Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium bromide 200 micrograms/ml Solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each 3ml of injection contains 600 micrograms (0.6mg) of Glycopyrronium Bromide.
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for Injection
Clear and colourless solution
pH 2.0-3.0

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

To protect against the peripheral muscarinic actions of anticholinesterases such as neostigmine, 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.

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

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

Premedication
Adults, adolescents over 12 years old and elderly 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.

When Glycopyrronium Bromide 200 micrograms /ml Solution for Injection is administered intramuscularly it should be used 30-60 minutes before the induction of anaesthesia.
Paediatric population (1 month to 12 years of age):
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, adolescents over 12 years old and elderly 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.

Paediatric population (1 month to 12 years of age):
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, adolescents over 12 years old and elderly patients:
200 micrograms (0.2mg) intravenously per 1000 micrograms (1mg) of neostigmine 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.

Paediatric population (1 month to 12 years of age):
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.

Renal impairment

Dose reduction should be considered in patients with renal impairment (see sections 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to Glycopyrronium Bromide or to any of the excipients listed in section 6.1.

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, thyrotoxicosis, hypertension, congestive heart failure, 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. As glycopyrronium inhibits sweating, patients with increased temperature (especially children) should be observed closely.

Because of prolongation of renal elimination, repeated or large doses of glycopyrronium should be avoided in patients with uraemia. Anticholinergic drugs can cause ventricular arrhythmias when administered during inhalation anaesthesia especially in association with the halogenated hydrocarbons.

Unlike atropine, glycopyrronium bromide is a quaternary ammonium compound and does not cross the blood-brain barrier. It is therefore less likely to cause postoperative confusion which is a particular concern in the elderly patients. Compared to atropine, glycopyrronium has reduced cardiovascular and ocular effects.

This medicinal product contains less than 1 mmol sodium (23mg) per dose, i.e. essentially 'sodium free'.
The duration of effect of Glycopyrronium Bromide 200 micrograms /ml Solution for Injection may be prolonged in patients with renal impairment since glycopyrrolate is excreted mostly in urine as unchanged drug. Dosage adjustment may be needed for patients with renal impairment.
The injection can increase the tachycardia effect of sympathomimetic medicinal products.

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 anticholingergics 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; disopyramaide; MAOIs; nefopam; pethidine; phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations)
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 Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of Glycopyrronium Bromide 200 micrograms /ml Solution for Injection in pregnant women. Animal studies for glycopyrronium bromide are insufficient with respect to reproductive toxicity (see section 5.3). Use of Glycopyrronium Bromide 200 micrograms /ml Solution for Injection is not recommended during pregnancy.

Breast-feeding
It is unknown whether glycopyrronium is excreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Glycopyrronium Bromide 200 micrograms /ml Solution for Injection therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

Fertility
Human data concerning effects of glycopyrronium bromide on fertility are not available.

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 actions.

Adverse reactions listed by System Organ Class. Frequencies are defined using the following convention: very common: (>1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000); Not known: cannot be estimated from the available data
Tabulated list of adverse reactions:

System organ class	Adverse reaction	Frequency
Immune system disorders	Hypersensitivity Angioedema	Not known
Gastrointestinal disorders	Dry mouth	Very common
	Constipation Nausea Vomiting	Not known
Renal and urinary disorder	Urinary retention	Common - Very common
	Urinary urgency Micturition disorder	Not known
Nervous system disorders	Drowsiness	Common - Very common
	Confusion** Dizziness	Not known
Eye disorders	Visual disturbances	Common - Very common
	Angle closure glaucoma	Very rare

	Accommodation disorder Photophobia	Not known
Cardiac disorders	Tachycardia, palpitation and arrhythmias	Common - Very common
	Transient bradycardia	Not known
Respiratory, thoracic and mediastinal disorders	Bronchial secretion retention	Not known
Skin and subcutaneous tissue disorders	Flushing Dry skin Anhidrosis	Not known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL – Dublin 2; Tel: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

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

Treatment
To combat the peripheral anticholinergic effects of glycopyrronium 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 Glycopyrronium Bromide known to have been administered by the parenteral route.

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 (cycloplegia); 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

Absorption
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.

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

Elimination

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. Although the elimination half-life of Glycopyrronium Bromide from plasma is within 75 minutes, quantifiable levels may remain up to 8 hours after administration.

5.3 Preclinical safety data

Animal studies on acute toxicity and repeat dose toxicity do not show relevant effects of glycopyrronium bromide in addition to those already described in other sections of the SmPC.

Reproductive toxicity of glycopyrronium bromide has been only insufficiently characterized in animal studies. Data available from rat and mouse studies did not reveal teratogenic effects. Diminished rates of conception and of survival at weaning were observed in rats in a dose-related manner. Studies in dogs suggest that the decreased conception rate may be due to a diminished seminal secretion which is evident at high doses of glycopyrronium bromide. The clinical relevance of these findings is unclear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride
Hydrochloric Acid (for pH-adjustment)
Water for Injections

6.2 Incompatibilities

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.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear Type I glass ampoules: 10 x 1ml ampoules or 10 x 3ml ampoules packed in a cardboard carton.
Not all pack sizes may be marketed

6.6 Special precautions for disposal

For single use only. Discard any remaining contents after use.

Glycopyrronium Bromide 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.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ethypharm
194 Bureaux de la Colline - Bâtiment D
92213 Saint-Cloud Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0549/029/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

June 2023