SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Neostigmine LPH 15 mg tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 15 mg neostigmine bromide.

Excipient with known effect: lactose monohydrate 75 mg.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Tablet
White tablets, 6 mm in diameter, having embossed on one side the inscription “Mi”.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Neostigmine LPH is indicated for adults and children over 6 years of age for:
- Symptomatic treatment of myasthenia gravis;
- Treatment of paralytic ileus;
- Post-operative urinary retention following the exclusion of the mechanical obstruction diagnosis.

4.2 Dosage and Method of Administration

Oral forms have a slower onset of action compared with intravenous administration, but the duration of action is longer and the intensity of action more uniform.

Myasthenia gravis

Dosage

Adults
The recommended dose is of 15 - 30 mg neostigmine bromide, administered during the day, within the period in which muscle strength is needed (for example, on rising and before mealtimes). The scheme of administration must be established for each patient individually and the dose must be adjusted when necessary. Generally, the duration of action is of approximately 2 - 4 hours.

The total daily dose is in the range of 75 - 375 mg neostigmine bromide (5 - 25 tablets of Neostigmine LPH). Some patients may require higher doses, but the possibility of occurrence of a cholinergic crisis must be considered.

Generally, the treatment must be administered also during night-time.
Children over 6 years of age and teenagers
The recommended dose is of 15 mg of neostigmine bromide (1 tablet of Neostigmine LPH).

Generally, the usual dose must be adjusted based on the clinical response and is comprised between 15-90 mg of neostigmine bromide per day.

Other indications
Adults: the recommended dose is of 15 - 30 mg of neostigmine bromide (1 - 2 tablets of Neostigmine LPH).

Children over 6 years of age: 2.5 – 15 mg neostigmine bromide for one dose.

The frequency of daily administration of these doses is established for each patient individually.

Elderly:
Dose adjustments are not required for elderly patients.

Method of Administration
Tablets must be swallowed wholly, with a glass of water.

4.3 Contraindications

Hypersensitivity to neostigmine bromide, to other bromides or to any of the excipients listed under section 6.1
Gastro-intestinal mechanical obstruction or of the urinary tract.
Bronchial asthma
Parkinson's Disease
Peritonitis

4.4 Special Warnings and Precautions for Use

The greatest therapeutic benefit is obtained in the long duration treatment in patients in which swallowing disturbances do not occur. In acute crises of myasthenia, with respiratory disturbances, the intravenous administration must be considered, following to make as soon as possible the transition to the oral form.

The patient must be advised to keep a daily record of the symptoms, which is useful in establishing the optimal therapeutic scheme.

Prior to the initiation of the treatment with neostigmine, other causes of muscular strength reduction must be eliminated.

The medicine must be administered with caution in patients with bronchial asthma, bradycardia, acute coronary syndrome, cardiac arrhythmias, hypotension, peptic ulcer, vagotonia, hyperthyroidism or epilepsy.

It must not be administered in high doses in patients with disorders that cause the increase of intestinal absorption of neostigmine.

High doses can cause paradoxal muscular block.

High doses of neostigmine bromide can cause muscarinic-type effects, which can require administration of atropine and of other anticholinergic medicines. Decrease of gastro-intestinal motility given by anticholinergics may influence absorption of neostigmine bromide .

The strict monitoring of treatment-induced manifestations is recommended, as myasthenia crises and cholinergic crises given by overdose are similar as symptomatology, but the treatment is different.

The requirement for neostigmine can decrease after thymectomy, or when is administered in association with immunosuppressant medicines or glucocorticoids.

Neostigmine LPH contains lactose monohydrate. Patients with rare hereditary disorders such as galactose intolerance, lactase deficiency (Lapp) or glucose-galactose malabsorption syndrome should not take this medicine.

4.5 Interaction with Other Medicinal Products and Other Forms of Interaction

Neostigmine effect can be antagonized by medicines that interfere with neuromuscular transmission: neomycin, streptomycin, kanamycin, clindamycin, colistin. These antibiotics must be used during treatment with neostigmine only if absolutely necessary. Neostigmine doses must be adjusted accordingly.

Respiratory depressant effect of barbiturates and morphine may be potentiated by neostigmine bromide.
Atropine and other anticholinergics may be administered in combination with neostigmine bromide, because it antagonises the muscarinic-type effect, in particular bradycardia and exocrine glands hypersecretion. However, the routine administration is not recommended as the muscarinic-type effects may be the first signs of overdose and masking them by administering atropine may prevent the early recognition of a cholinergic crisis.

Neostigmine should not be administered during anaesthesia with cyclopropane or halothane; it can still be used after discontinuing the administration of these medicines.

Neostigmine administration in combination with beta-blocker medicines should be approached cautiously due to the risk of bradycardia.

Generally, anaesthetics, antiarrhythmic medicines and other medicines that interfere with neuromuscular transmission should be used with caution in patients with myasthenia gravis receiving neostigmine.

Neostigmine administration in combination with choline esters is contraindicated because it favours the installation of neuromuscular block and can extend apnoea.

4.6 Fertility, Pregnancy and Lactation

The safety of neostigmine administration during pregnancy and lactation has not been established.

Therefore, the administration of neostigmine during pregnancy in pregnant women with myasthenia gravis can be made only after the assessment of the therapeutic ratio to mother / potential risk to the foetus.

In terms of administration for intestinal or bladder atony, the administration of neostigmine during pregnancy is not recommended.

In man, neostigmine bromide is excreted in the milk; therefore, the administration is not recommended during breastfeeding.

In mothers with myasthenia gravis breastfeeding is contraindicated due to the passage of cholinergic anti-receptors in breast milk.

4.7 Effects on Ability to Drive and Use Machines

Through the adverse reactions it may cause, neostigmine may affect the ability to drive and use machines.

4.8 Undesirable effects

The most common adverse reactions are due to the cholinergic action and are represented by nausea, hypersalivation, bradycardia, faintness, myosis, abdominal cramps and muscle twitching. These side effects may be reversible with dose reduction or by administering atropine.

Other adverse reactions that can appear are presented below:

Immune system disorders: reactions of hypersensitivity and anaphylaxis.

Nervous system disorders: dizziness, convulsions, unconsciousness, drowsiness, headache, dysarthria.

Eye disorders: myosis and vision disturbances.

Cardiac disorders: arrhythmia (including bradycardia, tachycardia, atrioventricular block, nodal rhythm), ECG changes, cardiovascular arrest, syncope.

Vascular disorders: arterial hypotension.

Respiratory, thoracic and mediastinal disorders: increased bronchial secretions, respiratory depression, bronchospasm.

Skin and subcutaneous tissue disorders: rashes and urticaria.

Gastrointestinal disorders: nausea, vomiting, flatulence and increased peristalsis, diarrhoea.

Renal and urinary disorders: increased frequency of micturition.

Musculoskeletal and connective tissue disorders: muscle cramps, twitching, arthralgia.

General and topical administration disorders: diaphoresis, feeling of heat in the skin, weakness.

4.9 Overdose

Neostigmine overdose causes a cholinergic crisis, manifested by increased muscle weakness and respiratory muscle damage, which can lead to death. Since the cholinergic crisis has manifestations similar with the myasthenia gravis crisis, a correct diagnosis is imposed, as therapeutic measures are radically different.
The two types of crises can be differentiated both clinically and by using edrophonium chloride.
The treatment of the cholinergic crisis requires the immediate discontinuation of the neostigmine treatment.

Other manifestations of overdose are:
- muscarinic effects - abdominal cramps, increased peristalsis, diarrhoea, nausea, vomiting, hypersalivation, increased bronchial secretions, sweating and myosis.
- nicotinic effects: muscle cramps, twitching, generalized muscle weakness. Bradycardia and hypotension may occur.
Atropine can be used as antidote for fighting muscarinic effects. Measures for sustaining vital functions may be required, e.g. oro-tracheal intubation and assisted ventilation.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: other nervous system medicines, parasympathomimetics; anticholinesterases, ATC code: N07AA01

Neostigmine bromide belongs to the group of parasympathomimetic substances with indirect action (anticholinesterases), moderate reversible.
Neostigmine inhibits the hydrolysis of acetylcholine by competing with it for binding to acetylcholinesterase at sites where cholinergic transmission occurs. Neostigmine enhances the cholinergic action by facilitating the transmission of impulses at the neuromuscular junction. It has effect on skeletal muscles and possibly on the nerve ganglia cells and neurons in the central nervous system.

5.2 Pharmacokinetic Properties

Neostigmine bromide is absorbed in a small proportion from the gastro-intestinal tract. A dose of 15 mg neostigmine bromide administered orally is equivalent to 0.5 mg of neostigmine methylsulphate administered intravenously.

The plasma elimination half-life is of approximately 1.3 hours.

Neostigmine is hydrolysed by cholinesterase and is metabolised at the level of hepatic microsomal enzymes. The proportion of binding to serum albumin is between 15 and 25%.

5.3 Preclinical Safety Data

Not available.

6. PHARMACEUTICAL PROPERTIES

6.1 List of excipients

Lactose monohydrate
Magnesium stearate
Talc
Anhydrous colloidal silicon dioxide
Sodium starch glycolate type A

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years

6.4 Special Precautions for Storage

Store below 25°C, in the original packaging.

6.5 Nature and Contents of the Packaging

Carton box with one PVC/Al blister containing 20 tablets.
Carton box with 3 PVC/Al blisters, each containing 20 tablets.
Carton box with 100 PVC/Al blisters, each containing 20 tablets.

6.6 Special Precautions for Disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Labormed Pharma S.A.
Bd. Theodor Pallady nr. 44B, 3rd City District, Bucharest
Romania

8. MARKETING AUTHORISATION NUMBER

6677/2014/01-02-03

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Authorisation renewal - July 2014

10. DATE OF REVISION OF THE TEXT

July 2014