

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Neostigmine Metilsulfate 2.5mg/ml Solution for Injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml contains 2.5mg neostigmine metilsulfate.

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

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

Posology

Adults

For the treatment of Myasthenia gravis, 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.

For reversal of non-depolarising neuromuscular blocking agents, 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. For management of post-operative distension, ileus and urinary retention the usual dose is 0.5 to 2.5mg by subcutaneous or intramuscular injection.

Paediatric population

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. For reversal of non-depolarising neuromuscular blocking agents, the same dosage can be used as that of adults. For management of post-operative distension, ileus or urinary retention, 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.

Method of administration

Neostigmine Metilsulfate 2.5mg/ml Solution for Injection may be administered intramuscularly, subcutaneously or intravenously. Where the intravenous route is used, administration must be by very slow injection.

4.3 Contraindications

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

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 interactions

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

Pregnancy

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.

Breast-feeding

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

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Neostigmine Metilsulfate 2.5mg/ml Solution for Injection has moderate influence on the ability to drive and use medicines. Drowsiness and dizziness may occur, which may impair the physical and mental abilities required to drive or to use machines.

4.8 Undesirable effects

Adverse reactions (Table 1) are ranked under heading of frequency, the most frequent first, using the following convention: Very common: ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$); not known (cannot be estimated from the available data)

System Organ Class	Adverse reaction	Frequency
Immune system disorders	Anaphylactic reaction	Not known
Metabolism and Nutrition disorders	Anorexia	Not known
Nervous system disorders	Drowsiness Dizziness	Not known
Cardiac disorders	Cardiac arrest/ Asystolic arrest Bradycardia Arrhythmias	Not known
Gastrointestinal disorders	Nausea, Vomiting Abdominal pain Diarrhoea Oropharyngeal secretions increased	Not known

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

HPRA Pharmacovigilance,

Website: www.hpra.ie

4.9 Overdose

Symptoms

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.

Management

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

Pharmacotherapeutic group: Anticholinesterases, ATC code: N07AA01

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

5.2 Pharmacokinetic properties

Absorption

Neostigmine is poorly absorbed from the gastrointestinal tract.

Biotransformation

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.

Elimination

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

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

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 and other handling

For single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements. The product should be used immediately after opening.

7 MARKETING AUTHORISATION HOLDER

Mercury Pharmaceuticals (Ireland) Ltd
4045 Kingswood Road

Citywest Business Park
Co Dublin
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0073/037/001

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

May 2021