

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Neostigmine Injection BP 2.5 mg/ml, Solution for Injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 2.5 mg Neostigmine Metilsulfate.

For a 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

The symptomatic treatment of myasthenia gravis where oral therapy is impractical.

Reversal of the effects of non-depolarising neuromuscular blocking agents.

The management of post-operative distension, paralytic ileus and urinary retention, where mechanical obstruction has been out-ruled.

4.2 Posology and method of administration

Neostigmine Injection BP may be administered intramuscularly, subcutaneously or intravenously. Where the intravenous route is used, administration must be by very slow injection.

Treatment of myasthenia gravis

Adults: Doses 1 to 2.5 mg may be given by I.M. or S.C. injection at intervals during the day when strength is most needed. The total daily dose is usually in the range of 5 to 20 mg but higher doses may be required by some patients.

Children: Neonatal myasthenia can be treated with an initial dose of 0.1mg intramuscularly. Thereafter, the dosage should be titrated individually and is usually in the range of 0.05 to 0.25mg by injection. Treatment is rarely needed beyond eight weeks of age.

Reversal of non-depolarising neuromuscular blocking agents

Adults and children: The usual dose is 0.05 to 0.07mg per kg body weight, given concomitantly with or after atropine sulphate, by slow intravenous injection over a period of 60 seconds. Additional neostigmine may be required to restore normal muscle power but a total of 5mg for adults and 2.5mg for children should not be exceeded. If preferred, the atropine sulphate may be administered prior to the neostigmine.

Management of post-operative distension, ileus and urinary retention

Adults: The usual dose is 0.5 to 2.5mg by subcutaneous or intramuscular injection.
Children: The usual dose is 0.125 to 1.0mg by subcutaneous or intramuscular injection.

Elderly: There is no evidence to suggest that neostigmine has any special effects in the elderly. However, elderly patients may be more susceptible to dysrhythmias than younger adults.

4.3 Contraindications

Use in patients hypersensitive to neostigmine.

Patients with a known sensitivity to Neostigmine should not be treated with the drug.

Use in conjunction with suxamethonium as neostigmine potentiates the depolarising myoneuronal blocking effects of this agent.

It should not be administered to patients with Peritonitis, Mechanical Obstruction of the Intestinal or Urinary Tracts, or in Doubtful Bowel Viability.

4.4 Special warnings and precautions for use

Neostigmine should not be used in conjunction with cyclopropane, halothane or thiopental as it may potentiate their vagotonic effect; however it may be used after withdrawal of these agents. Neostigmine should be used with caution in patients with bradycardia, hyperthyroidism, cardiac arrhythmias, peptic ulcer, bronchial asthma, recent coronary occlusion, epilepsy, hypotension or Parkinsonism.

Bradycardia may occur, possibly to a dangerous level in patients receiving Neostigmine Metilsulfate by IV injection, unless Atropine is given simultaneously. Patients who are Hyperreactive to Neostigmine, experience a severe cholinergic reaction to the drug. Therefore, Atropine Sulphate should always be available as an antagonist for the muscarinic effects of Neostigmine.

Although there are no specific dosage requirements in the elderly, these patients may be more susceptible to Dysrhythmias than younger patients.

If only part used discard the remaining solution.

4.5 Interaction with other medicinal products and other forms of interaction

Neostigmine may potentiate the vagotonic effects of cyclopropane, halothane and thiopental. Antimuscarinic agents such as atropine antagonise the muscarinic effect of neostigmine. Bradycardia and hypotension have been reported following administration of neostigmine to patients receiving betablockers.

Neuromuscular Blocking Agents: Neostigmine effectively antagonises the effect of Non-depolarizing muscle relaxants (e.g. Tubocurarine, Gallamine or Pancuronium) and this interaction is used to therapeutic advantage to reverse muscle relaxation after surgery. Neostigmine does not antagonise, and it may in fact prolong, the phase I block of depolarizing muscle relaxants such as Succinylcholine.

Anticholinesterase agents are sometimes effective in reversing Neuromuscular Block induced by Aminoglycoside Antibiotics. However, Aminoglycoside Antibiotics and other drugs that interfere with Neuromuscular transmission should be used cautiously, if at all, in patients with Myasthenia Gravis and the dose of Neostigmine may have to be adjusted accordingly.

4.6 Fertility, pregnancy and lactation

The safety for use in human pregnancy and lactation has not been established. Therefore, this product should not be used during pregnancy or lactation unless considered essential by the physician.

Although the possible hazards to mother and child must be weighed against the potential benefits in every case. Experience with Myasthenia Gravis has revealed no untoward effect of the drug on the course of pregnancy. As the

severity of Myasthenia Gravis often fluctuates considerably, particular care is required to avoid cholinergic crisis due to overdosage of Neostigmine.

Only negligible amounts of Neostigmine Metilsulfate are excreted in breast milk. Nevertheless, attention should be paid to possible effects on the breast-feeding infant.

4.7 Effects on ability to drive and use machines

Drowsiness and dizziness may occur, which may impair the physical and mental abilities required to drive or to use machines.

4.8 Undesirable effects

Side effects may include anorexia, nausea, vomiting, abdominal cramps and diarrhoea, bradycardia, cardiac dysrhythmia, increased oropharyngeal secretions, drowsiness or dizziness.

4.9 Overdose

Extremely high doses may produce CNS symptoms of agitation, fear or restlessness. Death may result from cardiac arrest or respiratory paralysis and pulmonary oedema. In patients with Myasthenia Gravis, in whom over dosage is most likely to occur, fasciculation and adverse parasympathomimetic effects may be mild or absent making cholinergic crisis difficult to distinguish from Myasthenia crisis.

Overdosage may lead to a 'cholinergic crisis' characterised by both muscarinic and nicotinic effects. The muscarinic effects may include abdominal cramps, increased peristalsis, nausea, vomiting, involuntary defaecation and urination, sweating, salivation, increased bronchial secretions, miosis, bradycardia and hypotension.

Nicotinic effects include involuntary twitchings, fasciculations and generalised weakness. Muscle weakness is a symptom both of cholinergic crisis and of myasthenia gravis; it is extremely important to distinguish between these two conditions as their treatments are radically different.

Treatment: Maintenance of adequate respiration is of primary importance. Tracheostomy, Bronchial aspiration and postural drainage may be required.

Neostigmine Metilsulfate should be discontinued immediately and 1 – 4mg of Atropine Sulphate administered IV. Additional doses of Atropine may be given every 5 – 30 minutes as needed to control muscarinic symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Neostigmine inhibits cholinesterase enzyme activity and thus potentiates the physiological actions of acetylcholine.

5.2 Pharmacokinetic properties

Neostigmine is poorly absorbed from the gastrointestinal tract. Following parenteral administration as the metilsulfate, neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Mean plasma half-lives of 0.89 and 1.20 hours have been obtained after intravenous and intramuscular injections, respectively. Neostigmine is excreted in the urine both as unchanged drug and as metabolites.

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

Dilute Sulphuric Acid
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf Life

Unopened: 4 years.
The product should be used immediately after opening.

6.4 Special precautions for storage

Keep the ampoules in the outer carton in order to protect from light.
Do not store above 25°C.

6.5 Nature and contents of container

1 ml, amber glass ampoules, glass type I Ph. Eur.

Pack size: 10 x 1 ml ampoules.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

For single use only. Discard any unused content. The product should be used immediately after opening.

7 MARKETING AUTHORISATION HOLDER

Antigen Pharmaceuticals Ltd.
Roscrea
Co. Tipperary

8 MARKETING AUTHORISATION NUMBER

PA0073/037/01

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979
Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

December 2010