SUMMARY OF PRODUCT CHARACTERISTICS

1.0 Name of the medicinal product

1.1 Name of the medicinal product

Stigmine

Neostigmine Methylsulfate Injection USP 2.5 mg/mL.

INN name of the API: Neostigmine Methylsulfate

1.2 Strength

2.5 mg/mL

1.3 Pharmaceutical form

Injection

2.0 Qualitative and quantitative composition

Qualitative:

Neostigmine Methylsulfate

List of Excipients

Sodium Chloride and Water for Injection.

Quantitative:

Neostigmine Methyl sulfate: 2.5 mg, Sodium Chloride: 9.0 mg, Water for Injection: q.s to 1 mL.

Composition:

S.No.	Material	Quantity per mL	Quantity Per Ampoule	Pharmacopeial status	Category
1	Neostigmine methylsulfate*	2.5 mg	2.5 mg	USP	Active
2	Sodium hydroxide	9.0 mg	9.0 mg	USP	Tonicity agent
3	Water for Injection	q.s to 1.0 mL	q.s to 1.0 mL	USP	Solvent

3.0 Pharmaceutical form

Injection.

4.0 Clinical particulars

4.1 Therapeutic indications

Indications: Myasthenia Gravis, antagonist to non-depolarizing neuromuscular blockade, Paralytic Ileus, Post-operative Urinary Retention; Paroxysmal Supraventricular Tachycardia.

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

4.2 Posology and method of administration

Neostigmine Methyl sulfate should be given very slowly by the IV route. A syringe of Atropine Sulfate 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of the self-limiting nature of the disease in neonates, the daily dosage should be reduced until the drug can be withdrawn.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.

Other Indications:

Adults: 0.5 – 2.5 mg Neostigmine Methyl sulfate 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 Methyl sulfate in the elderly.

Method of administration

Symptomatic control of myasthenia gravis: One mL of the 1:2000 solution (0.5 mg) subcutaneously or intramuscularly. Subsequent doses should be based on the individual patient's response. In most patients, however, oral treatment with Neostigmine bromide tablets, 15 mg each, is adequate for control of symptoms.

Prevention of postoperative distention and urinary retention: 0.25 mg subcutaneously or intramuscularly as soon as possible after operation; repeat every 4 to 6 hours for two or three days.

Treatment of postoperative distention: One mL of 1:2000 solution (0.5 mg) subcutaneously or intramuscularly, as required.

Treatment of urinary retention: One mL of the 1:2000 solution (0.5 mg) subcutaneously or intramuscularly. If urination does not occur within an hour, the patient should be catheterized. After the patient has voided, or the bladder has been emptied, continue the 0.5 mg injections every three hours for at least 5 injections.

Reversal of Effects on Nondepolarizing Neuromuscular Blocking Agents: When Neostigmine Methylsulfate Injection is administered intravenously, it is recommended that atropine sulfate (0.6 to 1.2 mg) also be given intravenously using separate syringes. Some authorities have recommended that the atropine be injected several minutes before the Neostigmine rather than concomitantly. The usual dose is 0.5 to 2 mg Neostigmine Methyl sulfate Injection given by slow intravenous injection, repeated as required. Only in exceptional cases should the total dose

Neostigmine exceed 5 mg. It is recommended that the patient be well ventilated and a patent airway maintained until complete recovery of normal respiration is assured. The optimum time for administration of the drug is during hyperventilation when the carbon dioxide level of the blood is low. It should never be administered in the presence of high concentrations of halothane or cyclopropane. In cardiac cases and severely ill patients, it is advisable to titrate the exact dose of Neostigmine required, using a peripheral nerve stimulator device. In the presence of bradycardia, the pulse rate should be increased to about 80/minute with atropine before administering Neostigmine.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

4.3 Contraindications

Use of Neostigmine is contraindicated in patients with hypersensitivity to Neostigmine or to any of the excipients in this injection.

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 depolarizing 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 hyper reactive to Neostigmine experience a severe cholinergic reaction to the drug. Atropine sulfate 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 Methyl sulfate should not be given during cyclopropane or halothane anaesthesia; although it may be used after withdrawal of these agents.

Excipients

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

The label shall state the following:

Protect from light and store at less than 30°C.

If only part used discard the remaining solution.

4.5 Interaction with other medicinal products 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 Methyl sulfate 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 Methyl sulfate 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

Adverse effects of Neostigmine are chiefly those of exaggerated response to parasympathetic stimulation.

Nervous system disorders

Cholinergic syndrome, especially at high doses. In patients with myasthenia gravis, cholinergic crisis may be difficult to distinguish from myasthenia crisis.

Eye disorders

Miosis, lacrimation increased

Cardiac disorders

Bradycardia, decreased cardiac conduction, in severe cases possibly leading to heart block or cardiac arrest

Vascular disorders

Hypotension

Respiratory, thoracic or mediastinal disorders

Increased bronchial secretion, bronchospasm

Gastrointestinal disorders

Nausea, vomiting, diarrhoea, abdominal cramps, salivary hypersecretion.

Increased intestinal motility may result in involuntary defecation.

Skin and subcutaneous tissue disorders

Hyperhidrosis

Musculoskeletal, connective tissue and bone disorders

Muscle spasms

Renal and urinary disorders

Urinary incontinence

4.9 Overdose

Neostigmine Methyl sulfate 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, in coordination, 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 Methyl sulfate should be discontinued immediately and 1 – 4 mg of Atropine Sulfate 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.

5.0 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 Pharmacokinetics

Neostigmine is a quaternary ammonium compound and is poorly absorbed from the gastrointestinal tract. Following Parenteral administration as the methyl sulfate, 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 data.

6.0 Pharmaceutical particulars

6.1 List of excipients

Sodium Chloride and Water for Injection.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 Months

6.4 Special precautions for storage

Store below 30°C.

6.5 Nature and contents of container

1mL USP type-I clear ampoule. Each five ampoules are placed in a tray and such tray is packed in a monocarton along with package insert.

6.6 Special precautions for disposal and other handling

Use as directed by a physician.

If only part used discard the remaining solution.

7.0 Registrant

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8.0 Name and address of manufacturer

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9.0 Date of revision of the text

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