SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Glycopyrronium Bromide 0.2 mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of injection contains 200 micrograms (0.2mg) of glycopyrronium bromide (glycopyrrolate).

Excipient with known effect:

Sodium Chloride: contains 9 mg per ml

For the 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 associated with the use of suxamethonium or due to cardiac vagal reflexes.

4.2 Posology and method of administration

Posology

Premedication:

Adults and Elderly: 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 antisialagogue effect which may be unpleasant for the patient.

Paediatric population: 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 antisialagogue effect which may be unpleasant for the patient.

Intra-operative use:

Adults and Elderly: 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: A single dose of 200 micrograms (0.2mg) by intravenous injection should be used. Alternatively, a single dose of 4 to 8 micrograms/kg (0.004 to 0.008mg/kg) up to a maximum of 200 micrograms (0.2mg) may be used. This dose may be repeated if necessary.

Reversal of residual non-depolarising neuromuscular block:

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

Paediatric population: 10 micrograms/kg (0.01mg/kg) intravenously with 50 micrograms/kg (0.05mg/kg) neostigmine or the equivalent dose of pyridostigmine. Glycopyrrolate Injection may be administered simultaneously from the same syringe

with the anticholinesterase; greater cardiovascular stability results from this method of administration.

Method of administration:

Glycopyrrolate Injection is for intravenous or intramuscular injection.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

In common with other antimuscarinic drugs caution is advised in patients with prostatic hypertrophy, paralytic ileus, pyloric stenosis and closed angle glaucoma. Quaternary ammonium compounds in large dose have been shown to block the nicotinic muscle end plate receptors. This must be evaluated prior to its administration in patients with myasthenia gravis.

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.

Extreme caution is advised in patients with gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, acute myocardial infarction, thyrotoxicosis, coronary artery disease, cardiac dysarythmias, 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 glycopyrrolate inhibits sweating, patients with increased temperature (especially children) should be observed closely.

Because of prolongation of renal elimination, repeated or large doses of Glycopyrronium Bromide 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, glycopyrrolate 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, glycopyrrolate has reduced cardiovascular and ocular effects.

This medicine contains less than 1 mmol sodium (23 mg) per ml, that is to say 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 anticholingergics and corticosteroids may result in increased intraocular pressure.

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

Ritodrine: tachycardia

There is increased risk of antimuscarinic side effects in patients taking drugs with antimuscarinic effects such as MAOIs, amantadine, clozapine, tricyclic antidepressants, disopyramaide, antihistamines, pethidine, phenothiazines (increased antimuscarinic side effects of phenothiazines but reduced plasma concentrations) and nefopam.

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

For use as indicated, animal studies are of very limited relevance (see section 5.3). Use in human pregnancy has not been systematically evaluated. This product should only be used in pregnancy if considered essential.

Breast-feeding

May reach breast milk but in amounts probably too small to be harmful. Caution is advised when considering administration to a nursing mother.

Fertility

There are no data on the effects of glycopyrronium bromide on male or female fertility. For non-clinical studies please refer to section 5.3

4.7 Effects on ability to drive and use machines

Glycopyrrolate has moderate influence on the ability to drive and use machines. 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. Do not operate or drive heavy machinery unless the drug has been shown not to interfere with mental or physical ability.

4.8 Undesirable effects

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
Eye disorders	Accommodation disorder	Not known
Cardiac disorders	Tachycardia, Palpitations	Not known
Gastrointestinal disorders	Dry mouth	Not known

Skin and subcutaneous tissue disorders	Anhidrosis	Not known
Renal and urinary disorders	Micturition disorder	Not known

Other side effects of anti-muscarinics include-

System Organ Class	Adverse reaction	Frequency
Nervous system disorders	Confusion* Dizziness	Not known
Eye disorders	Angle closure glaucoma Accommodation disorder Photophobia	Very rare Not known
Cardiac disorders	Bradycardia**	Not known
Respiratory, thoracic and mediastinal disorders	Bronchial secretion retention	Not known
Gastrointestinal disorders	Constipation Nausea Vomiting	Not known
Skin and subcutaneous tissue disorders	Flushing Dry skin	Not known
Renal and urinary disorders	Micturition urgency Urinary retention	Not known

*Particularly in elderly

** Followed by tachycardia, palpitation and arrhythmias

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

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 the Yellow Card Scheme

Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

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

Management

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quaternary ammonium antimuscarinic

ATC Code: A03AB02

Mechanism of action:

Glycopyrrolate 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.

Glycopyrrolate antagonizes 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 glycopyrrolate 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 Injection has been used successfully as an adjunct to reversal by neostigmine when atropine has been used as the preoperative anticholinergic. The use of Glycopyrronium Injection as an adjunct to reversal by neostigmine of non-

depolarising muscle relaxants is associated with less initial tachycardia and better protection against the cholinergic effects of neostigmine compared to reversal with a mixture of neostigmine and atropine.

5.2 Pharmacokinetic properties

Absorption

With intravenous injection, the onset of action is generally evident within one minute. 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.

Elimination

Glycopyrrolate 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.

5.3 Preclinical safety data

Safety Pharmacology

Acute toxicity of glycopyrrolate was studied in mice and rats. Following intraperitoneal administration, the LD50 was estimated to be 107 mg/kg in mice and 196 mg/kg in rats. Following oral dosing, the LD50 was estimated to be 1150 mg/kg in rats. Chronic oral administration doses of 4, 16, and 64 mg/kg for up to 27 weeks in dogs produced mydriasis, cycloplegia, xerostomia, emesis, occasional lacrimation, injection of sclera and rhinorrhea. There were no changes in organ weight and histopathology showed no drug- related changes. Safety in human pregnancy and lactation has not been established.

Teratogenicity

Although reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate.

Toxicity to reproduction and development

Diminished rates of conception and of survival at weaning were observed in rats, in a dose-related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate. The significance of this for man is not clear.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium Chloride

Hydrochloric Acid

Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

3 years

Chemical and physical in-use stability has been demonstrated for 48 hours at 25°C.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass ampoules with 1 ml injection solution packed in 10 x1 ml.

6.6 Special precautions for disposal

To be mixed with isotonic sodium chloride, 5% or 10% glucose solution. The pH must not exceed 6.0 in the diluted solution.

7 MARKETING AUTHORISATION HOLDER

Novumgen Limited
20-22 Wenlock Road,
London, N1 7GU,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 55863/0107

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12/07/2024

10 DATE OF REVISION OF THE TEXT

12/07/2024