Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:

Neo- pyrolate 0.5mg/2.5mg Injection

2. Qualitative and quantitative composition

Each 1ml contains:
Glycopyrrolate…….0.5mg
Neostigmine Metilsulfate ……..2.5mg

For the full list of excipients, see section 6.1

3. Pharmaceutical form

Clear, colorless sterile solution for injection.

4. Clinical particulars

4.1 Therapeutic indications

Reversal of residual non-depolarising (competitive) neuromuscular block.

4.2 Posology and method of administration

Posology

Adults and Elderly: 1-2 ml intravenously over a period of 10-30 seconds [equivalent to neostigmine metilsulfate 2500 micrograms (2.5mg) with glycopyrrolate 500 micrograms (0.5mg) to neostigmine metilsulfate 5000 micrograms (5mg) with glycopyrrolate 1000 micrograms (1mg)].

Alternatively, 0.02ml/kg intravenously over a period of 10-30 seconds may be used [equivalent to neostigmine metilsulfate 50 micrograms/kg (0.05mg/kg) with glycopyrrolate 10 micrograms/kg (0.01mg/kg)].

Paediatric population: 0.02ml/kg intravenously over a period of 10-30 seconds [equivalent to neostigmine metilsulfate 50 micrograms/kg (0.05mg/kg) with glycopyrrolate 10 micrograms/kg (0.01mg/kg)]. Alternatively, dilute to 10ml with Water for Injections BP or Sodium Chloride injection BP 0.9% w/v and administer 1ml per 5kg bodyweight.

These doses may be repeated if adequate reversal of neuromuscular blockade is not achieved. Total doses in excess of 2ml are not recommended as this dose of neostigmine may produce depolarising neuromuscular block.

Method of administration
Glycopyrrolate-Neostigmine injection is for intravenous administration

4.3 Contraindications

- Neo-Pyrolate Injection should not be given to patients with hypersensitivity to either of the two active ingredients.
- Neo-Pyrolate Injection should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.
- Neo-Pyrolate Injection should not be given in conjunction with suxamethonium as Neostigmine potentiates the depolarizing myoneural blocking effects of this agent.
- Anticholinesterase-antimuscarinic combinations such as neostigmine plus glycopyrrolate should be avoided in patients with a prolonged QT interval.

4.4 Special warnings and precautions for use

Administer with caution to patients with bronchospasm (extreme caution), or severe bradycardia.

Administration of anticholinesterase agents to patients with intestinal anastomosis may produce rupture of the anastomosis or leakage of intestinal contents.

Although Glycopyrrolate-Neostigmine Injection has been shown to have less impact on the cardiovascular system than atropine with neostigmine metilsulfate, use with caution in patients with coronary artery disease, congestive heart failure, cardiac dysrhythmias, hypertension, thyrotoxicosis and cardiac insufficiency.

Use with caution in patients with epilepsy or Parkinsonism.

As glycopyrrolate inhibits sweating, patients with increased temperature (especially children) should be observed closely.

In common with other antimuscarinic drugs caution is advised in patients with prostatic hypertrophy, paralytic ileus, pyloric stenosis and closed angle glaucoma.

Anticholinergic drugs can cause ventricular arrhythmias when administered during inhalation anaesthesia especially in association with the halogenated hydrocarbons.

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.

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.

Neostigmine metilsulfate: Glycopyrrolate or alternatively atropine, given before or with neostigmine, prevents bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

4.5 Interaction with other medicinal products and other forms of interaction

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis.

Non-depolarizing neuromuscular block induced by the muscle relaxants used in anesthesia; neuromuscular block induced by aminoglycoside antibiotics and antiarrhythmic agents.

Aminoglycosides -Effects of Neostigmine antagonised by aminoglycosides

Chloroquine and Hydroxychloroquine - effects of Neostigmine may be diminished because of potential for Chloroquine and Hydroxychloroquine to increase symptoms of myasthenia gravis

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

Clindamycin - Effects of Neostigmine antagonised by Clindamycin

Lithium - Effects of Neostigmine antagonised by lithium

Muscle Relaxants, non-depolarising - Neostigmine antagonises effects of non-depolarising muscle relaxants

Polymyxins - Effects of Neostigmine antagonised by polymyxins

Procainamide - Effects of Neostigmine antagonised by Procainamide

Propafenone -Effects of Neostigmine possibly antagonised by Propafenone

Propranolol -Effects of Neostigmine antagonised by Propranolol

Quinidine -Effects of Neostigmine antagonised by Quinidine

Suxamethonium -Neostigmine enhances effects of Suxamethonium

Antimuscarinics - Effects of parasympathomimetics antagonised by antimuscarinics

4.6 Pregnancy and Lactation

Pregnancy
For use as indicated, animal studies (see section 5.3) are of very limited relevance. Use in human pregnancy has not been systematically evaluated.

Breast-feeding
May reach breast milk but in amounts probably too small to be harmful.

4.7 Effects on ability to drive and use machines

This medicine may cause your eyesight to become weak and this could interfere with your ability to drive or operate machinery safely.

4.8 Undesirable effects

Adverse events are which have been associated with Glycopyrrolate-Neostigmine injection are given below, listed by system organ class and frequency.

Undesirable effects are especially likely to occur at treatment onset or at dose increase.

The undesirable effects are listed below by organ class and the following frequency convention:
Very common: (≥1/10)
Common: (≥1/100)
Uncommon: (≥1/1,000, <1/100)
Rare: (≥1/10,000, <1/1000)
Very rare: (<1/10,10,000)
Not known – cannot be estimated from the available data."

Tabulated list of adverse reactions for Glycopyrrolate component of Glycopyrrolate-Neostigmine Injection:

System Organ Class	Adverse reaction	Frequency
Nervous system disorders	Confusion** Dizziness	Not known
Eye disorders	dilatation of the pupils, photophobia, Angle closure glaucoma	Not known
Cardiac disorders	Transient bradycardia,	Not known

Respiratory, thoracic and mediastinal disorders	Bronchial secretion reduced	Not known
Gastrointestinal Disorders	Dry mouth, 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

Followed by tachycardia, palpitation and arrhythmias
**Particularly in elderly

Tabulated list of adverse reactions for Neostigmine component of Gylcopyrolate-Neostigmine Injection:

System Organ Class	Adverse reaction	Frequency
Cardiac disorders	Bradycardia, cardiac dysrhythmias	Not known
Respiratory, thoracic and mediastinal disorders	increased oropharyngeal secretions	Not known
Gastrointestinal Disorders	increased gastrointestinal activity	Not known

Glycopyrrolate-Neostigmine component of injection can give rise to hypersensitivity, angioedema and anaphylactic reaction. If severe neostigmine-induced muscarinic side effects occur (bradycardia, increased oropharyngeal secretions, decreased cardiac conduction rate, increased sweating, bronchospasm or increased gastrointestinal activity etc), these may be treated by the intravenous administration of Glycopyrrolate Injection 200-600 micrograms (0.2-0.6mg) or atropine 400-1200 micrograms (0.4-1.2mg).

4.9 Overdose

Symptoms

Signs of neostigmine overdosage include nausea, vomiting, diarrhoea, excessive salivation and sweating, increased oropharyngeal secretions,

miosis, bradycardia or tachycardia, cardiospasm, bronchospasm, incoordination, muscle cramps, fasciculation and paralysis.

Management

The treatment of overdosage depends upon whether signs of anticholinesterase or anticholinergic overdosage are predominant presenting features.

This may be treated by the administration of Glycopyrrolate Injection 200-600 micrograms (0.2 0.6mg) or atropine 400-1200 micrograms (0.4-1.2mg). In severe cases, respiratory depression may occur and artificial ventilation may be necessary in such patients. Signs of glycopyrrolate overdosage (tachycardia, ventricular irritability etc) may be treated by the administration of neostigmine metilsulfate 1000 micrograms (1.0mg) for each 1000 micrograms (1.0mg) of glycopyrrolate known to have been administered. As glycopyrrolate is a quaternary ammonium agent, symptoms of overdosage are peripheral rather than central in nature; centrally acting anticholinesterase drugs such as physostigmine are therefore unnecessary to treat glycopyrrolate overdosage.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Quaternary ammonium antimuscarinic ATC Code: NO7AA51

Mechanism of action:

Glycopyrrolate is a quaternary ammonium anticholinergic agent. Glycopyrrolate has a more gradual onset and longer duration of action than atropine. Neostigmine metilsulfate is a quaternary ammonium anticholinesterase. Glycopyrrolate-Neostigmine Injection is associated with less initial tachycardia and better protection against the subsequent cholinergic effects of neostigmine metilsulfate than a mixture of atropine and neostigmine metilsulfate. In addition, residual central anticholinergic effects are minimised due to the limited penetration of Glycopyrrolate into the central nervous system. Administration of glycopyrrolate with neostigmine metilsulfate is associated with greater cardiostability than administration of glycopyrrolate and neostigmine metilsulfate separately.

Glycopyrrolate-Neostigmine Injection can be used when atropine has been used as a pre-operative anticholinergic.

5.2 Pharmacokinetic properties

Absoprtion

Glycopyrrolate and Neostigmine Metilsulfate are routinely administered

simultaneously to reverse residual non-depolarising (competitive) neuromuscular block. Numerous clinical studies, which demonstrate this to be a safe and effective combination, have been published.

Over 90% of the glycopyrrolate disappears from serum within 5 minutes following intravenous administration. The drug is rapidly excreted into bile with highest concentrations being found 30 to 60 minutes after dosing with some product being detected up to 48 hours after administration.

Distribution

Glycopyrrolate is also rapidly excreted into urine with the highest concentrations being found within 3 hours of administration. Over 85% of product is excreted within 48 hours. It has subsequently been confirmed in a single dose pharmacokinetic study using radio immunological assay procedures that glycopyrrolate as rapidly distributed and/or excreted after intravenous administration. The terminal elimination phase was relatively slow with quantifiable plasma levels remaining up to 8 hours after administration. The elimination half-life was 1.7 hours.

Neostigmine Metilsulfate is extensively hydrolyzed in the blood. In one study, following intravenous administration, the plasma concentration declined to about 8% of its initial value after 5 minutes with a distribution half-life of less than one minute.

Elimination

Elimination half-life ranged from about 15-30 minutes. Trace amounts of Neostigmine Metilsulfate could be detected in the plasma after one hour. In a study in non-myasthenic patients, the plasma half-life was 0.89 hours.

5.3 Preclinical safety data

Although reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate, safety in human pregnancy and lactation has not been established. Diminished rates of conception and of survival at weaning were observed in rats, in a dose related manner. Studies in dogs suggest that this may be due to diminished seminal secretion which is evident at high doses of glycopyrrolate. The significance of this for man is not clear.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Di-Sodium Hydrogen Phosphate dodecahydrate
- Citric Acid Anhydrous
- Water for Injection.

6.2 Incompatibilities

Do not mix glycopyrrolate and Neostigmine Metilsulfate Injection with any other preparation.

6.3 Shelf-Life

2 years

6.4 Special Precautions for storage

Store below 30°C

6.5 Nature and Content of container

The product is aseptically filled in 1ml glass USP type I ampoule, further packed in 10x1ml bleach board carton with P.V.C tray & insert.

6.6 Special precautions for disposal and other handling

If only part of an ampoule is used, discard the remaining solution. Keep this medicine out of the sight and reach of children.

7. Marketing Authorization Holder

Brookes Pharma Private Limited
58 & 59, Sector 15, Korangi Industrial Area, Karachi-Pakistan

8. Marketing Authorization Number

CTD8278

9. Date of first authorization/renewal of the authorization

Date of first authorization-12 /03/2003
Renewal of the authorization- 23/08/2024

10. Date of revision of the text

13/05/2025