

Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Neostigmine-hameIn 2.5 mg/ml Injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 2.5 mg of neostigmine methylsulphate.
1 ampoule with 1 ml contains 2.5 mg neostigmine methylsulphate.

Excipients with known effect:

This medicinal product contains approximately 3.54 mg sodium per ml.
This should be taken into consideration by patients on a controlled sodium diet.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Indications: Myasthenia gravis, antagonist to non-depolarizing neuromuscular blockade, paralytic ileus.

Routes of Administration: Neostigmine methylsulphate may be administered by IV, IM or SC injection.

4.2 Posology and method of administration

Neostigmine methylsulphate should be given very slowly by the IV route. A syringe of atropine sulphate should always be available to counteract severe cholinergic reactions should they occur.

Myasthenia gravis: 1 – 2.5 mg by IM or SC injection at intervals throughout the day, when maximum strength is needed. The usual duration of action of a dose is two to four hours. The total daily dose is usually 5 – 20 mg by injection but higher doses may be needed by some patients.

Neonatal myasthenia gravis may be treated with 0.1 mg neostigmine intramuscularly initially. Thereafter, the dose must be titrated individually. But is usually 0.05 – 0.25 mg IM or 0.03 mg/kg IM, every two – four hours. Because of the self-limiting nature of the disease in neonates, the daily dosage should be reduced until the drug can be withdrawn.

Older Children: (Under 12 years of age) May be given 0.2 – 0.5 mg by injection as required. Dosage requirements should be adjusted according to the response of the patient.

Antagonist to Non-depolarizing Neuromuscular Blockade: Reversal of neuromuscular blockade with Neostigmine should not be attempted unless there is spontaneous recovery from paralysis.

Adults and Children: A single dose of neostigmine 0.05 – 0.07 mg/kg body-weight and Atropine 0.02 – 0.03 mg/kg body weight, by slow IV injection over one minute is usually adequate for complete reversal of Non-depolarizing Muscle Relaxants within 5 – 15 minutes. The maximum recommended dose of neostigmine in adults is 5 mg and in children 2.5 mg.

Atropine and neostigmine may be given simultaneously, but in patients with bradycardia, the pulse rate should be increased to 80 per minute with atropine before administering neostigmine.

Paralytic Ileus

Adults: 0.5 – 2.5 mg Neostigmine methylsulphate by SC or IM injection.

Children: 0.125 – 1 mg by injection. Doses may be varied according to the individual needs of the patient.

Elderly: There are no specific dosage recommendations for neostigmine methylsulphate in the elderly.

4.3 Contraindications

Use of neostigmine is contraindicated in patients with hypersensitivity to neostigmine or to any of the excipients listed in section 6.1.

Neostigmine should not be administered to patients with mechanical obstruction of gastrointestinal or urinary tracts, peritonitis or doubtful bowel viability.

Neostigmine should not be used in conjunction with depolarising muscle relaxants such as suxamethonium as neuromuscular blockade may be potentiated.

4.4 Special warnings and precautions for use

Neostigmine should be used with extreme caution in patients with asthma as the parasympathomimetic action of neostigmine may cause bronchoconstriction.

Bradycardia, with the potential for progression to asystole, may occur in patients receiving neostigmine by intravenous injection unless atropine is given simultaneously. Extreme caution should be employed when treating patients with pre-existing bradycardia, cardiac arrhythmia or recent coronary occlusion.

Patients who are hyperreactive to neostigmine experience a severe cholinergic reaction to the drug. Atropine sulphate should always be available as an antagonist for the muscarinic effects of neostigmine.

Neostigmine should be used with caution in patients with epilepsy, vagotonia, hyperthyroidism, peptic ulceration or parkinsonism.

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

Elderly

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

Inhaled anaesthetics

Neostigmine Methylsulphate should not be given during cyclopropane or halothane anaesthesia; although it may be used after withdrawal of these agents.

4.5 Interaction with other medicaments and other forms of interaction

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.

Other Drugs: Atropine antagonises the muscarinic effects of neostigmine, the interaction is utilised to counteract the muscarinic symptoms of the neostigmine toxicity.

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 Pregnancy and lactation

The use of neostigmine methylsulphate during pregnancy or lactation has not been established. 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 methylsulphate 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

Not applicable.

4.8 Undesirable effects

System Organ Class	Adverse reaction	Frequency
<i>Immune system disorders</i>	Hypersensitivity, angioedema, anaphylactic reaction.	Not known
<i>Nervous system disorders</i>	Cholinergic syndrome, especially at high doses. In patients with myasthenia gravis, cholinergic crisis may be difficult to distinguish from myasthenia crisis (see section 4.9).	Not known
<i>Eye disorders</i>	Miosis, lacrimation increased	Not known
<i>Cardiac disorders</i>	Bradycardia, decreased cardiac conduction, in severe cases possibly leading to heart block or cardiac arrest	Not known
<i>Vascular disorders</i>	Hypotension	Not known
<i>Respiratory, thoracic or mediastinal disorders</i>	Increased bronchial secretion, bronchospasm	Not known
<i>Gastrointestinal disorders</i>	Nausea, vomiting, diarrhoea, abdominal cramps, salivary hypersecretion. Increased intestinal motility may result in involuntary defecation.	Not known
<i>Skin and subcutaneous tissue disorders</i>	Hyperhidrosis	Not known
<i>Musculoskeletal, connective tissue and bone disorders</i>	Muscle spasms	Not known
<i>Renal and urinary disorders</i>	Urinary incontinence	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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form: <https://sideeffects.health.gov.il>

4.9 Overdose

Symptoms: Neostigmine methylsulphate overdosage may include cholinergic crisis, which is characterised by nausea, vomiting, diarrhoea, excessive salivation and sweating, increased bronchial secretions, miosis, bradycardia or tachycardia, cardiospasm, bronchospasm, incoordination, muscle cramps, fasciculation and paralysis. 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 overdosage is most likely to occur, fasciculation and adverse parasympathomimetic effects may be mild or absent making cholinergic crisis difficult to distinguish from myasthenia crisis.

Treatment: Maintenance of adequate respiration is of primary importance. Tracheostomy, bronchial aspiration and postural drainage may be required; Respiration can be assisted mechanically or with oxygen, if necessary.

Neostigmine methylsulphate should be discontinued immediately and 1 – 4 mg of atropine sulphate administered IV. Additional doses of atropine may be given every 5 – 30 minutes as needed to control muscarinic symptoms. Atropine overdosage should be avoided as tenacious secretions and bronchial plugs may result.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Neostigmine inhibits cholinesterase activity and prolongs and intensifies the muscarinic and nicotinic effects of acetylcholine. The anticholinesterase actions of neostigmine are reversible. It is used mainly for its action on skeletal muscle and less frequently to increase the activity of smooth muscle. Neostigmine is used in the treatment of myasthenia gravis.

5.2 Pharmacokinetic properties

Neostigmine is a quaternary ammonium compound and is poorly absorbed from the gastrointestinal tract. Following parenteral administration as the methylsulphate, neostigmine is metabolised partly by hydrolysis of the ester linkage and is excreted in the urine both as unchanged drug and as metabolites. The half-life of neostigmine is only one to two hours.

5.3 Preclinical safety data

No further information other than that which is included in the Summary of Product Characteristics.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for Injections

6.2 Incompatibilities

Neostigmine may be diluted with water for injections. Stability of the injection cannot be guaranteed once it has been diluted.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Protect from light and store at less than 25°C.

6.5 Nature and Content of Container

1 ml glass ampoules hermetically sealed under flame at the gauging point. The ampoules are packed in cartons to contain 10 ampoules.

6.6 Special precautions for disposal/ instructions for use/ handling

Use as directed by a physician.
If only part used discard the remaining solution.

7. MARKETING AUTHORISATION HOLDER

Pharma medis Ltd.
4 Fireberg St.
Holon, Israel

8. MANUFACTURER

Siegfried Hameln GmbH
Langes Feld 13, 31789 Hameln, Germany

9. MARKETING AUTHORITY NUMBER

151.23.33874.00

10. DATE OF REVISION OF THE TEXT

Revised in January 2021 according to MOH guidelines.