

NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Neostigmine Methylsulfate Injection, solution for injection, 2.5 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL contains 2.5 mg neostigmine methylsulfate.

Excipient with known effect

This medicinal product contains approximately 3.54 mg sodium per each 1 mL ampoule – see section 4.4.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for Injection.

A clear, colourless, sterile solution at pH 4.5 to 6.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Reversal of the effects of non-depolarising neuromuscular blocking agents (e.g. tubocurarine, pancuronium, etc.)
- Prophylaxis and treatment of post-operative intestinal atony and urinary retention.
- Treatment of myasthenia gravis during acute exacerbations, when the condition is severe or in neonates.

4.2 Dose and method of administration

Neostigmine can be given as an intramuscular (IM), intravenous (IV) or subcutaneous (SC) injection. When neostigmine is given, a syringe of atropine sulphate should be available to counteract severe cholinergic reactions, if they occur. Do not mix atropine with other medicines in the same syringe as compatibility data are not available.

ANTAGONIST TO NON-DEPOLARISING NEUROMUSCULAR BLOCKADE

Usually, reversal of neuromuscular blockade with neostigmine should not be attempted until spontaneous recovery from paralysis is evident. It is recommended that the patient be well ventilated and patent airway maintained until complete recovery of normal respiration is affirmed.

Adult

A single dose of neostigmine 0.5 to 2.5 mg (0.05 – 0.07 mg/kg) to be administered simultaneously (in separate syringes) with atropine sulphate 0.6-1.2 mg (0.02 to 0.03 mg/kg) by slow IV injection over 1 minute is generally adequate for complete reversible of non-depolarising muscle relaxants within 5 to 15 minutes. The maximum recommended dose of neostigmine in adults is 5 mg.

Children

The suggested dose in children is 0.05 mg/kg/dose and atropine sulphate 0.02 mg/kg/dose by slow IV injection over 1 minute. Maximum recommended dose of neostigmine in children is 2.5 mg.

Neostigmine and atropine are often given simultaneously in separate syringes, but in patients with bradycardia, the pulse rate should be increased to about 80 beats/minute with atropine before administering Neostigmine Methylsulfate Injection.

The speed of recovery from neuromuscular blockade is primarily determined by the intensity of the block at the time of antagonism. It is also influenced by other factors including the presence of drugs (e.g. anaesthetic drugs, antibiotics and antiarrhythmic drugs) and physiological changes (e.g. electrolyte and acid-base imbalance, renal impairment). These factors may prevent successful reversal with Neostigmine or lead to re-curarisation after apparently successful reversal. It is imperative that the patients should not be left unattended until these possibilities have been excluded.

MYASTHENIA GRAVIS

Adults

1 mg to 2.5 mg given as an IM or SC injection at intervals throughout the day when greater strength may be needed (e.g. mornings and before meals), giving a total daily dose of 5 to 20 mg. Duration of action of a single dose is 2 to 4 hours.

Neonates

0.05-0.25 mg as an IM injection every 2-4 hours, half an hour before feeding. Treatment is not usually required beyond 8 weeks of age. Because the condition is usually self limiting the daily dosage should gradually be reduced until the medicine can be withdrawn.

Older Children

0.2 to 0.5 mg by injection as required. Dosage should be adjusted according to response. When large doses of Neostigmine are given to myasthenic patients, atropine sulphate may be required to counteract the muscarinic side effects.

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INTESTINAL ATONY

Prophylaxis

0.25 mg as an IM or SC injection before or immediately after the operation, repeated every 4 to 6 hours for 2 to 3 days.

Treatment

0.5 mg as an IM or SC injection repeated at intervals of 4 to 6 hours.

URINARY RETENTION

Prophylaxis

0.25 mg as an IM or SC injection as for intestinal atony.

Treatment

0.5 mg as an IM or SC injection and apply warmth to lower abdomen. After patient has voided continue 0.5 mg SC or IM every 3 hours for at least 5 injections. If there has been no urinary response within one hour of the first dose, the patient should be catheterised.

4.3 Contraindications

- Mechanical obstruction of intestinal or urinary tract.
- Known hypersensitivity to neostigmine.
- Peritonitis.

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

Sodium content

This medicine contains 3.54 mg (or 0.15 mmol) sodium per each 1 mL ampoule (i.e. less than 1 mmol sodium (23 mg) per 1 mL ampoule), that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines 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 medicines

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 medicines 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 use of neostigmine 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.

Breast feeding

Evidence indicates that only negligible amounts of neostigmine enter breast milk, nevertheless, the possibility of adverse effects on the breast-feeding infant should be considered.

Fertility

No data available.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

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

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 medicine is important. It allows

continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

Symptoms

Neostigmine Methylsulfate overdose 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 overdose 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 overdose should be avoided as tenacious secretions and bronchial plugs may result.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Cholinesterase inhibitor which reversibly inhibits the hydrolysis of acetylcholine thereby potentiating its action.

Neostigmine is an anticholinesterase agent which inhibits reversibility the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase. As a result, acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated.

Neostigmine is therefore capable of producing a generalised cholinergic response, including miosis, increased tonus of intestinal and skeletal musculature, constriction of bronchi and ureters, bradycardia and stimulation of salivary and sweat glands. In addition, neostigmine has a direct cholinomimetic effect on skeletal muscle and to a lesser extent to increase the activity of smooth muscle.

Because of its quaternary ammonium structure, in moderate doses, neostigmine does not cross the blood-brain barrier to produce CNS effects. Extremely high doses, however, produce CNS stimulation followed by CNS depression.

5.2 Pharmacokinetic properties

Following IV administration the elimination half-life ranges from 47 to 60 minutes and after IM administration 50 to 91 minutes. Approximately 80% of a single IM dose of neostigmine is excreted in the urine in 24 hours, about 50% as unchanged neostigmine and the remainder as metabolites.

The major site of uptake is in the liver. It is metabolised partly by the hydrolysis of the ester linkage

and partly by microsomal enzymes in the liver.

5.3 Preclinical safety data

Genotoxicity

No data available.

Carcinogenicity

No data available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for Injections

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25°C. Protect from light.

6.5 Nature and contents of container

1mL glass ampoules hermetically sealed under flame at the gauging point.
The ampoules are packed in cartons containing 5 or 10 ampoules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Neostigmine Methylsulfate Injection solution contains no antimicrobial agents.

The ampoules are intended for single use only and any solution remaining from an opened container should be discarded.

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE

Prescription Medicine

8. SPONSOR

Max Health Ltd
PO Box 44452 Pt Chevalier
Auckland 1246

Ph: (09) 815 2664

9. DATE OF FIRST APPROVAL

19 March 2015

10. DATE OF REVISION OF THE TEXT

26 August 2021

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
2	<ul style="list-style-type: none">• Excipient with known effect added
4.4, 4.5, 4.6, 4.8, 4.9	<ul style="list-style-type: none">• Updated information to current reference document.
6.5	<ul style="list-style-type: none">• Added pack size of 5 and not all pack sizes may be marketed.
8	<ul style="list-style-type: none">• Updated sponsor PO Box details