NEW ZEALAND DATA SHEET

1. PRODUCT NAME

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Solution for injection containing 2.5 mg/mL neostigmine methylsulfate.

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 who have undergone recent intestinal or bladder surgery and in patients with bronchial asthma.

Use with caution in patients with cardiac disease and cardiovascular disorders including arrhythmias, bradycardia, recent myocardial infarction or coronary occlusion, and hypotension as well as in patients with, epilepsy, vagotonia, Parkinsonism, peptic ulceration, renal impairment, Addison's disease or hyperthyroidism.

With large doses, simultaneous parenteral administration of atropine sulphate may be advisable. Atropine sulphate should always be available along with other anti-shock medications (adrenaline) in case of hypersensitivity to neostigmine.

Neostigmine may prolong the depolarising neuromuscular blocking action of depolarising muscle relaxants such as suxamethonium and prolonged apnoea may result (see section 4.5 Interaction with other medicines and other forms of interaction).

Neostigmine should not be given whilst anaesthesia with cyclopropane and halothane continues but may be used after withdrawal of these agents.

As the severity of myasthenia gravis can fluctuate considerably, care is required to avoid cholinergic crisis due to overdosage with neostigmine (see section 4.9 Overdose).

Caution should be exercised when used on the post-surgical patient as respiratory problems caused by post-operative pain or sedation may be potentiated/aggravated.

4.5 Interaction with other medicines and other forms of interaction

CORTICOSTEROIDS
Corticosteroids may decrease the anticholinesterase effects of neostigmine. Conversely anticholinesterase effects may increase after stopping corticosteroids.

DEPOLARISING MUSCLE RELAXANTS
Neostigmine may prolong the Phase 1 block of depolarising muscle relaxants such as suxamethonium. Prolonged respiratory depression with extended periods of apnoea may occur.

ATROPINE
Atropine reverses the muscarinic effects of neostigmine. This interaction is used to counteract the muscarinic symptoms of neostigmine toxicity, however masking the signs of overdosage can lead to inadvertent induction of cholinergic crisis with the use of atropine.

AMINOGLYCOSIDES, LOCAL/GENERAL ANAESTHETICS, ANTIARRYTHMIC AGENTS
Anticholinesterase agents can be effective in reversing neuromuscular block induced by aminoglycoside antibiotics. Aminoglycoside antibiotics, local and some general anaesthetics, antiarrhythmic agents and other medicines that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis. The dose of neostigmine may need to be increased accordingly.

Quinine, chloroquine, hydroxychloroquine, beta-blockers and lithium may reduce the effectiveness of treatment with neostigmine.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category B2

The maternal need for neostigmine may be absolute in the context of myasthenia gravis. Cholinergic effects in the neonate are rare.

The safety of neostigmine in pregnancy has not been established with respect to possible adverse effects on foetal development. Anticholinesterase agents may cause uterine irritability and induce premature labour when given IV to pregnant women near term. Therefore, neostigmine should not be used in pregnant women or those likely to become pregnant unless the expected benefits outweigh any potential risk.

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 reactions generally associated with neostigmine overdosage are:

Cardiovascular: Cardiac arrhythmias (especially bradycardia), hypotension, cardiac arrest, syncope.

Central Nervous System: Headache, dizziness, convulsions, loss of consciousness, coma, drowsiness, restlessness, ataxia, slurred speech, agitation and fear.

Gastrointestinal: Nausea, vomiting, diarrhoea, flatulence, abdominal cramps, increased peristalsis and involuntary defaecation.

Genitourinary: Involuntary urination or desire to urinate.

Musculoskeletal: Muscle cramps, fasciculation, general weakness and paralysis.

Respiratory: Increased oral, pharyngeal and bronchial secretion, dyspnoea, bronchospasm, respiratory depression, respiratory arrest, tight chest and wheezing.

Allergic: Allergic reactions including anaphylaxis.

Skin: Rash and urticaria

Other: Increased sweating and salivation, miosis, vision changes, nystagmus and lacrimation.

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

Overdosage with neostigmine can cause cholinergic crisis, which is characterised by increasing muscle weakness. Myasthenic crisis is due to an increase in severity of the disease and may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Cholinergic crisis can lead to respiratory paralysis, which may result in death, while myasthenic crisis is extreme muscle weakness.

The differentiation between the two crises is extremely important as treatment is different for each. The two types of crises can be differentiated by the use of edrophonium and clinical judgement.

SYMPTOMS
Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretion, salivation, diaphoresis and miosis. Nicotinic effects consist of muscular cramps, fasciculations and general weakness. Bradycardia and hypotension may also occur.

TREATMENT
The treatment of cholinergic crisis requires the discontinuation of all cholinergic medication. The immediate use of atropine is also recommended, muscarinic effects are controlled with IV atropine sulphate (1 to 2 mg) followed by IM atropine sulphate every 2 to 4 hours. Assistance of ventilation may be required if respiration is severely depressed.

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 25ºC. 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 10 ampoules.

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
P O Box 65 231
Mairangi Bay
Auckland 0750

Ph: (09) 815 2664

9. DATE OF FIRST APPROVAL

19 March 2015

10. DATE OF REVISION OF THE TEXT

06 November 2019

SUMMARY TABLE OF CHANGES

Date of Revision	Section changed	Summary of new information
06 Nov 2019	• 1, 2, 4.2, 6.6 • 1, 4.6, 4.8, 5.2, 9, 10	• Spelling of Methylsulphate changed to Methylsulfate • Corrections in line with data sheet template.