PRODUCT MONOGRAPH

PrMESTINON® Tablets, 60 mg
PrMESTINON®-SR (Slow-Release) Tablets, 180 mg

(Pyridostigmine Bromide Tablets)

Antimyasthenic - Cholinergic

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ACTIONS:

Pyridostigmine is a cholinergic agent which acts primarily by the inhibition of cholinesterase. It enhances cholinergic action by facilitating the transmission of impulses across neuromuscular junctions. It also has a direct cholinomimetic effect on skeletal muscle and possibly on autonomic ganglion cells and neurons of the central nervous system. Because of its quaternary ammonium structure, moderate doses of pyridostigmine do not cross the blood-brain barrier to produce CNS effects. Extremely high doses, however, produce CNS stimulation followed by CNS depression, in addition to a depolarizing neuromuscular blockade.

Pyridostigmine is an analog of neostigmine. However, it differs from neostigmine in certain clinically significant respects; for example, pyridostigmine is more effectively absorbed from the alimentary tract than is neostigmine; with equipotent doses, pyridostigmine has a slower onset and longer duration of action, and produces fewer gastrointestinal side effects than neostigmine. After oral administration, Mestinon®
generally has an onset of action of 20 minutes and a duration of action of approximately 6 hours; as for Mestinon\textsuperscript{®}-SR, it has an onset of action of 30 to 60 minutes and a duration of action of 6 to 12 hours.

**INDICATIONS:**
Mestinon\textsuperscript{®} and Mestinon\textsuperscript{®}-SR are indicated for the symptomatic treatment of myasthenia gravis. In acute myasthenic crises where difficulty in breathing and swallowing is present, the parenteral form should be used. The patient can be transferred to the oral form as soon as it can be tolerated.

**CONTRAINDICATIONS:**
Mestinon\textsuperscript{®} and Mestinon\textsuperscript{®}-SR are contraindicated in patients with known hypersensitivity to anticholinesterase agents. Because of the presence of the bromide ion, they should not be used in patients with a prior history of reaction to bromides. They are also contraindicated in patients with peritonitis or mechanical obstruction of the intestinal or urinary tract.

**WARNINGS:**
Mestinon\textsuperscript{®} and Mestinon\textsuperscript{®}-SR should be used with caution in patients with epilepsy, bronchial asthma, bradycardia, recent coronary occlusion, vagotonia, hyperthyroidism, cardiac arrhythmias or peptic ulcer. Large oral doses of the drug should be avoided in patients with megacolon or decreased gastrointestinal motility. In these patients, the drug may accumulate and result in toxicity when gastrointestinal motility is restored.
**PRECAUTIONS:**

**General:**
Although failure of patients to show clinical improvement may reflect underdosage, it can also be indicative of overdosage. It is important to differentiate between myasthenic crisis and cholinergic crisis caused by overdosage of Mestinon® or Mestinon®-SR. Both conditions result in extreme muscle weakness but require radically different treatment. (See Overdosage Section)

**Information for Patients:**
Complete restoration of muscle strength is rare in myasthenia gravis, and patients should be cautioned not to increase their dose, in an attempt to relieve their symptoms, without consulting their physician. The patient should be encouraged to keep a daily record of his or her condition to assist the physician in determining an optimal therapeutic regimen.

**Drug Interactions:**
Atropine antagonizes the muscarinic effects of pyridostigmine and this interaction may be utilized to counteract the effects of pyridostigmine. (See Overdosage Section)

Pyridostigmine bromide does not antagonize, and in fact may prolong the phase I block of depolarizing muscle relaxants such as succinylcholine or decamethonium.

Certain antibiotics, especially neomycin, streptomycin and kanamycin, have a mild but definite nondepolarizing blocking action which may accentuate neuromuscular block. These antibiotics should be used in the myasthenic patient only where definitely
indicated, and then careful adjustment should be made of adjunctive anticholinesterase dosage.

Local and some general anesthetics, antiarrhythmic agents and other drugs that interfere with neuromuscular transmission should be used cautiously, if at all, in patients with myasthenia gravis; the dose of pyridostigmine bromide may have to be increased accordingly.

In severe myasthenia gravis, neostigmine has been used in combination with pyridostigmine to provide the benefits of short and long-term activity; because of the possibility of reduced intestinal motility and increased toxicity, this combination should be used only under strict medical supervision.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:**
Carcinogenicity and mutagenicity studies have not been performed with pyridostigmine bromide.

A fertility and general reproductive performance study was performed in rats at dosages of 15 and 40 mg/kg/day. There were no adverse effects on pregnancy rate, average number of implantation sites, average number of embryos per dam, percent resorptions, duration of gestation, litter size, pup viability or pup growth.

**Pregnancy:**
Teratogenic effects: Pregnancy category B
Reproductive studies have been performed in rats at dosages up to 40 mg/kg/day (2 times the maximum recommended human dose; 4.6 times the average recommended
These studies have revealed no evidence of impaired fertility or harm to the fetus due to pyridostigmine bromide. There are, however, no adequate and well controlled studies in pregnant women. However, pyridostigmine bromide, like other cholinesterase inhibitors, contains a quaternary ammonium and, therefore, would be expected to cross the placenta only to a limited extent. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic effects:
Of newborn infants whose mothers have received anticholinesterase drugs for treatment of myasthenia gravis, 10 to 20 percent were observed to have transient muscular weakness.

Nursing Mothers:
It is not known whether pyridostigmine bromide is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from pyridostigmine in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:
See Dosage and Administration Section.
ADVERSE REACTIONS:
Side effects are generally due to an exaggeration of pharmacological effects of which increased salivation and fasciculation are the most common. Abdominal cramps and diarrhea may also occur.

The following additional adverse reactions have been reported following the use of Mestinon® and Mestinon®-SR:

**Respiratory:** Increased bronchial secretions.

**Gastrointestinal:** Nausea, vomiting, increased peristalsis.

**Musculoskeletal:** Muscle cramps.

**Dermatologic:** Urticaria, rash.

**Miscellaneous:** Miosis, diaphoresis, weakness, allergic reactions.

SYMPTOMS AND TREATMENT OF OVERDOSAGE:
As is true of all anticholinesterase agents, overdosage of Mestinon® or Mestinon®-SR can cause cholinergic crisis, which is characterized by increasing muscle weakness and which, through involvement of the muscles of respiration, may result in 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. However, such differentiation is extremely important, because increases in the dose of pyridostigmine bromide or other drugs in this class in the presence of cholinergic crisis or of a refractory or "insensitive" state could have grave consequences. The two types of crises may be differentiated by the use of Tensilon® (edrophonium chloride) as well as by clinical judgment.
Treatment of the two conditions differs radically. Whereas the presence of myasthenic crisis requires more intensive anticholinesterase therapy, cholinergic crisis calls for the prompt withdrawal of all drugs of this type. The immediate use of atropine in cholinergic crisis is also recommended. A syringe containing 1 mg of atropine sulfate should be immediately available to be given in aliquots intravenously to counteract severe cholinergic reactions.

Atropine also may be used to abolish or minimize gastrointestinal side effects or other muscarinic reactions; but such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

**DOSAGE AND ADMINISTRATION:**
The dosage, route and frequency of administration depend on the requirements and clinical response of the patients. The dosage schedule should be adjusted for each patient and changed as the need arises. Dosage requirements in patients with myasthenia gravis may vary from day to day, according to remissions and exacerbations of the disease and the physical and emotional stress suffered by the patient. Larger portions of the label daily dose may be given at times when the patient is more prone to fatigue (afternoon, mealtimes, etc.).

In the initial treatment of myasthenia gravis, oral Mestinon® and Mestinon®-SR should be started at a dosage smaller than that required to produce maximum strength, and daily dosage gradually increased at intervals of 48 hours or more. Changes in oral dosage may take several days to show results. When a further increase in dosage produces no corresponding increase in muscle strength, dosage should be reduced to
the previous level so that the patient receives the smallest dose necessary to produce maximum strength.

**Note:** For information on a diagnostic test for myasthenia gravis, and for the evaluation and stabilization of anticholinesterase therapy, see Product Monograph on Tensilon® (edrophonium chloride injection).

The immediate effect of a Mestinon®-SR 180 mg tablet is about equal to that of a 60 mg conventional tablet; however, the duration of drug action, although varying in individual patients, averages 2 ½ times that of a 60 mg dose. One to three 180 mg tablets, once or twice daily (180 mg to 1.08 g a day), will usually be sufficient to control symptoms; however, the needs of individual patients may vary markedly from this average. For optimal control, it may be necessary to use conventional tablets or syrup in conjunction with Mestinon®-SR therapy. Mestinon®-SR tablets are particularly useful for bedtime administration in patients who are very weak upon awakening.

**Mestinon® and Mestinon®-SR tablets should be swallowed whole. Do not crush.** However, in certain cases, Mestinon® and Mestinon®-SR tablets, can be cut in half; but Mestinon®-SR tablets should not be crushed or quartered since this would destroy too much of the sustained release matrix.

Due to the slow-release mechanism of the tablet, the matrix may pass through the intestinal system intact. However, it should be noted that the medicinal ingredient has
been released through the gastro-intestinal tract over an 8 to 12 hour passing time and only the matrix is rejected.

HOW SUPPLIED:


Mestinon®-SR capsule-shaped, flattened on two sides with a single score on one face, light straw coloured tablets, embossed MES V 180, each containing 180 mg pyridostigmine bromide. Nonmedicinal ingredients: calcium phosphate, carnauba wax, isopropyl alcohol and magnesium stearate. Energy: 2.3 kJ (0.5 kcal). Gluten-, lactose-, paraben-, sodium-, sulfite-, and tartrazine-free. Bottles of 30. Store in a dry place between 15 and 30°C (59 and 86°F), in a well-closed container with the desiccant enclosed.

Note: Because of the hygroscopic nature of the Mestinon® and Mestinon®-SR tablets, mottling may occur. This does not affect their efficacy.
CHEMISTRY AND PHARMACOLOGY:

Chemical Name: 3-Hydroxy-1-methylpyridinium bromide dimethylcarbamate

Structural Formula:

![Structural Formula]

Molecular Formula: C$_9$H$_{13}$BrN$_2$O$_2$
Molecular Weight: 261.12 Daltons

Description: Pyridostigmine Bromide is a hygroscopic, white or practically white, crystalline powder having an agreeable, characteristic odour. It is freely soluble in water, in alcohol, and in chloroform; slightly soluble in solvent hexane; and practically insoluble in ether.

Pharmacology:
Pyridostigmine inhibits the hydrolysis of acetylcholine by competing with acetylcholine for attachment to acetylcholinesterase at sites of cholinergic transmission. The pyridostigmine-enzyme complex is hydrolysed at a much slower rate than the acetylcholine-enzyme complex, resulting in accumulation of acetylcholine at cholinergic synapases with prolonged and exaggerated effects. The generalized cholinergic responses produced by pyridostigmine include miosis, increased tonus of intestinal and skeletal musculature, constriction of bronchi and ureters, bradycardia, and stimulation of secretion by salivary and sweat glands.
Following oral administration of Mestinon®-SR, the mean peak pyridostigmine plasma concentration is reached by 2 hours. The remainder of the dose is released over 8-12 hours. When administered concomitantly with food, the time to reach mean peak plasma concentration can be increased to about 3 hours; however, the extent of absorption of pyridostigmine is not affected.

Pyridostigmine does not bind to plasma protein. The drug has been reported to cross the placenta and, after large oral doses, to decrease fetal plasma cholinesterase activity. Animals administered radioactive-labelled pyridostigmine orally showed presence of radioactivity in most tissues except brain, fat, thymus, and intestinal wall.

In a comparative pharmacokinetic study, determined in 10 healthy subjects given pyridostigmine bromide (4 mg i.v. over 30 minutes, and 60 mg orally), the oral availability as measured by the AUC ratio was 11.5% to 18.9% (\(\bar{x}=14.3\%\)). The mean \(t_{1/2}\) of the plasma level decline after oral dosing was 200 minutes, twice as long as the terminal elimination \(t_{1/2}\) after intravenous infusion (97 minutes), indicating that absorption may proceed at a slower rate than elimination.

Pyridostigmine not only undergoes hydrolysis by cholinesterases but is also metabolized by microsomal enzymes in the liver. The major metabolite of pyridostigmine is 3-hydroxy-N-methylpyridinium. Patients with severe myasthenia gravis appear to metabolize and excrete the drug faster than patients having a milder form of the disease. Pyridostigmine and its metabolites are excreted in the urine by tubular secretion. Approximately 10% of the administered dose is excreted in the urine.
as intact drug in 24 hours, but a considerable individual variation in urinary excretion patterns has been shown by patients with myasthenia gravis.

**TOXICITY:**
The acute toxicity of pyridostigmine bromide in mice and in rats is summarized in the following table:

<table>
<thead>
<tr>
<th>ANIMAL</th>
<th>ROUTE</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; ± S.E.</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>i.v.</td>
<td>2.0 ± 0.8 mg/kg</td>
<td>Tremors, Straub reaction, exophthalmia</td>
</tr>
<tr>
<td>Mice</td>
<td>i.m.</td>
<td>3.25 ± 0.2 mg/kg</td>
<td>Tremors, exophthalmia, salivation (watery), lacrimation, respiratory failure</td>
</tr>
<tr>
<td>Rats</td>
<td>i.v.</td>
<td>2.25 ± 0.2 mg/kg</td>
<td>Tremors, piloerection, lacrimation, bloody tears, respiratory failure</td>
</tr>
<tr>
<td>Rats</td>
<td>i.m.</td>
<td>3.4 ± 0.3 mg/kg</td>
<td>Salivation, tremors, lacrimation, bloody tears</td>
</tr>
</tbody>
</table>

The LD<sub>50</sub> for pyridostigmine in rats fed by the oral route is reported to be 86 mg/kg body weight.

An assessment of the morphological changes in rats caused by pyridostigmine has shown that respiratory failure occurred within 1 hour and resulted in death in four of the six animals that received a single oral dose of 80 mg/kg body weight. No
spontaneous death occurred in animals given a single dose of 20 to 40 mg of Pyridostigmine per kg of body weight, although these doses caused a marked reduction of the acetylcholinesterase activity in the whole blood and in the erythrocytes. The histological findings in the skeletal muscles of these animals revealed, particularly in the diaphragm, unequivocal, severe lesions within 24 hours, characterized by disseminated single fibre necrosis or necrosis of grouped fibres associated with infiltrates of polymorphonuclear neutrophilic granulocytes, lymphoid and histiocytic cells. The staining of the motor endplates in areas where necrosis occurred revealed marked changes of the nerve endings: their ramifications were mostly rarefied, shortened, and plump.
REFERENCES: