1 NAME OF THE MEDICINAL PRODUCT

Pyridostigmine 30, Pyridostigmine 60

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of **Pyridostigmine 30** contains 30mg pyridostigmine bromide
Each tablet of **Pyridostigmine 60** contains 60mg pyridostigmine bromide
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablets for oral use

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of myasthenia gravis.

4.2 Posology and method of administration

Adults
Oral dosage forms:
Multiple doses of 30 to 120 mg are given at intervals throughout the day.

The total daily dose is usually in the range of 120 - 1200 mg but doses higher than these may be needed by some patients according to dose titration.

Children
Children under 6 years old should receive an initial dose of 30 mg of pyridostigmine bromide.
Children 6 - 12 years old should receive 60 mg. Dosage should be increased gradually, in increments of 30 mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range to 30 - 360 mg.

Special populations
Elderly
There are no specific dosage recommendations in elderly patients.

Renal impairment
Pyridostigmine is mainly excreted unchanged by the kidney, therefore lower doses may be required in patients with renal disease and treatment should be based on titration of drug dosage to effect.

Hepatic impairment
There are no specific dosage recommendations in patients with hepatic impairment.

4.3 Contraindications

Pyridistigmine is contraindicated for patients with:
- Hypersensitivity to the active substance, bromides or to any of the excipients listed in section 6.1
- Mechanical gastro-intestinal or urinary obstruction

4.4 Special warnings and precautions for use

Extreme caution is required when administering to patients with obstructive respiratory diseases like bronchial asthma and chronic obstructive pulmonary disease (COPD).

Care should also be taken in patients with:
- Arrhythmias such as bradycardia and AV block (elderly patients may be more susceptible to dysrhythmias than the young adult)
- Recent coronary occlusion
- Hypotension
- Vagotonia
- Peptic ulcer
- Patients who have undergone gastrointestinal surgery
- Epilepsy or Parkinsonism
- Hyperthyroidism

When relatively large doses of pyridostigmine are taken by myasthenic patients it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects. It should be noted that the slower gastrointestinal motility caused by these drugs may affect the absorption of pyridostigmine.

In all patients the possibility of "cholinergic crisis", due to overdosage of pyridostigmine, and its differentiation from "myasthenic crisis", due to increased severity of the disease, must be borne in mind. Both types of crisis are manifested by increased muscle weakness, but whereas myasthenic crisis may require more intensive anticholinesterase treatment, cholinergic crisis calls for immediate discontinuation of this treatment and institution of appropriate supportive measures, including respiratory assistance.

The requirement for pyridostigmine is usually markedly decreased after thymectomy or when additional therapy (steroids, immunosuppressant drugs) is given.

Patients with rare hereditary problems of galactose intolerance, the total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Immunosuppressant drugs
The requirement for pyridostigmine bromide could be decreased when additional therapy (steroids, immunosuppressant drugs) is given although peak plasma concentration and AUC of pyridostigmine may be decreased by high doses of corticosteroids.

Methylcellulose
Methylcellulose and medicine containing methylcellulose as excipients can completely inhibit absorption of pyridostigmine bromide.

Antimuscarinics
Atropine and Hyoscine antagonise the muscarinic effects of pyridostigmine bromide.It should be noted that the slower gastro-intestinal motility caused by these drugs may affect the absorption of pyridostigmine bromide.

Muscle Relaxants
Pyridostigmine antagonises the effect of non-depolarising muscle relaxants (e.g. pancuronium and vecuronium). Pyridostigmine may prolong the effect of depolarising muscle relaxants (e.g. suxamethonium).

Others
Aminoglycoside antibiotics, local and some general anesthetics, antiarrhythmic agents, and other drugs that interfere with neuromuscular transmission may interact with pyridostigmine bromide.

4.6 Fertility, Pregnancy and lactation

Pregnancy:
The safety of pyridostigmine 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 pyridostigmine in pregnant patients with myasthenia gravis has revealed no untoward effect of the drug on the course of pregnancy. Pyridostigmine bromide crosses the placenta barrier. Excessive doses of pyridostigmine bromide should be avoided; the newborn child should be monitored for possible effects.

Intravenous application of pyridostigmine bromide can induce contraction of the uterus (especially in the last period of pregnancy).

As the severity of myasthenia gravis often fluctuates considerably, particular care is required to avoid cholinergic crisis, due to overdosage of the drug, but otherwise management is no different from that in nonpregnant patients.

Breastfeeding:
Observations indicate that only negligible amounts of pyridostigmine are excreted in breast milk; nevertheless, due regard should be paid to possible effects on the breast-feeding infant

4.7 Effects on ability to drive and use machines

Due to miosis and accommodation disorders caused by pyridostigmine bromide or an inadequate treatment of Myasthenia gravis, Pyridostigmine may impair visual acuity and consequently the ability to react as well as the ability to drive and use machines.

4.8 Undesirable effects

As with all cholinergic products, Pyridostigmine may have unwanted functional effects on the autonomic nervous system. Muscarine-like adverse effects may be exhibited as nausea, vomiting, diarrhoea, abdominal cramps, increased peristaltic and increased bronchial secretion, salivation, bradycardia and miosis.

The primary nicotinic effects are muscle spasms, fasciculation and muscular weakness.

Adverse reactions are listed below according to system organ class and frequency.

Frequencies are defined according to the following convention:
Very common (≥1/10), Common (≥1/100 to <1/10), Uncommon (≥1/1,000 to <1/100), Rare (≥1/10,000 to <1/1,000) Very rare (<1/10,000) Not known (cannot be estimated from the available data)

Eye disorders
Frequency not known: Miosis, increased lacrimation, accommodation disorders

Cardiac disorders
Frequency not known: Arrhythmia (including bradycardia, tachycardia, AV block), as well as syncope and hypotension (see section 4.9)

Respiratory, thoracic and mediastinal disorders
Frequency not known: Increased bronchial secretion combined with bronchoconstriction

Gastrointestinal disorders
Frequency not known: Nausea, vomiting, diarrhoea, abdominal cramps, gastrointestinal hypermotility, salivary hypersecretion

Skin and subcutaneous tissue disorders
Frequency not known: Rash (disappears usually soon after ceasing of medication. Bromide containing medicines

should no longer be used), hyperhydrosis

Musculoskeletal and connective tissue disorders
Frequency not known: Increased muscle weakness fasciculation (muscle twitching), tremors and muscle cramps or muscle hypotonia (see section 4.9)

Renal and urinary disorders
Frequency not known: Urinary urgency
Because these symptoms may be an indication of cholinergic crisis, the physician should be notified immediately to clarify the diagnosis (see section 4.9)

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il/

4.9 Overdose
Overdosage may lead to “cholinergic crisis” characterised by severe muscarinic and nicotinic symptoms of marked muscle weakness. Cardiovascular and respiratory failure may occur.

Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretions, salivation, hyperhydrosis and miosis. Nicotinic effects consist of muscular cramps, fasciculations and general weakness up to paralysis.

Hypotension up to cardiovascular collapse, bradyarrhythmia, up to cardiac arrest may also occur.

Central nervous system effects may include agitation, confusion, slurred speech, nervousness, irritation, visual hallucinations.

Artificial ventilation should be instituted if respiration is severely depressed.
Atropine sulphate 1 to 2mg intravenously is an antidote to the muscarinic effects.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Nervous system, parasympathomimetics, anticholinesterases, pyridostigmine, ATC code: N07AA02.

Pyridostigmine is an antagonist to cholinesterase, the enzyme which normally destroys acetylcholine. The action of pyridostigmine can briefly be described, therefore, as the potentiation of naturally occurring acetylcholine. Pyridostigmine has a more prolonged action than neostigmine although it is somewhat slower to take effect (generally taking 30 - 60 minutes). Because it has a weaker "muscarinic" action than neostigmine, it is usually much better tolerated by myasthenic patients in whom the longer action is also an advantage.

5.2 Pharmacokinetic properties
Oral pyridostigmine bromide is poorly absorbed. Maximum plasma concentrations occur at 1 to 2 hours and it is eliminated by the kidney largely unchanged with a half-life of 3 to 4 hours.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Lactose, corn starch stearic acid, silicone dioxide colloidal, ethyl cellulose, magnesium stearate.

6.2 Incompatibilities
None known.

6.3 Shelf life
The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage
Store below 25°C in original package

6.5 Nature and contents of container
Pyridostigmine 30: Blister packs containing 21 tablets.
Pyridostigmine 60: Blister packs containing 30 tablets.

7 REGISTRATION HOLDER
Rafa Laboratories Ltd, POB 405, Jerusalem 9100301

Registration no:

Pyridostigmine 30: 051 77 25053
Pyridostigmine 60: 145 41 31869

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