GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

(PL 20910/0006)

UKPAR

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GLYCOPHYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

PL 20910/0006

LAY SUMMARY

On 22\textsuperscript{nd} December 2009, the MHRA granted Taro Pharmaceuticals (Ireland) Limited a Marketing Authorisation (licence) for the medicinal product Glycopyrronium Bromide 200 micrograms/ml Injection (PL 20910/0006). This is a prescription only medicine (POM).

Glycopyrronium Bromide belongs to a group of medicines called anti-muscarinic drugs. Glycopyrronium Bromide 200 micrograms/ml Injection may be given:

- to protect against some of the unwanted effects of drugs such as neostigmine or pyridostigmine, which are given to reverse the effect 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.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Glycopyrronium Bromide 200 micrograms/ml Injection outweigh the risks, hence a Marketing Authorisation has been granted.
GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

PL 20910/0006

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 200 micrograms/ml Injection (PL 20910/0006) to Taro Pharms Ireland on 22nd December 2009. The product is Prescription only medicine used to protect against some of the unwanted effects of drugs such as neostigmine or pyridostigmine, reduce salivary secretions and prevent slowness of the heartbeat during surgery.

This is a standard national abridged Marketing Authorisation Application for Glycopyrronium Injection containing glycopyrronium (200mcg) as the active ingredients in a solution for injection via IV or IM administration. The reference medicinal product is Robinul Injection 200 μl/ml (PL 15372/0004) licensed 1/7/1997 (COA from PL 00100/0054, licensed 17/3/81).

Glycopyrronium bromide 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.
**PHARMACEUTICAL ASSESSMENT**

**ACTIVE SUBSTANCE – GLYCOPYRRONIUM BROMIDE**

Chemical Name: Pyrrolidinium, 3-[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl-, bromide

3-Hydroxy-1,1-dimethylpyrrolidium bromide α-cyclopentylmandelate

Molecular Formula: $C_{19}H_{28}BrNO_3$

Chemical Structure:

![Chemical Structure Image]

and enantiomer

Molecular Weight: 398.3402 g/mol

Properties: Glycopyrronium is a white crystalline solid with a melting point 193-198 °C and is soluble in water and methanol.

Glycopyrronium bromide is the subject of DMF. A letter of access to the DMF is provided.

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.

An appropriate specification based on the -USP has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active glycopyrronium bromide is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.
Appropriate stability data has been provided.

**DRUG PRODUCT**

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

All excipients are controlled to their respective European Pharmacopoeia specifications. Satisfactory certificates of analysis have been provided for all excipients.

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

**Pharmaceutical development**
The objective of the product development programme was to produce solution for injection that could be considered a generic medicinal product of Robinul Injection 200micrograms/ml (PL 15372/0004).

The pharmaceutical development data submitted are satisfactory.

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

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

**Finished product specification**
The finished product specification 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 polypropylene ampoules that are hermetically sealed and are tamperproof.

Specifications and Certificates of Analysis for all packaging have been provided. These are satisfactory. The primary packaging has been shown to comply with guidelines concerning materials in contact with parenteral products.

**Stability**
Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 18 months has been set with storage conditions “Do not store above 25°C”, “Keep container in the outer carton” and “Protect from light”.

ADMINISTRATIVE
Expert Report
A pharmaceutical expert report has been written by a suitably qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

Summary of Product Characteristics (SPC)
This is consistent with the SPC for the reference product and is satisfactory.

Labelling
These are satisfactory.

Patient Information Leaflet (PIL)
This is consistent with the PIL for the reference product and is satisfactory.

MAA Form
This is satisfactory.

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

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

1. INTRODUCTION
This is a National Abridged Application by Taro Pharmaceuticals Ireland Limited for a solution for injection containing 200 micrograms/ml of Glycopyrronium Bromide. The application is submitted in accordance with Article 10.1 in Directive 2001/83/EC claiming essential similarity with the UK originator product Robinul Injection, 200 micrograms/ml, by Anpharm Limited, Ireland (PL 15372/0004), which has had a license in the UK since 09/03/81.

2. 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.

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 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.

3. INDICATIONS
• To protect against the peripheral muscarinic actions of anticholinesterases such as Neostigmine and Pyridostigmine, used to reverse residual neuromuscular blockade 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. DOSE AND DOSAGE SCHEDULE

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

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.

Intraoperative use:

Adults and Elderly patients:
By intravenous injection: 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.

5. **TOXICOLOGY**  
No new data is presented and none is required for this application.

6. **CLINICAL PHARMACOLOGY**  
The application is based on essential similarity to Robinul Injection. Both the proposed product and essentially similar product are indicated for parenteral use and as such will be readily available via the IV and IM 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.

7. **EFFICACY**  
No new data is presented and none is required for this application.

8. **SAFETY**  
No new data is presented and none is required for this application.

9. **EXPERT REPORT**  
The Clinical Expert Report has been written by an appropriately qualified person and is a suitable summary of the clinical aspects of the dossier.

10. **SUMMARY OF PRODUCT CHARACTERISTICS**  
This is consistent with the SPC for the reference product and satisfactory.

11. **PATIENT INFORMATION LEAFLET**  
The Patient Information Leaflet is satisfactory.

12. **LABELLING**  
The labelling is satisfactory.

13. **MAA**  
The Marketing Authorisation Application form is satisfactory.

14. **CONCLUSION**  
The grant of a marketing authorisation is recommended.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
The important quality characteristics of Glycopyrronium Bromide 200 micrograms/ml injection (PL 20910/0006) 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 applications of this type.

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

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

BENEFIT-RISK ASSESSMENT
The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with Glycopyrronium Bromide is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is considered to be positive.
GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

PL 20910/0006

**STEPS TAKEN FOR ASSESSMENT**

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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 12th August 2005</td>
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GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

PL 20910/0006

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

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SUMMARY OF PRODUCT CHARACTERISTICS

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 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
• To protect against the peripheral muscarinic actions of anticholinesterases such as Neostigmine and Pyridostigmine, used to reverse residual neuromuscular blockade 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
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. Larger doses may result in a profound and prolonged antisialagogue effect which may be unpleasant for the patient.

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.

Intraoperative use:

Adults and Elderly patients:
By intravenous injection: 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 glycopyrrolate 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.

*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

*Ritodrine:* tachycardia

### 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 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 is injected into the deltoid muscle rather than into the gluteal or vastus lateralis muscles. Although the elimination half life of glycopyrronium from plasma is within 75 minutes, quantifiable levels may remain up to 8 hours after administration.

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

Following either intravenous or intramuscular administration, 50% of glycopyrronium 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 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
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
Translucent 1 ml polypropylene ampoules.
Pack sizes: 10 x 1 ml ampoules.
20 x 1 ml ampoules.

6.6 Special precautions for disposal
Keep out of reach and sight of children.
For single use only.

Use immediately after opening.
Discard any unused solution immediately after initial use in accordance with local requirements.
The injection should not be used if any particles are present.
Do not use if the ampoule is damaged or if the contents are discoloured.

7 MARKETING AUTHORISATION HOLDER
Taro Pharmaceuticals Ireland Ltd,
Lourdes Road,
Roscrea,
Co. Tipperary,
Ireland.

8 MARKETING AUTHORISATION NUMBER(S)
PL 20910/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
22/12/2009

10 DATE OF REVISION OF THE TEXT
22/12/2009
PATIENT INFORMATION LEAFLET (PIL)

PACKAGE LEAFLET: INFORMATION FOR THE USER
GLYCOPYRRONIUM BROMIDE 200 MICROGRAMS/ML INJECTION

Read all of this leaflet carefully before you start using 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. 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 Glycopyrronium Bromide 200 micrograms/ml Injection is 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. How to store Glycopyrronium Bromide 200 micrograms/ml Injection
6. Further information

1. WHAT GLYCOPYRRONIUM BROMIDE 200 micrograms/ml INJECTION IS AND WHAT IT IS USED FOR

Glycopyrronium bromide belongs to a group of medicines called anti-muscarinic drugs. Glycopyrronium Bromide 200 micrograms/ml Injection may be given:

- To protect against some of the unwanted effects of drugs such as neostigmine or pyridostigmine, which are given 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 slowing of the heartbeat during surgery.

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 use Glycopyrronium Bromide 200 micrograms/ml Injection:
- if you are allergic (hypersensitive) to glycopyrronium bromide or any of the other ingredients of this medicine.
- if you have glaucoma
- if you suffer from myasthenia gravis (a disorder that causes extreme muscle weakness and fatigue)
- if you have an enlarged prostate
- if you have stomach or bowel problems.

Take special care with Glycopyrronium Bromide 200 micrograms/ml Injection:
- if you have Down’s Syndrome
- if you are over 60 years of age
- if you are a child
- 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 have a history of high blood pressure, coronary artery disease or irregular heart beats
- if you are receiving inhalation anaesthesia (to put you asleep before an operation) as it may cause a change in your normal heart rhythm
- if you have gastric reflux (a condition in which the liquid stomach contents backs up (regurgitates) into the gutlet
- if you have diarrhoea
- if you have ulcerative colitis (a chronic inflammation of the large intestine (colon) which can cause abdominal pain, diarrhoea and bleeding from the back passage)
- if you have a high temperature (as the drug will inhibit sweating).

Avoid repeated or large doses if you have kidney disease.
Always **tell your doctor or nurse** about any of these conditions before having your injection.

**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. 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.

Use of glycopyrronium bromide along with one or more similar medicines 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:

- tricyclic antidepressants (for example amitriptyline or imipramine) or monoamine oxidase inhibitor (MAOIs) antidepressants (for example phenelzine, tranylcypramine)
- clozapine (used to treat schizophrenia)
- phenothiazines used to treat severe mental problems or nausea, vomiting or vertigo (for example chlorpromazine, fluphenazine, prochlorperazine, trifluoperazine)
- antihistamines used to treat allergies (for example promethazine)
- nefopam (used to treat acute and chronic pain)
- pethidine (used to treat moderate to severe pain)
- domperidone or metoclopramide (used to treat nausea and vomiting)
- ketoconazole (used to treat fungal infections)
- amantadine, levodopa (used to treat Parkinson’s disease)
- memantine (used to treat Alzheimer’s disease)
- parasympathomimetics (these are drugs that affect chemicals in the body which are involved in transmission of nerve impulses to a muscle) (for example carbachol, neostigmine, physostigmine)
- ritodrine (used to prevent uncomplicated premature labour)
- corticosteroids used to treat various conditions including asthma and inflammatory disease (for example prednisolone)
- slow-dissolving digoxin tablets, disopyramide (used to treat heart problems).

Glycerol trinitrate tablets (used to treat angina) may not dissolve under the tongue as usual owing to the dry mouth which glycopyrronium bromide causes.

**Pregnancy and breast-feeding:**

Always **tell your doctor** if you are pregnant, think you might be pregnant or are trying to become pregnant. Glycopyrronium Bromide 200 micrograms/ml Injection should be used during pregnancy only if considered essential by the doctor.

You **should not breast-feed** if you are taking this medicine.

**Driving and using machines:**

**Do not drive or use machines** because this medicine can cause blurred vision, dizziness and other effects that may affect your ability to do so. Do not drive or use machinery until these effects have gone.

**Important information on some of the ingredients of Glycopyrronium Bromide 200 micrograms/ml Injection**

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

3. **HOW TO USE GLYCOPHYRRONIUM BROMIDE 200 micrograms/ml INJECTION**

Glycopyrronium bromide will be given to you as an injection either into a vein (intravenous) or into a muscle (intramuscular) by a doctor or nurse.
The following doses may be given:

**When given before an operation:**
**Adults and elderly patients:**
A single dose of 200-400 micrograms or 4-5 micrograms per kilogram of bodyweight to a maximum of 400 micrograms given by injection into a vein or muscle.

**Children:**
4-8 micrograms per kilogram of body weight to a maximum of 200 micrograms, preferably given by injection into a vein or alternatively into a muscle.

**When given during an operation:**
**Adults and elderly patients:**
A single dose of 200-400 micrograms or 4-5 micrograms per kilogram of body weight to a maximum of 400 micrograms given by injection into a vein. This dose may be repeated if necessary.

**Children:**
A single dose of 4-8 micrograms per kilogram of body weight up to a maximum of 200 micrograms. This dose may be repeated if necessary.

**At the end of an operation (for control of side effects of neostigmine in reversing neuromuscular block):**
**Adults and elderly patients:**
200 micrograms per 1000 micrograms (1 mg) of neostigmine or the equivalent dose of pyridostigmine given by injection into a vein.
Alternatively, 10-15 micrograms per kilogram of body weight with 50 micrograms per kilogram of body weight of neostigmine or equivalent dose of pyridostigmine.

**Children:**
10 micrograms per kilogram of body weight with 50 micrograms per kilogram of body weight of neostigmine or the equivalent dose of pyridostigmine given by injection into a vein.

Glycopyrronium bromide and neostigmine or pyridostigmine may be administered together from the same syringe.

**If you use more Glycopyrronium Bromide 200 micrograms/ml Injection than you should:**
Tell your doctor or nurse if you think you have been given too much Glycopyrronium Bromide 200 micrograms/ml Injection. The effects of overdose can be treated 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 use 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, although not everyone gets them. The following side effects can occur:
- changes in heart rate (fast/irregular heart beats)
- confusion may occur in the elderly
- urge to pass water but inability to do so
- nausea
- vomiting
- giddiness
- flushing and dryness of the skin
- enlarged pupils with loss of focus
- intolerance to light
- constipation
- dry mouth
- reduced bronchial secretions

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 200 micrograms/ml INJECTION**

   Keep out of the reach and sight of children.
   Do not use Glycopyrronium Bromide 200 micrograms/ml Injection after the expiry date (EXP) which is stated on the label and carton. The expiry date refers to the last day of that month.
   Do not store above 25°C.
   Keep the ampoule in the outer carton in order to protect from light.
   For single use only.
   Use immediately after opening.
   Discard any unused solution immediately after initial use in accordance with local requirements. Medicines should not be disposed of via waste water or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.
   The injection should not be used if particles are present.
   Do not use Glycopyrronium Bromide 200 micrograms/ml Injection if the ampoule is damaged or if the contents are discoloured.

6. **FURTHER INFORMATION**

   **What Glycopyrronium Bromide 200 micrograms/ml Injection contains**

   The active substance is glycopyrronium bromide.
   Each millilitre (ml) of sterile solution contains 200 micrograms of the active substance glycopyrronium bromide.
   The other ingredients are sodium chloride, hydrochloric acid and water for injections.

   **What Glycopyrronium Bromide 200 micrograms/ml Injection looks like and contents of the pack**

   Glycopyrronium Bromide 200 micrograms/ml Injection is a clear, colourless, sterile solution for injection. Each 1 ml of sterile solution for injection contains 200 micrograms of glycopyrronium bromide (200 micrograms/ml).

   Pack sizes: 1 ml polypropylene (plastic) ampoules in packs of 10 or 20.
   Not all pack sizes may be marketed.

**Marketing Authorisation Holder and Manufacturer**

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Lourdes Road,
Roscrea,
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For any further information about this medicinal product, please contact the
Marketing Authorisation Holder, Taro Pharmaceuticals Ireland Limited.

This leaflet was last approved on MM/YYYY

**APPROVED
By MHRA at 2:42 pm, Dec 22, 2009**
UKPAR Glycopyrronium Bromide 200micrograms/ml Injection
PL 20910/0006

LABELLING

Glycopyrronium Bromide
200 micrograms/ml Injection
Solution for injection

For intravenous or intramuscular injection

Do not store above 25°C.
Keep out of the reach and sight of children.
Keep the stoppers in their original position.
For single use only.
Do not re-use.
Immediately after opening, discard any unused solution.

The injection should not be used if particles are present.

1. Remove the stopper by twisting it to the left.

2. Hold the ampoule by the neck, twist the ampoule to open.

3. Insert the needle, take up solution and inject.

10 x 1 ml polypropylene ampoules

H/B/H4.5 x 22 x 91mm
PRINT SIDE
DATE.11-04-2005

The applicant has confirmed that the batch number and expiry date will be overprinted in the area marked "OVER PRINT"