

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Robinul-Neostigmine Injection
Glycopyrronium Bromide 0.5mg and Neostigmine Metilsulfate 2.5mg in 1ml solution for Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains 500 micrograms (0.5mg) of glycopyrrolate (Glycopyrronium bromide) and 2.5mg of neostigmine metilsulfate.

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

Robinul-Neostigmine Injection is for intravenous administration.

Adults and older patients: 1 - 2ml 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)].

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. Contraindications

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

Robinul-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 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 Robinul-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.

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 applicable.

4.8. Undesirable effects

The glycopyrrolate component of Robinul-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 Robinul-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 Robinul Injection (glycopyrrolate) 200 - 600 micrograms (0.2 - 0.6mg) or atropine 400 - 1200 micrograms (0.4 - 1.2mg).

4.9. Overdose

The treatment of overdosage depends upon whether signs of anticholinesterase or anticholinergic overdosage are predominant presenting features. Signs of neostigmine overdosage (bradycardia, increased oropharyngeal secretions, bronchospasm etc) may be treated by the administration of Robinul Injection (glycopyrrolate) 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 overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Robinul (glycopyrrolate) is a quaternary ammonium anticholinergic agent. The quaternary ammonium moiety renders Robinul highly ionised at physiological pH and it thus penetrates the blood brain and placental barriers poorly. Robinul has a more gradual onset and longer duration of action than atropine. Neostigmine metilsulfate is a quaternary ammonium anticholinesterase. Robinul-Neostigmine Injection is associated with less initial tachycardia and better protection against the subsequent cholinergic effects of neostigmine than a mixture of atropine and neostigmine. In addition, residual central anticholinergic effects are minimised due to the limited penetration of Robinul into the central nervous system. Administration of glycopyrrolate with neostigmine is associated with greater cardiostability than administration of glycopyrrolate and neostigmine metilsulfate separately.

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

5.2. Pharmacokinetic properties

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. A number of pertinent clinical studies were included in the product licence application for Robinul Injection, approved in March 1981.

In the PL Application for Robinul Injection it was demonstrated that over 90% of the glycopyrrolate disappeared from serum within 5 minutes following intravenous administration. The drug was 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. Glycopyrrolate is also rapidly excreted into urine 85% of product was excreted within 48 hours. It has subsequently been confirmed in a single dose pharmacokinetic study using radioimmunological assay procedures that glycopyrrolate was 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.

The pharmacokinetics of neostigmine metilsulfate are described in Martindale. 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 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

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
Citric Acid
Sodium Hydroxide
Water for Injections

6.2. Incompatibilities

Do not mix Robinul-Neostigmine Injection with any other product.

6.3. Shelf life

2 years.

6.4. Special precautions for storage

Do not store above 25°C.
Keep in outer carton.

6.5. Nature and contents of container

Robinul-Neostigmine Injection is presented in clear one point cut glass ampoules packed in cardboard cartons to contain 10 ampoules.

6.6. Special Precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Anpharm Limited
Roscrea
County Tipperary
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

PL 15372/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

1st July, 1997.

10. DATE OF REVISION OF THE TEXT

May 2009