Proposed Package Insert

1. NAME OF THE MEDICINAL PRODUCT

PREFER 60 (Pyridostigmine Bromide Tablets USP 60 mg)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg of Pyridostigmine bromide.
Each Tablet contains 288.750 mg Anhydrous Lactose.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Uncoated tablet.
White to off white, round, flat-faced tablet debossed with "C60" one side and quadrisect scored on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Pyridostigmine Bromide Tablets USP 60 mg is useful in the treatment of myasthenia gravis

4.2 Posology and method of administration

When using Pyridostigmine Bromide Tablets USP 60 mg it is important to remember that the full effect appears gradually, usually within 15-30 minutes.

Use in Adult
1 - 3 tablets (60 -180 mg) 2 - 4 times daily, or higher doses if required. The total daily dose is usually in the range of 5 - 20 tablets (300 -1200 mg) but doses higher than these may be needed by some patients.

Use in Children
Children under 6 years old should receive an initial dose of 30 mg of Pyridostigmine Bromide Tablets USP 60 mg. Children 6 - 12 years old should receive 60 mg. Dosage should increase gradually, in increments of 15 - 30 mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30 - 360 mg.

Patients with swallowing difficulties can take tablets broken into small pieces instead of the whole tablets. In myasthenia gravis, one dose is effective for approximately four hours during the day whilst at night (owning to reduced physical activity), a longer duration of effect of around 6 hours can be expected. It is recommended that the times of administration be chosen so that the maximum effect coincides with the most strenuous physical exertion, e.g. when getting up and at mealtimes.

Special Dosage Instructions
The required dose must be carefully titrated when used in paediatrics. In cases of neonatal myasthenia, generally one treatment with neostigmine (Prostigmin) is preferred. However, if this appears unsuitable due to excessively cholinergic side effects, then Pyridostigmine Bromide Tablets USP 60 mg can be administered. In these cases, the following serves as a rough guideline: 5 - 10 mg by mouth in tablet form, 30 - 60 minutes before food. Treatment over the eight week if life is required only in extremely rare cases of congenital and familial infantile myasthenia. Pyridostigmine is mainly eliminated unchanged via the kidneys. Lower doses may therefore be indicated in patients presenting with kidney disease. The dose should be adjusted in line with the desired effect.

Method of administration
For oral use. Pyridostigmine Bromide Tablets USP 60 mg should be taken with water.

4.3 Contraindications

Pyridostigmine is contraindicated in mechanical obstruction of the intestinal or urinary tract and known allergy to the preparation.

Proposed Package Insert

4.4 Special warnings and precautions for use

Precautions
Pyridostigmine is mainly excreted unchanged by the kidney. Therefore, lower does may be required in patients with renal diseases, and treatment should be based on titration of drug dosage to effect.

Warnings
Although failure of patients to show clinical improvement may reflect under dosage, it can also be indicative of overdose. As is true of all cholinergic drugs, overdosage of pridostigmine may result in cholinergic crisis, a state characterized by increasing muscle weakness which, through involvement of the muscles of respiration, may lead to death. Myasthenic crisis due to an increase in the severity of the disease is also accompanied by extreme muscle weakness, and thus may be difficult to distinguish from cholinergic crisis on a symptomatic basis. Such differentiation is extremely important, since increases in doses of pyridostigmine or other drugs of this class in the presence of cholinergic crisis or of a refractory or "Insensitive" state could have a grave consequence. The different diagnosis of the two types of crisis may require the use of Tensilon (edrophonium chloride) as well as clinical judgment. The treatment of the two conditions obviously differs radically. Whereas the presence of myasthenia gravis suggests the need for more intensive anti-cholinergic therapy, the diagnosis of cholinergic crisis, calls for the prompt withdrawal of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended. Atropine may abolish or obtund gastrointestinal side effects or other muscarinic reactions: but such use, by masking the signs of overdose, can lead to inadvertent induction of cholinergic crisis

Lactose intolerance: This tablet contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency of glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

Pyridostigmine antagonizes the action of curare-like non-depolarising muscle relaxants. Atropine counteracts the cholinergic effects of pyridostigmine.

4.6 Fertility, pregnancy and lactation

Reproduction studies in laboratory animals have not ndicated any risks to the foetus but no controlled studies have so far been conducted in pregnant women. Therefore, this medication should only be used during pregnancy strictly as directed, with careful dosing and under medical supervision.

Since the possibility of pyridostigmine diffusing into breast milk cannot be ruled out, nursing mothers are advised to refrain from breast feeding their babies during treatment.

4.7 Effects on ability to drive and use machines

The effects of Pyridostigmine Bromide Tablets USP 60 mg on the ability to drive and operate machinery have not been established.

4.8 Undesirable effects

Like all cholinergic drugs, pyridostigmine can have undesirable functional effects on the autonomic nervous system.

Muscarine-type effects can manifest themselves as nausea, vomiting, diarrhoea, stomach cramps, increased peristalsis and bronchial secretion, salivation and lacrimation as well as bradycardia and miosis. Nicotine-type side effects consist mainly of muscle cramps, muscle twitches and muscle weakness.

Like other bromide-containing drugs, therapy with pyridostigmine bromide can occasionally cause skin rash, although this generally disappears rapidly once medication has been discontinued. Further use of pyridostigmine bromine or other bromine-containing preparations is then contra-indicated.

4.9 Overdose

Symptoms:
Overdose of pyridostigmine or other cholinesterase inhibitors may lead to cholinergic crisis that manifeste themselves in, among other things, pronounced muscle weakness or exacerbated muscle weakness in patients with myasthenia. If such a situation is overlooked, life is endangered due to paralysis of the respiratory muscles. Bradycardia and paradoxically, tachycardia are other possible effects.

Treatment:
Counter measures include the immediate withdrawal of pyridostigmine or other cholinergic and the slow intravenous administration of 1 - 2 mg atropine sulphate. Depending on the pulse rate, this dose is to be repeated at intervals of two to four hours if required.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: **Anticholinesterases**
ATC code: N07AA02

Pyridostigmine is an cholinesterase inhibitor. It is characterized by the gentle onset, smooth course, comparatively long duration and gradual decline of its cholinergic action. Pyridostigmine has an antagonistic effect on non-deplorising muscle relaxants only. It has a synergistic effect on depolarizing muscle relaxants.

5.2 Pharmacokinetic properties

Absorption
Pyridostigmine, like other medicines of the same type, is not fully absorbed from the intestinal tract. Bioavailability following oral administration is 3-8%. Considerably higher doses are therefore required for oral as opposed to parenteral administration.

Distribution
Peak plasma concentrations were reached in the fasting state approximately 1.5 – 2 hours after administration of 120mg pyridostigmine. The increase in active ingredient is delayed when taken with food. The distribution volume averages 1.4 L/kg body weight. Pyridostigmine is not noticeably bound to plasma proteins and does not cross the blood-brain barrier. Blood plasma levels of 20-60 ng/ml are required in order to obtain the desired therapeutic effect with myasthenia gravis.

Metabolism
Pyridostigmine is metabolized to 3-hydroxy-N-methylpyridine and other unidentified metabolites.

Elimination
Mean values of around 1.5 hours are given for the elimination half-life. This can, however, be prolonged up to three times over in individual cases. Mean plasma clearance in healthy volunteers is given as 0.36 – 0.64 L/kg/h. No confirmed data are available regarding the potential accumulation of unchanged pyridostigmine or active metabolites. Since the dosage must, in any case, be adjusted individually, this point is devoid of practical significance. Pyridostigmine is largely eliminated unchanged (75 – 81 %) via the kidneys. One part (18 – 21 %) appears as the 3-hydroxy-N-methyl-pyridine metabolite in the urine. Other unidentified metabolites account for 1 – 4 %.

Kinetics in Specific Clinical Situations
Impaired liver function has no relevant effect on the kinetics of Pyridostigmine. The elimination half-life increases approximately four-fold and plasma clearance can fall by up to around one-fifth in the case of age of disease induced kidney failure.

5.3 Preclinical safety data

Not applicable

Proposed Package Insert

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:
Anhydrous lactose
Colloidal silicon dioxide
Stearic acid

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30ºC. Store in the original package to protect from light and moisture.

6.5 Nature and contents of container

10 tablets packed in ALU-ALU blister and 10 such blisters packed in 1 carton along with pack insert.
Box of 100 tablets.

6.6 Special precautions for disposal and other handling

No special requirements

7. MANUFACTURER

Centaur Pharmaceuticals Pvt. Ltd.
Plot No.4, Hinjewadi Phase II, International Biotech Park, Pune, Maharashtra, IN-411057 India

8. PRODUCT REGISTRATION HOLDER

Mansa Healthcare Sdn Bhd
B-05-3A, 3 Two Square, No 2, Jalan 19/1, 46300 Petaling Jaya, Selangor, Malaysia

9. MARKETING AUTHORISATION NUMBER(S)

MALxxxxxxxxAZ

10. DATE OF REVISION OF THE TEXT

1-Mar-2025