



## SUMMARY OF PRODUCT CHARACTERISTICS

### PRODUCT SUMMARY

#### 1. NAME OF THE MEDICINAL PRODUCT

Glycopyrrolate-Neostigmine Injection.

#### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 0.5mg of glycopyrrolate USP and 2.5mg of neostigmine metilsulfate BP/PhEur.

#### 3. PHARMACEUTICAL FORM

Clear, colourless sterile solution for injection intended for parenteral administration presented in 1ml clear, type 1, Ph.Eur. glass ampoules.

#### 4 CLINICAL PARTICULARS

##### 4.1. Therapeutic Indications

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

##### 4.2. Posology and Method of Administration

Glycopyrrolate-Neostigmine injection is for intravenous administration.

*Adults and older patients:* 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)].

*Children:* 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.

#### **4.3 Contra-Indications**

Glycopyrrolate-Neostigmine Injection should not be given to patients with known hypersensitivity to either of the two active ingredients. Glycopyrrolate-Neostigmine Injection should not be given to patients with mechanical obstruction of the gastrointestinal or urinary tracts.

Glycopyrrolate-Neostigmine Injection should not be given in conjunction with suxamethonium as neostigmine potentiates the depolarising myoneural blocking effects of this agent.

#### **4.4. Special Warnings and Special Precautions for Use**

Administer with caution to patients with bronchospasm, severe bradycardia or glaucoma. 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 or thyrotoxicosis. Use with caution in patients with epilepsy or Parkinsonism. The product should be used cautiously in pyrexial patients due to inhibition of sweating.

#### **4.5. Interactions with other Medicinal Products and other Forms of Interaction**

Neostigmine potentiates the depolarising myoneural blocking effects of suxamethonium (see contra-indications above).

#### **4.6. Pregnancy and Lactation**

Reproduction studies in rats and rabbits revealed no teratogenic effects from glycopyrrolate. Safety in human pregnancy and lactation has not been established. However, 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. The safety of neostigmine metilsulfate in pregnancy and lactation has not been established.

#### **4.7. Effects on Ability to Drive and Use Machines**

Not relevant as the product is for intra-operative use.

#### **4.8. Undesirable Effects**

The glycopyrrolate component of Glycopyrrolate-Neostigmine Injection can give rise to dry mouth, difficulty in micturition, cardiac dysrhythmias, disturbances of visual accommodation and inhibition of sweating. The neostigmine component of Glycopyrrolate-Neostigmine Injection can give rise to bradycardia, increased oropharyngeal secretions, cardiac dysrhythmias and increased gastrointestinal activity. If severe neostigmine-induced muscarinic side effects occur (bradycardia, increased oropharyngeal secretions, decreased cardiac conduction rate, 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**

The treatment of overdose depends upon whether signs of anticholinesterase or anticholinergic overdose are predominant presenting features. Signs of neostigmine overdose (bradycardia, increased oropharyngeal secretions, bronchospasm etc) 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 overdose (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 overdose are peripheral rather than central in nature; centrally acting anticholinesterase drugs such as physostigmine are therefore unnecessary to treat glycopyrrolate overdose.

## **5 PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic Properties**

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**

Glycopyrrolate is a quaternary ammonium anti-muscarinic agent. The quaternary ammonium moiety renders glycopyrrolate highly ionised at physiological pH and it thus penetrates the blood brain and placental barriers poorly. Excretion is through bile and urine as unchanged drug. Neostigmine metilsulfate is a quaternary ammonium anticholinesterase. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. It is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites.

### **5.3. Pre-clinical 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**

Disodium Hydrogen Phosphate Dodecahydrate BP/PhEur.  
Citric Acid Monohydrate BP/Ph.Eur.  
Sodium Hydroxide BP/ Ph.Eur.  
Water for Injections BP/ Ph.Eur.

### **6.2. Incompatibilities**

Do not mix Glycopyrrolate Neostigmine Injection with any other product.

**6.3. Shelf Life**

2 years.

**6.4. Special Precautions for Storage**

Store below 25°C. Protect from light.

**6.5. Nature and Content of Container**

Glycopyrrolate Neostigmine Injection is presented in clear glass ampoules packed in cardboard cartons to contain 5 or 10 ampoules.

**6.6. Instructions for Use, Handling and Disposal**

Keep out of reach of children.

If only part of an ampoule is used, discard the remaining solution.

**ADMINISTRATIVE DETAILS**

**7. MARKETING AUTHORISATION HOLDER**

Antigen International Ltd.  
Roscrea  
Co. Tipperary  
Ireland.

**8. MARKETING AUTHORISATION NUMBER**

PL 02848/0200

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION**

3 March 1998

**10. DATE OF (PARTIAL) REVISION OF THE TEXT**

29 January 1998