# NEOSTIGMINE

# GENTIMIN

℞

500 mcg/mL Solution for Injection
(I.M./I.V./S.C.)
CHOLINESTERASE INHIBITOR

**PRODUCT DESCRIPTION:**
Clear and colouless solution.

**FORMULATION/COMPOSITION:**
Each vial contains:
Neostigmine methylsulfate BP..... 500 mcg

**PHARMACODYNAMICS AND PHARMACOKINETICS:**
Neostigmine is a quaternary ammonium compound and, as the bromide, is poorly absorbed from the gastrointestinal tract. After parenteral doses as the metilsulfate, neostigmine is rapidly eliminated and is excreted in the urine both as unchanged drug and metabolites. Neostigmine undergoes hydrolysis by cholinesterases and is also metabolised in the liver. Protein binding to human serum albumin is reported to range from 15 to 25%. Penetration into the CNS is poor. Neostigmine crosses the placenta and very small amounts are distributed into breast milk.

**INDICATIONS:**
Neostigmine is a quaternary ammonium compound that inhibits cholinesterase activity and thus prolongs and intensifies the physiological actions of acetylcholine. It probably also has direct effects on skeletal muscle fibres. The anticholinesterase actions of neostigmine are reversible.
Neostigmine is used in the treatment of myasthenia gravis and has been used as an alternative to edrophonium in the diagnosis of myasthenia gravis. It is used in anaesthesia to reverse the neuromuscular blockade produced by competitive neuromuscular blockers. It is also used in the management of paralytic ileus. Neostigmine has been used in the management of postoperative urinary retention but has generally been superseded by catheterisation. It is sometimes used to lower intra-ocular pressure in the management of glaucoma and to reduce rises in intra-ocular pressure associated with ophthalmic surgery, although other parasympathomimetics are usually used when such miotics are required.

**DOSAGE AND MODE/ROUTE OF ADMINISTRATION:**
Neostigmine is given as the bromide and as the metilsulfate. Neostigmine bromide is given by mouth and has been used topically as eye drops; the metilsulfate is given by intramuscular, intravenous, or subcutaneous injection.
The manufacturers state that 0.5 mg of neostigmine metilsulfate by intravenous injection is approximately equivalent in effect to I to 1.5 mg of neostigmine metilsulfate by intramuscular or subcutaneous injection, or 15 mg ofneostigmine bromide by mouth.
In the treatment of myasthenia gravis, neostigrnine bromide is given by mouth in a total daily dose usually between 75 and 300 mg, divided throughout the day, and if necessary the night, according to individual response; larger portions of the total dose may be given at times of greater fatigue. The maximum daily dose that most patients can tolerate is 180 mg. A usual total daily dose in children is 15 to 90 mg by mouth. In patients in whom oral therapy is impractical neostigmine metilsulfate may be given in doses of 0.5 to 2.5 mg by intramuscular or subcutaneous injection at intervals, giving a total daily dose usually in the range 5 to 20 mg. Single doses in children have ranged from 200 to 500 micrograms.
In the treatment of neonatal myasthenia gravis doses in the range 50 to 250 micrograms of the metilsulfate by intramuscular or subcutaneous injection, or I to 5 mg of the bromide by mouth, have been given usually every 4 hours; treatment is rarely needed beyond 8 weeks of age.
To reverse neuromuscular blockade produced by competitive neuromuscular blockers, the usual adult dose in the UK is 50 to 70 micrograms/kg given by intravenous injection over a period of 60 seconds; in the USA lower doses of 0.5 to 2 mg are used. Additional neostigmine may be given until the muscle power is normal but a total of 5 mg should not be exceeded. The patient should be well ventilated until complete recovery of normal respiration is assured. To counteract any muscarinic effects 0.6 to 1.2 mg of atropine sulfate is given by intravenous injection with or before the dose of neostigmine; it has been suggested that in the presence of bradycardia atropine sulfate should be given several minutes before neostigmine. Glycopyrronium bromide has been used as an alternative to atropine sulfate.
In the treatment of paralytic ileus and postoperative urinary retention, doses of 15 to 30 mg of the bromide by mouth, or more usually 0.5 mg of the metilsulfate by subcutaneous or intramuscular injection, have been used.

**CONTRAINDICATIONS:**
Hypersensitivity to the active substance or to any of the excipients.
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.

**PRECAUTIONS, WARNINGS:**
Neostigmine is contraindicated in patients with mechanical intestinal or urinary-tract obstruction, or eperitonitis. It should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma. It should be used with caution in patients with cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction, and hypotension, as well as in patients with vagotonia, epilepsy, hyperthyroidism, parkinsonism, renal impairment, or peptic ulcer disease. When neostigmine is given by injection, atropine should always be available to counteract any excessive muscarinic reactions; atropine may also be given before, or with, neostigmine to prevent or mm1m1se muscarinic side-effects but this may mask the initial symptoms of overdosage and lead to cholinergic crisis.
The UK manufacturer has advised that as the severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has also been reported that neonatal myasthenia may follow large doses during pregnancy. The amount of neostigmine distributed into breast milk is very small but breast-fed infants need to be monitored.
Large doses of neostigmine by mouth should be avoided in conditions where there may be increased absorption from the gastrointestinal tract. It should be avoided in patients known to be hypersensitive to neostigmine; the bromide ion from neostigmine bromide may contribute to the allergic reaction.

**PREGNANCY AND LACTATION:**
The use of Neostigmine Methylsulfate 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 Methylsulfate are excreted in breast milk. Nevertheless, attention should be paid to possible effects on the breast-feeding infant.

**INTERACTIONS:**
Drugs with neuromuscular blocking activity, such as the aminoglycosides, clindamycin, colistin, cyclopropane, and the halogenated inhalational anaesthetics, may antagonise the effects of neostigmine. A number of drugs, including quinine, chloroquine, hydroxycbloroquine, quinidine, procainamide, propafenone, lithium, and the beta blockers, that have the potential to aggravate myasthenia gravis can reduce the effectiveness of treatment with parasympathomimetics. Prolonged bradycardia has also occurred in patients receiving beta blockers when given neostigmine. Anticholinesterases, such as neostigmine, can inhibit the metabolism of suxamethonium and enhance and prolong its action.
Ophthalmic use of anticholinesterases, such as ecothiopate, should be undertaken with care in patients receiving neostigmine systemically for myasthenia gravis, because of possible additive toxicity.
Antimuscarinics such as atropine antagonise the muscarinic effects of neostigmine.

**ADVERSE DRUG REACTIONS:**
The side-effects of neostigmine are chiefly due to excessive cholinergic stimulation and most commonly include increased salivation, nausea and vomiting, abdominal cramps, and diarrhoea. Allergic reactions have been reported; rashes have been associated with the use of the bromide salt. Neostigmine penetrates the blood-brain barrier poorly and CNS effects are usually only seen with high doses.
Overdosage may lead to a 'cholinergic crisis', characterised by both muscarinic and nicotinic effects. These effects may include excessive sweating, lachrymation, increased peristalsis, involuntary defaecation and urination or desire to urinate, miosis, ciliary spasm, nystagmus, bradycardia and other arrhythmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear. Death may result from respiratory failure, due to a combination of the muscarinic, nicotinic and central effects, or cardiac arrest.
It has been reported that a paradoxical increase in blood pressure and heart rate may result from nicotinic stimulation of sympathetic ganglia, especially where atropine has been given to reverse the muscarinic effects.
In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased muscular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself.

**OVERDOSE AND TREATMENT:**
Symptoms
Neostigmine Methylsulfate 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 Methylsulfate should be discontinued immediately and 1 – 4mg 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.

**STORAGE CONDITIONS:**
Store at temperatures not exceeding 30°C.

**DOSAGE FORMS AND PACKAGING AVAILABLE:**
*Dosage form:* 500 mcg/mL Solution for Injection
*Packaging available:* USP type I clear glass ampoule x 1 mL (Box of 6's)

**INSTRUCTIONS AND SPECIAL PRECAUTIONS FOR HANDLING AND DISPOSAL:**
No special requirements.

Name and address of marketing authorization holder:
**GA2 PHARMACEUTICAL INC.**
3270 Gasanco Bldg., C. Armstrong Road,
Merville Access Road, Brgy. Kalayaan 201,
Pasay, Metro Manila

Imported by:
**MEDINOVA PHARMACEUTICAL INC.**
3270C Armstrong Road, Merville, Brgy. 201, Pasay City,
Metro Manila, Philippines

Name and address of manufacturer:
**TABLETS (India) Limited**
179, T.H. Road, Chennai - 600 081, India

**CAUTION:**
Foods, Drugs, Devices, and Cosmetics Act prohibits dispensing without prescription.

**ADR REPORTING STATEMENT:**
For suspected adverse drug reaction, report to the FDA: www.fda.gov.ph
Seek medical attention immediately at the first sign of any adverse drug reaction.

**FDA Reg. No.: DRP-6823-05**

Date of first authorization/Renewal of the authorization:
Date of revision of package insert: