004
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 19th October 2004
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 22nd July 2005
- 4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 3rd March 2006
- 5 Following assessment of the response the MHRA requested further information relating to the quality sections on 20th July 2006, 16th March 2007, 28th January 2008, and 5th March 2008; and for the clinical sections on 8th November 2007
- 6 The applicant responded to the MHRA's request, providing further information for the quality sections on 22nd October 2006, 7th November 2007, 9th February 2008, and 6th March 2008; and for the clinical sections on 9th February 2008 respectively
- 7 The application was determined on 1st April 2008

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Glycopyrronium Bromide 200 mcg/ml Injection is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 200 micrograms/ml Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml of sterile solution for injection contains 200 micrograms of glycopyrronium bromide.

Each 3 ml of sterile solution for injection contains 600 micrograms of glycopyrronium bromide.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless, sterile solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

1. 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.
2. As a pre-operative antimuscarinic agent to reduce salivary, tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.
3. As a pre-operative or intra-operative antimuscarinic to attenuate or prevent intra-operative bradycardia with the use of suxamethonium or due to cardiac vagal reflexes.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route of Administration: Intravenous or intramuscular injection.

Dosage:

Premedication:

Adults and elderly patients:

200 - 400 micrograms or 4 - 5 micrograms/kg to a maximum of 400 micrograms intravenously or intramuscularly.

Children:

4 - 8 micrograms/kg to a maximum of 200 micrograms intramuscularly or preferably by intravenous injection.

Larger doses may result in a profound and prolonged antisialagogue effect which may be unpleasant for the patient.

Intra-operative use:

Adults and elderly patients:

By intravenous injection: A single dose of 200 - 400 micrograms or 4 - 5 micrograms/kg to a maximum of 400 micrograms, repeated if necessary.

Children:

By intravenous injection: A single dose of 200 micrograms by intravenous injection should be used. Alternatively, a single dose of 4 - 8 micrograms/kg up to a maximum of 200 micrograms may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block:

Adults and older patients:

200 micrograms (0.2 mg) intravenously per 1000 micrograms (1 mg) neostigmine or the equivalent dose of pyridostigmine. Alternatively, a dose of 10 to 15 micrograms/kg (0.01 to 0.015 mg/kg) intravenously with 50 micrograms/kg (0.05 mg/kg) neostigmine or equivalent dose of pyridostigmine. Glycopyrronium bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Children:

10 micrograms/kg (0.01 mg/kg) intravenously with 50 micrograms/kg (0.05 mg/kg) neostigmine or the equivalent dose of pyridostigmine. Glycopyrronium bromide may be administered simultaneously from the same syringe with the anticholinesterase; greater cardiovascular stability results from this method of administration.

4.3 CONTRAINDICATIONS

In common with other antimuscarinics: angle-closure glaucoma; myasthenia gravis (large doses of quaternary ammonium compounds have been shown to block end plate nicotinic receptors); paralytic ileus; pyloric stenosis; prostatic enlargement.

Anticholinesterase-antimuscarinic combinations such as neostigmine plus glycopyrronium should be avoided in patients with a prolonged QT interval.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Antimuscarinics should be used with caution (due to increased risk of side effects) in Down's Syndrome, in children and in the elderly.

They should also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery) because of the increase in heart rate produced by their administration, coronary artery disease and cardiac arrhythmias, pyrexia (due to inhibition of sweating), pregnancy and breast feeding.

Because of prolongation of renal elimination, repeated or large doses of glycopyrronium bromide should be avoided in patients with uraemia.

Large doses of quaternary anticholinergic compounds have been shown to block end plate nicotinic receptors. This should be considered before using glycopyrronium 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 (23 mg) per dose, i.e essentially sodium-free.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Many drugs have antimuscarinic effects; concomitant use of two or more of such drugs can increase side-effects such as dry mouth, urine retention and constipation. Concomitant use can also lead to confusion in the elderly.

Anticholinergic agents may delay absorption of other medication given concomitantly.

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.

Ritodrine: tachycardia

Increased antimuscarinic side-effects: amantadine; tricyclic antidepressants; antihistamines; clozapine; disopyramide; MAOIs; nefopam; pethidine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations)

Possibly increased antimuscarinic side-effects: tricyclic (related) antidepressants

Domperidone/Metoclopramide: antagonism of effect on gastro-intestinal activity

Ketoconazole: reduced absorption of ketoconazole

Levodopa: absorption of levodopa possibly reduced

Memantine: effects possibly enhanced by memantine

Nitrates: possibly reduced effect of sublingual nitrates (failure to dissolve under the tongue owing to dry mouth)

Parasympathomimetics: antagonism of effect

4.6 PREGNANCY AND LACTATION

Data on the use of glycopyrronium bromide in pregnant women, other than on delivery, are not forthcoming, nor is there documentation concerning excretion in breast milk.

Although reproduction studies in rats and rabbits at up to 1000 times the human dose revealed no teratogenic effects from glycopyrronium bromide, safety in human pregnancy 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 the former may be due to diminished seminal secretion which is evident at high doses of glycopyrronium bromide. The significance of these findings for man is not clear. Although glycopyrronium bromide does not readily cross the placenta, the injection should only be prescribed to pregnant women when clearly necessary.

Caution is advised when considering administration to a nursing mother.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Glycopyrronium Bromide 200 micrograms/ml Injection is used in anaesthesia. It is not anticipated that patients will be driving or operating machinery under its influence. However, systemic administration of antimuscarinics may cause blurred vision, dizziness and other effects that may impair a patient's ability to perform skilled tasks such as driving. These activities should not be undertaken until any disturbance of visual accommodation or balance has resolved.

4.8 UNDESIRABLE EFFECTS

Side effects of antimuscarinics such as glycopyrronium bromide are basically extensions of the fundamental pharmacological action. These include constipation, transient bradycardia (followed by tachycardia, palpitations and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin.

Side effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting and giddiness.

4.9 OVERDOSE

Glycopyrronium bromide is a quaternary ammonium agent and symptoms of overdosage are peripheral rather than central in nature. Excessive peripheral anticholinergic effects may be countermanded by giving intravenously a quaternary ammonium anticholinesterase such as neostigmine methylsulphate in increments of 0.25mg in adults. The dose may be repeated every 5 – 10 minutes until anticholinergic over-activity is reversed or up to a maximum of 2.5mg. Proportionately smaller doses should be used in children.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Glycopyrronium bromide (ATC Code: A03AB02) is a quaternary ammonium antimuscarinic with peripheral effects similar to those of atropine. It is used similarly to atropine in anaesthetic practice. Given as a premedicant before general anaesthesia, it diminishes the risk of vagal inhibition of the heart and reduces salivary and bronchial secretions. Intra-operatively, it may be given to reduce bradycardia and hypotension induced by drugs such as suxamethonium, halothane or propofol. Glycopyrronium bromide may be used before, or with, anticholinesterases such as neostigmine to prevent their muscarinic adverse effects.

Antimuscarinic drugs are competitive inhibitors of the actions of acetylcholine at the muscarinic receptors of autonomic effector sites innervated by parasympathetic (cholinergic postganglionic) nerves, as well as being inhibitors of the action of acetylcholine on smooth muscle lacking cholinergic innervation.

Peripheral antimuscarinic effects that are produced as the dose increases are: decreased production of secretions from the salivary, bronchial and sweat glands; dilatation of the pupils (mydriasis) and paralysis of accommodation (cyclopegia); increased heart rate; inhibition of micturition and reduction in gastrointestinal tone; inhibition of gastric acid secretion.

Quaternary ammonium compounds are sparingly lipid soluble and do not readily pass lipid membranes such as the blood-brain barrier. Central effects are negligible.

5.2 PHARMACOKINETIC PROPERTIES

Following intravenous administration, onset of action occurs within one minute, with peak activity at around 5 minutes.

Following intramuscular injection, maximum plasma concentration and onset of action of glycopyrronium bromide is achieved within 30 minutes. Peak effects occur after approximately 30 - 45 minutes; vagal blocking effects last for 2 – 3 hours and antisialagogue effects persist for 7 - 8 hours. There is a faster absorption rate when glycopyrronium bromide is injected into the deltoid muscle rather than into the gluteal or vastus lateralis muscles. Although the elimination half life of glycopyrronium bromide from plasma is within 75 minutes, quantifiable levels may remain up to 8 hours after administration.

Cerebrospinal fluid levels of glycopyrronium bromide remain below detection level up to one hour after therapeutic dosing.

Following either intravenous or intramuscular administration, 50% of glycopyrronium bromide is excreted in the urine in 3 hours in non-uraemic individuals; renal elimination is considerably prolonged in patients with uraemia. Appreciable amounts are excreted in bile. In 48 hours, 85% has been excreted into the urine. About 80% of the excreted amount is as unchanged glycopyrronium bromide or active metabolites.

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

Hydrochloric acid, concentrated

Sodium chloride

Water for injections

6.2 INCOMPATIBILITIES

Glycopyrronium Bromide 200 micrograms/ml Injection has been shown to be physically compatible with the following agents commonly used in anaesthetic practice: Butorphanol,

Lorazepam, Droperidol, and Fentanyl Citrate, Levorphanol Tartrate, Pethidine Hydrochloride, Morphine Sulphate, Neostigmine, Promethazine and Pyridostigmine.

Glycopyrronium Bromide 200 micrograms/ml Injection has been shown to be physically incompatible with the following agents commonly used in anaesthetic practice: Diazepam, Dimenhydrinate, Methohexitone Sodium, Pentazocine, Pentobarbital Sodium and Thiopental Sodium.'

6.3 SHELF LIFE

1 ml ampoule- 24 months

3 ml ampoule- 18 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light

6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 glass ampoules, 1 ml and 3 ml.

Pack sizes:10 x 1 ml ampoules, 10 x 3 ml ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

For single use only.

Any unused solution should be discarded immediately after initial use.

The injection should not be used if particles are present.

7 MARKETING AUTHORISATION HOLDER

Taro Pharmaceuticals Ireland Limited,
Lourdes Road,
Roscrea,
Co. Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)

PL 20910/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2008

10 DATE OF REVISION OF THE TEXT

01/04/2008

PATIENT INFORMATION LEAFLET

Patient Information Leaflet

Glycopyrronium Bromide

200 micrograms/ml 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 further questions, please ask your doctor or pharmacist. This medicine has been prescribed for you personally and you should not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:

This leaflet contains information on:

1. What is Glycopyrronium Bromide 200 micrograms/ml Injection and what it is used for
2. Before you use Glycopyrronium Bromide 200 micrograms/ml Injection
3. How to use Glycopyrronium Bromide 200 micrograms/ml Injection
4. Possible side effects
5. Storing Glycopyrronium Bromide 200 micrograms/ml Injection
6. Further information

The active substance is glycopyrronium bromide. The other ingredients present are sodium chloride, hydrochloric acid and water for injections.

Marketing Authorisation Holder: Taro Pharmaceuticals Ireland Limited, Lourdes Road, Roscrea, Co. Tipperary, Ireland.

Manufacturer: Taro Pharmaceuticals Ireland Limited, Lourdes Road, Roscrea, Co. Tipperary, Ireland.

1. WHAT IS GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION AND WHAT IT IS USED FOR

The name of your medicine is Glycopyrronium Bromide 200 micrograms/ml Injection and its active ingredient is glycopyrronium bromide. It is a clear, colourless, sterile solution for injection. It is available in 1 ml and 3 ml glass ampoules. Each millilitre (ml) of sterile solution contains 200 micrograms of the active ingredient glycopyrronium bromide. The solution also contains the inactive ingredients sodium chloride, hydrochloric acid and water for injections. This product can come in the following pack sizes:
Glass Ampoules: 10 x 1 ml, 10 x 3 ml.

Glycopyrronium bromide is one of a group of medicines known as antimuscarinic agents. Antimuscarinic agents are used before and during inhalation anaesthesia to dry the bronchial and salivary secretions.

2. BEFORE YOU USE GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

Before you are given Glycopyrronium Bromide 200 micrograms/ml Injection, please read the following statements:

Do not take Glycopyrronium Bromide 200 micrograms/ml Injection:

If you have glaucoma; myasthenia gravis (a disorder that causes extreme muscle fatigue), an enlarged prostate, stomach or bowel problems.

Always tell the doctor or nurse about any of these before having your injection.

Take special care with Glycopyrronium Bromide 200 micrograms/ml Injection:

- in Down's Syndrome, the elderly and in children.
- if you have just had a heart attack.
- if you have a condition characterised by rapid heart beat (including over-active thyroid, heart failure or heart surgery).
- if you are pregnant or breast feeding.
- if you are receiving inhalation anaesthesia (to put you asleep before an operation) as it may cause a change in your normal heart rhythm.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially sodium free.

Let the doctor know if you suffer from:

- gastric reflux, diarrhoea, ulcerative colitis, high blood pressure.
- a high temperature (as the drug will inhibit sweating).

Avoid repeated or large doses in kidney disease.

Discuss with medical staff if appropriate.

If you are pregnant or if you are breast feeding:

Always tell your doctor if you are pregnant, think you might be pregnant or are trying to become pregnant.

Although glycopyrronium bromide will not readily pass into your baby's bloodstream, you will only be given the injection if clearly necessary.

Caution is advised if you are breast feeding.

Driving and using machines:

As glycopyrronium bromide is used in anaesthesia, it is unlikely that you will be driving or using tools or machines under its influence. However, use of this medicine can cause blurred vision, dizziness and other effects that may impair your ability to perform skilled tasks. Do not drive or use machinery until these effects have gone.

Taking other medicines:

Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those not prescribed.

Taking some medicines together can be harmful. Remember the doctor at the hospital may not have been informed if you have recently begun a course of treatment for another illness.

Simultaneous use of glycopyrronium bromide and one or more of many drugs possessing some of its properties can increase side-effects such as dry mouth, retention of urine and constipation. The elderly may become confused.

Please tell the doctor if you are taking, or have recently taken:

- amantadine, antidepressants (particularly tricyclics), antihistamines, clozapine, disopyramide.
- monoamine oxidase inhibitors (MAOIs), nefopam, pethidine, phenothiazines.
- domperidone or metoclopramide.
- ketoconazole.
- levodopa.
- memantine.
- parasympathomimetics.
- ritodrine.
- corticosteroids e.g. prednisolone.

- slow-dissolving digoxin tablets.

Sublingual nitrates may not dissolve under the tongue as well as usual owing to the dry mouth which glycopyrronium bromide causes.

3. HOW TO USE GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

Glycopyrronium bromide will be given to you as an injection either into a vein or into a muscle.

The usual dose is:

Before an Operation:

Adults and elderly patients:

By intravenous or intramuscular injection: A single dose of 200-400 micrograms or 4-5 micrograms per kilogram of your bodyweight to a maximum of 400 micrograms.

Children:

4-8 micrograms/kg to a maximum of 200 micrograms, preferably intravenously or alternatively by intramuscular injection.

During an operation:

Adults and elderly patients:

By intravenous injection: A single dose of 200-400 micrograms or 4-5 micrograms/kg to a maximum of 400 micrograms, repeated if necessary.

Children:

By intravenous injection: A single dose of 4-8 micrograms/kg up to a maximum of 200 micrograms, repeated if necessary.

At the end of an operation (for control of side effects of neostigmine in reversing neuromuscular block):

Adults and elderly patients:

By intravenous injection: 200 micrograms per 1000 micrograms (1mg) of neostigmine or the equivalent dose of pyridostigmine. Alternatively, 10-15 micrograms/kg with 50 micrograms/kg neostigmine or equivalent dose of pyridostigmine.

Children:

By intravenous injection: 10 micrograms/kg with 50 micrograms/kg of neostigmine or equivalent dose of pyridostigmine. Glycopyrronium bromide and neostigmine or pyridostigmine may be administered together from the same syringe.

If the dose of Glycopyrronium Bromide 200 micrograms/ml Injection has been too much for you:

Severe side effects can be reversed by repeated (5-10 minutes) injections of neostigmine metilsulfate 0.25 mg to a maximum of 2.5 mg. Proportionately smaller doses are used in children.

If you forget to take Glycopyrronium Bromide 200 micrograms/ml Injection:

A doctor, rather than you, will be responsible for administering your injection.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Glycopyrronium Bromide 200 micrograms/ml Injection can have side effects. These include constipation, heart rate variations, reduced bronchial secretions, urge to pass water but inability to do so, enlarged pupils with loss of focus, intolerance of light, dry mouth, flushing and dryness of the skin.

Side effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting and giddiness.

If you notice any side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

5. STORING GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

Keep out of the reach and sight of children.

Do not store above 25°C.

Keep the ampoule in the outer carton in order to protect from light.

Do not use after the expiry date, which is printed on the label and carton.

Do not use if the ampoule is damaged or if the contents are discoloured.

For single use only.

Use immediately after opening.

Discard any unused solution.

The injection should not be used if particles are present.

6. FURTHER INFORMATION

For any further information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

Taro Pharmaceuticals Ireland Ltd.,
Lourdes Road,
Roscrea,
County Tipperary,
Ireland
Tel: + 353 (0) 505 24300
info@taro.ie

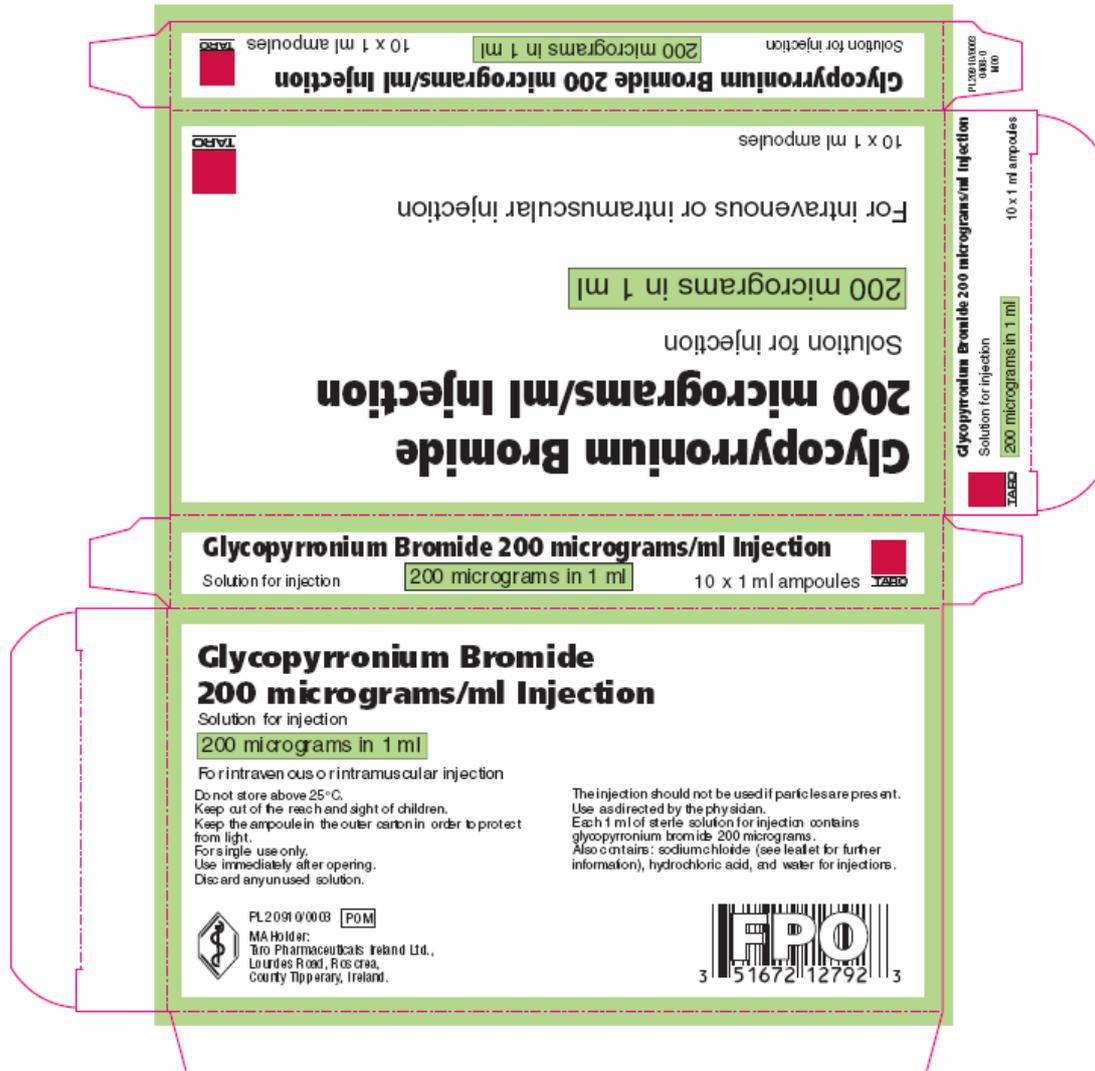
This leaflet was last approved on MM/YYYY

PL number: PL 20910/0003 (Glass ampoules)

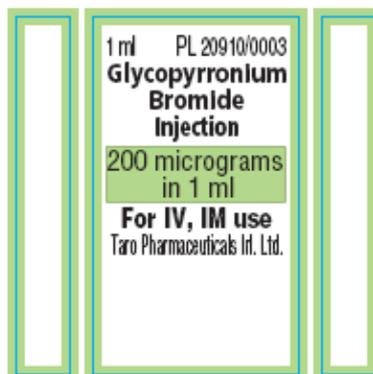
LABELLING

200mcg in 1ml presentation

Carton



Ampoule label



600mcg in 3ml presentation

Carton



Ampoule label

