Professional information for Neostigmine Methylsulphate Fresenius

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

Neostigmine Methylsulphate 0,5 mg/1 ml (Ampoules) Fresenius solution for injection

Neostigmine Methylsulphate 2,5 mg/1 ml (Ampoules) Fresenius solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml ampoule contains 0,5 mg Neostigmine methylsulphate.

Each 1 ml ampoule contains 2,5 mg Neostigmine methylsulphate.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless solution in amber ampoules.

pH: 4,5 – 6,5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Atony of the smooth muscle of the gastrointestinal tract: Paralytic ileus and abdominal distension.
- Atony of the smooth muscle of the urinary bladder: Post-operative dysuria.
- Myasthenia gravis.
- 2,5 mg/ml injection: Termination of the effects of competitive neuromuscular blocking agents such as d-tubocurarine and gallamine.

4.2 Posology and method of administration

Children's dose:

A suggested dose for children is 50 mcg per kg body mass.

Paralytic ileus, abdominal distension or dysuria:

0,5 to 1,0 mg subcutaneously or intramuscularly.

Termination of the effects of neuromuscular blockade:

2 to 3 mg given by slow intravenous injection over a period of 60 seconds. Additional Neostigmine Methylsulphate Fresenius may be given until the muscle power is normal but a total of 5 mg should not be exceeded. Atropine sulphate may be given concomitantly at a dose of 0,6 – 1,2 mg to control adverse effects. The recommended ratio of atropine to neostigmine given, varies from 1:2 to 1:3.

Myasthenia gravis:

1 to 2,5 mg daily in divided doses subcutaneously or intramuscularly.

Method of administration

Neostigmine Methylsulphate Fresenius may be administered by intravenous (IV), intramuscular (IM) or subcutaneous (SC) injection.

Neostigmine Methylsulphate Fresenius should be given very slowly by the IV route.

4.3 Contraindications

- Hypersensitivity to neostigmine methylsulphate or to any of the excipients of **Neostigmine Methylsulphate Fresenius** listed in section 6.1.
- Mechanical intestinal or urinary obstruction.
- In conjunction with depolarising muscle relaxants, such as suxamethonium.
- During cyclopropane or halothane anaesthesia, although it may be used after withdrawal of these medicines.
- Patients with diabetes, gangrene or peritonitis.

4.4 Special warnings and precautions for use

Allergic reactions have been reported.

Neostigmine Methylsulphate Fresenius should be used with extreme caution in patients who have undergone recent intestinal or bladder surgery, and in patients with bronchial asthma, as the parasympathomimetic action of neostigmine may cause bronchoconstriction. Patients who are hyperreactive to neostigmine experience a severe cholinergic reaction to the medicine.

When **Neostigmine Methylsulphate Fresenius** is given by injection, atropine should always be available to counteract any excessive muscarinic reactions.

When **Neostigmine Methylsulphate Fresenius** injection is used for myasthenia gravis; absence of clinical improvement may be indicative of overdosage or underdosage. Overdosage may lead to a cholinergic crisis characterised by muscle weakness affecting respiration. Increase in the severity of the disease may lead to myasthenic crisis also characterised by severe muscle weakness. Differential diagnosis can be aided by the edrophonium chloride test. If 0,1 ml (1 mg) or at most 0,2 ml (2 mg) of edrophonium chloride is given intravenously, a marked improvement indicates myasthenic crisis. Any other response, whether equivocal or exacerbation of symptoms, must be considered to be cholinergic in origin.

Bradycardia, with the potential for progression to asystole, may occur in patients receiving neostigmine by intravenous injection unless atropine is given simultaneously.

Neostigmine Methylsulphate Fresenius should be used with caution in patients with bronchial asthma, cardiovascular disorders including, cardiac dysrhythmias, pre-existing bradycardia, recent myocardial infarction or coronary occlusion, epilepsy, hypotension, hyperthyroidism, Parkinsonism, peptic ulceration or vagotonia.

As the severity of myasthenia gravis can fluctuate considerably, **Neostigmine Methylsulphate Fresenius** should be used with caution in patients with myasthenia gravis to avoid provoking a cholinergic crisis with increased muscular weakness.

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

Neostigmine Methylsulphate Fresenius should be used with caution in elderly patients, these patients may be more susceptible to dysrhythmias than younger patients.

As **Neostigmine Methylsulphate Fresenius** is excreted mainly by the kidneys, caution is advised in cases of impaired renal function and Addison's disease.

4.5 Interaction with other medicines and other forms of interaction

Anticholinesterase medicines are sometimes effective in reversing neuromuscular block induced by aminoglycoside antibiotics. However, aminoglycosides, clindamycin, colistin, cyclopropane and the halogenated inhalation anaesthetics possess neuromuscular blocking activity and may antagonize the effects of **Neostigmine Methylsulphate Fresenius**. These medicines must be used with care in conjunction with **Neostigmine Methylsulphate Fresenius** in patients with myasthenia gravis.

Hypotension and prolonged bradycardia have occurred in patients receiving beta-adrenoceptor blocking agents following administration of **Neostigmine Methylsulphate Fresenius.**

Some antidysrhythmic medicines such as quinidine may antagonise **Neostigmine Methylsulphate Fresenius** action by interfering with neuromuscular transmission. Chloroquinine, hydroxychloroquine, beta-blockers and lithium may also reduce the effectiveness of treatment with **Neostigmine Methylsulphate Fresenius**.

Administration of methylprednisone to patients receiving **Neostigmine Methylsulphate Fresenius** or pyridostigmine has exacerbated symptoms and produced profound weakness often necessitating assisted ventilation.

Neostigmine Methylsulphate Fresenius 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.

Neostigmine Methylsulphate Fresenius can inhibit the metabolism of suxamethonium and enhance and prolong its action. Prolonged respiratory depression with extended periods of apnoea may occur.

Atropine antagonises the muscarinic effects of **Neostigmine Methylsulphate Fresenius**, the interaction is utilised to counteract the muscarinic symptoms of the neostigmine toxicity.

4.6 Fertility, pregnancy and lactation

Pregnancy

Neostigmine Methylsulphate Fresenius is contraindicated during pregnancy and lactation (see section 4.3).

The severity of myasthenia gravis often fluctuates considerably during pregnancy, particular care is needed to avoid cholinergic crisis caused by overdosage; it has been reported that neonatal myasthenia may follow administration of large doses during pregnancy.

Breastfeeding

The amount of **Neostigmine Methylsulphate Fresenius** distributed into breast milk is very small, but breastfed infants need to be monitored.

4.7 Effects on ability to drive and use machines

There is no information of the effects of **Neostigmine Methylsulphate Fresenius** on the ability to drive and use machines. Patients should be advised to take special care before performing tasks requiring their attention, until they know how **Neostigmine Methylsulphate Fresenius** will affect them.

4.8 Undesirable effects

After the administration of **Neostigmine Methylsulphate Fresenius** the following side effects may occur:

System organ class (SOC)	**Frequency Not known (cannot be estimated from the available data)**
Immune system disorders	Hypersensitivity, angioedema, anaphylactic reaction
Nervous system disorders	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)
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	Anorexia, nausea, vomiting, abdominal cramps, diarrhoea, salivary hypersecretion. Increased intestinal motility may result in involuntary defecation.
Skin and subcutaneous tissue disorders	Hyperhidrosis
Musculoskeletal, connective tissue and bone disorders	Muscle cramps, fasciculation, weakness
Renal and urinary disorders	Urinary incontinence.

Reporting of suspected adverse reactions:

Health care providers are asked to report any suspected adverse drug reactions to the Holder of the Certificate of Registration at the following email address: safety.fksa@fresenius-kabi.com and to the relevant medicine's regulatory authority in the country where the product is marketed.

Reporting suspected adverse reactions after authorisation of **Neostigmine Methylsulphate Fresenius** is important. It allows continued monitoring of the benefit/risk balance of **Neostigmine Methylsulphate Fresenius**. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Overdosage may include cholinergic crisis, which is characterised by nausea, vomiting, diarrhoea, sweating, lacrimation, watery nasal discharge, eructation, increased peristalsis, involuntary defaecation, urination or the desire to urinate, flushing, muscle cramps, miosis, conjunctival congestion, ciliary spasm, brow ache, nystagmus, restlessness, agitation, fear, excessive dreaming, hallucinations, convulsions, slurred speech, tight chest, wheezing, increased bronchial secretion combined with bronchoconstriction, bradycardia and hypotension, cardiospasm, scattered fasciculations and eventually severe weakness and paralysis, convulsions and coma. Paradoxical effects may also occur due to interaction between nicotinic and muscarinic actions. Accordingly, there may be tachycardia and hypertension.

Death may follow due to cardiac arrest or central respiratory paralysis and pulmonary oedema. The major symptom of overdosage in myasthenia gravis is increased muscular weakness. 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 Fresenius should be discontinued immediately. Give atropine sulphate 1 – 2 mg intravenously to control the muscarinic effects.

The dose may be repeated intramuscularly every 2 – 4 hours as necessary to control muscarinic symptoms. Further treatment is symptomatic and supportive. Atropine overdosage should be avoided as tenacious secretions and bronchial plugs may result.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 5.3. Cholinomimetics (cholinergics)

Pharmacotherapeutic group: Parasympathomimetics, anticholinesterases

ATC code: N07AA.

Neostigmine is a reversible cholinesterase inhibitor which intensifies the muscarinic and nicotinic effects of acetylcholine. It is used mainly for its action on skeletal muscle and less frequently to increase the activity of smooth muscle.

5.2 Pharmacokinetic properties

Neostigmine is a quaternary ammonium compound and is absorbed poorly after oral administration. The major site of uptake is in the liver. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sulphuric acid (for pH-adjustment)

Water for injection.

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

0,5 mg ampoules: 48 months.

2,5 mg ampoules: 60 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

6.5 Nature and contents of container

1 ml amber, type 1 glass OPC ampoules packed in blister trays and placed in an outer carton.

Boxes of 10 ampoules.

6.6 Special precautions for disposal and other handling

If only part used discard the remaining solution.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Fresenius Kabi Manufacturing SA (Pty) Ltd

6 Gibaud Road

Korsten

Port Elizabeth 6020

South Africa

8. REGISTRATION NUMBERS

Neostigmine Methylsulphate 0,5 mg/1 ml (Ampoules) Fresenius: C907 (Act 101/1965)

Neostigmine Methylsulphate 2,5 mg/1 ml (Ampoules) Fresenius: W/5.3/260

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Neostigmine Methylsulphate 0,5 mg/1 ml (Ampoules) Fresenius: Not applicable.

Neostigmine Methylsulphate 2,5 mg/1 ml (Ampoules) Fresenius: 19 September 1989

10. DATE OF REVISION OF THE TEXT

20 September 2021