

PRODUCT SUMMARY

1. NAME OF THE MEDICINAL PRODUCT

Neostigmine Injection BP 2.5mg in 1ml.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1ml of solution contains neostigmine methylsulphate BP

3. PHARMACEUTICAL FORM

Clear, colourless, sterile aqueous solution intended for parenteral administration to human beings.

4 CLINICAL PARTICULARS

4.1. Therapeutic Indications

Neostigmine inhibits cholinesterase enzyme activity and thus potentiates the physiological actions of acetylcholine.

Neostigmine Injection BP has the following indications : Antagonist to non-depolarising neuromuscular blockade; myasthenia gravis; paralytic ileus; post-operative urinary retention.

4.2. Posology and Method of Administration

Routes of administration : Intramuscular, subcutaneous or slow intravenous injection.

When administering Neostigmine Injection BP, a syringe of atropine sulphate should always be available to counteract possible severe cholinergic reactions. Where the intravenous route is used, administration must be by very slow injection.

Antagonist to non-depolarising neuromuscular blockade.

Generally, reversal of neuromuscular blockade should not be attempted until there are signs of spontaneous recovery from paralysis. The patient should be well ventilated and a patent airway maintained until normal respiration is fully restored.

Adults and children : A single dose of Neostigmine Injection BP 0.05 - 0.07mg/kg bodyweight and atropine sulphate 0.02 - 0.03mg/kg body-weight, by slow intravenous injection over 60 seconds, will usually achieve complete reversal of non-depolarising neuromuscular blockade within 5 - 15 minutes. Additional neostigmine may be required but a total of 5mg for adults and 2.5mg for children should not be exceeded. The two drugs are often administered simultaneously, but in patients with bradycardia the pulse rate should be increased to about 80/minute with atropine before giving the neostigmine.

Although the speed of recovery from neuromuscular blockade is determined mainly by the intensity of the block at the time of antagonism, it is also influenced by other factors such as the presence of drugs (e.g. anaesthetics, antibiotics, antiarrhythmic agents) and physiological changes (e.g. electrolyte and acid-base disturbances, renal impairment). Because these factors may prevent successful reversal of blockade or may lead to re-rarisation following apparently successful reversal, it is essential that patients be observed carefully until such possibilities have been excluded.

MYASTHENIA GRAVIS

Adults: Doses of 1 - 2.5mg may be given by intramuscular or subcutaneous injection at intervals during the day when strength is most needed. The usual duration of action of a dose is 2 - 4 hours. The total daily dose is usually in the range of 5 - 20mg, but higher doses may be required by some patients.

Newborn infants: Neonatal myasthenia may be treated with an initial dose of 0.1mg intramuscularly. Thereafter, the dosage should be titrated individually and is usually in the range 0.05 - 0.25mg by injection. Treatment is not usually needed beyond eight weeks of age, except in the rare conditions of congenital and familial infantile myasthenia.

Older children: A dose of 0.2 - 0.5mg may be given by injection as required. The dosage should be adjusted according to the response.

OTHER INDICATIONS

Adults: The usual dose is 0.5 - 2.5mg by subcutaneous or intramuscular injection.

Children: The usual dose is 0.125 - 1mg by injection.

The frequency of these doses may be varied according to the needs of the patient.

Elderly: There are no specific dosage recommendations for elderly patients.

4.3. Contra-Indications

Neostigmine should not be administered to patients with gastro-intestinal or urinary obstruction. Neostigmine should not be given to patients with a known hypersensitivity to the drug. Neostigmine should not be used in conjunction with depolarising muscle relaxants such as suxamethonium, as the neuromuscular blockade may be potentiated and prolonged apnoea may result.

4.4. Special Warnings and Precautions for Use

Neostigmine should be used with particular caution in patients with myotonic dystrophy, bronchial asthma, bradycardia, recent coronary occlusion, hypotension, vagotonia, peptic ulceration, epilepsy or Parkinsonism.

Care should be taken in patients with hyperthyroidism, renal impairment (dose reduction might be required).

Bradycardia may occur, possibly to a serious degree, with intravenous injection of neostigmine unless atropine is given simultaneously. The requirement for neostigmine is usually decreased after thymectomy, or when additional therapy (steroids, immunosuppressant drugs) is given.

Neostigmine should not be administered during cyclopropane or halothane anaesthesia, although it may be used after withdrawal of these agents.

Although there is no evidence to suggest that neostigmine has any special effects in elderly patients, these patients may be more susceptible to dysrhythmias than younger adults.

4.5. Interaction with other Medicinal Products and other Forms of Interaction

- Anti-arrhythmic: Effects of neostigmine antagonised by procainamide and quinidine; possibly antagonized by propafenone;
- Antibacterials: Effects of neostigmine antagonised by aminoglycosides, clindamycin and polymyxins;
- Antimalarials: Effects of neostigmine may be diminished because of potential for chloroquine and hydroxychloroquine to increase symptoms of myasthenia gravis;
- Antimuscarinics: Effects of parasympathomimetics antagonised by antimuscarinics;
- Beta-blockers: Effects of neostigmine antagonised by propranolol;
- Lithium: Effects of neostigmine antagonised by lithium;
- Muscle Relaxants Neostigmine enhances effects of suxamethonium. Neostigmine antagonises effects of non-depolarising muscle relaxants.

Atropine is an antidote to the muscarinic effects of neostigmine.

4.6. Pregnancy and Lactation

The safety of neostigmine in pregnancy and lactation has not been established. Although experience with neostigmine in pregnant patients with myasthenia gravis has revealed no untoward effects of the drug on the course of pregnancy, the possible hazard to mother and child must be weighed against the potential benefits in individual cases. Although only negligible amounts of neostigmine appear to be excreted in breast milk, consideration should be given to the possible effects on the breast-fed infant.

4.7. Effects on Ability to Drive and Use Machines

Nil.

4.8. Undesirable Effects

Possible side effects may include nausea, vomiting, increased salivation, diarrhoea, abdominal cramps and bradycardia. Allergic reactions have been reported.

4.9. Overdose

Overdosage may lead to a 'cholinergic crisis' characterised by both muscarinic and nicotinic effects. Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, involuntary defecation and urination, sweating, salivation, increased bronchial secretions, miosis, bradycardia and hypotension.

Nicotinic effects may include involuntary twitching, fasciculations and generalised weakness. Muscle weakness is a symptom both of cholinergic crisis and of myasthenia gravis. It is extremely important to distinguish between these two conditions as their treatments are radically different.

Atropine sulphate 1 - 2mg intravenously is an antidote to the muscarinic effects of neostigmine. Supportive treatment should be given as required; artificial respiration should be instituted if respiratory depression is severe.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Acetylcholine is a chemical transmitter with a wide range of actions within the body. Its action is transient as it is rapidly destroyed by cholinesterase. Neostigmine inhibits cholinesterase and thus prolongs and intensifies the physiological actions of acetylcholine.

The main actions of neostigmine that are of therapeutic importance are concerned with the skeletal neuromuscular junction, the intestine and the smooth muscle of the urinary tract. Neostigmine reverses the antagonism caused by non-depolarising neuro-muscular blocking agents. The drug augments the motor activity of the small and large bowel and it causes contraction of smooth muscle fibres of the ureters and urinary bladder.

5.2 Pharmacokinetic Properties

Neostigmine is a quaternary ammonium compound and is poorly absorbed from the gastrointestinal tract. 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.

5.3 Pre-clinical Safety Data

No further relevant information other than that which is included in other sections of the Summary of Product Characteristics.

PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Dilute Sulphuric Acid BP
Water for Injections BP

6.2 Incompatibilities

None known.

6.3 Shelf-Life

4 years

6.4 Special Precautions for Storage

Keep in outer carton.
Do not store above 25°C.

6.5 Nature and Content of Container

1ml, amber glass ampoules, glass type 1 Ph. Eur. Packed in cardboard cartons to contain 10 x 1ml ampoules.

6.6 Special precautions for disposal

For SC, IV, or IM injection.
Use as directed by the physician.

If only part used, discard the remaining solution.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

Antigen International Ltd.,
Roscrea,
Co. Tipperary,
Ireland.

8. MARKETING AUTHORISATION NUMBER(S)

PL 2848/5916R.

**9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE
AUTHORISATION**

1997

10. DATE OF (PARTIAL) REVISION OF THE TEXT

April 2008