MESTINON

NAME OF THE MEDICINE
Pyridostigmine Bromide.

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\text{C}_9\text{H}_{13}\text{BrN}_2\text{O}_2
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CAS number: 101-26-8

Description:
Mestinon contains, as active substance, pyridostigmine bromide, chemically described as the dimethylcarbamic ester of 1-methyl-3-hydroxypyridinium bromide. It occurs as a white or nearly white, hygroscopic, crystalline powder. It is freely soluble in alcohol and chloroform but practically insoluble in ether.

Mestinon 10 mg tablets also contain the excipients lactose, magnesium stearate, silica - colloidal anhydrous, starch – maize, starch – potato and talc – purified.

Mestinon 60 mg tablets also contain the excipients acacia, iron oxide red, iron oxide yellow, magnesium stearate, paraffin – hard, paraffin – liquid, povidone, silica - colloidal anhydrous, starch – maize, starch – potato, starch – rice, sucrose, and talc – purified.

Mestinon Timespan 180 mg tablets also contains the excipients calcium phosphate, carnauba wax, magnesium stearate, silica - colloidal anhydrous and zein.

Pharmacology:

Action: Cholinergic antimyasthenic.

Mestinon possesses cholinergic properties due to competitive inhibition of cholinesterase enzyme which normally hydrolyses acetylcholine at the cholinergic synapses and neuro-effector junctions. Thus, the drug causes generalised cholinergic response including increased tone of skeletal and intestinal musculature, miosis, uterine and bronchial spasm, bradycardia, increased secretion of exocrine glands (e.g. saliva, sweat) etc. In addition, pyridostigmine has a direct cholinomimetic effect on skeletal muscle.

Pharmacokinetics:

Duration of Action: Mestinon has a variable duration of action in patients with myasthenia gravis, depending on the physical and emotional stress suffered by the patient and the severity of the disease. After oral administration, the drug generally has an onset of action of 30-45 minutes and a duration of action of 3-6 hours.

The longer intervals between doses of Mestinon compared with neostigmine facilitate treatment in myasthenia gravis; once control has been achieved the effect persists overnight. In certain
cases Mestinon may be combined with neostigmine (e.g. Mestinon during the day and in the evening, neostigmine in the morning).

**Absorption:** Only about 40% of an oral dose of Mestinon is absorbed, significant amounts being destroyed in the gastrointestinal tract. The presence of permanently-charged quaternary ammonium groups confers high water solubility. Thus pyridostigmine shows greatest absorption in the duodenum, but overall absorption is poor and variable.

**Distribution:** Mestinon is distributed to the extracellular fluid. It does not enter the CNS. The plasma area under the curve after 4 hours is relatively constant (6,000-10,000 ng/mL/minute). Pyridostigmine has been reported to cross the placenta and to decrease foetal plasma cholinesterase activity after large oral doses. Following oral administration of 14C labelled pyridostigmine to animals, radioactivity was present in most tissue except brain, intestinal wall, fat and thymus.

**Plasma Levels:** 20 to 60 ng/mL, despite wide dose variations.

**Half-Life:** 1.5 to 4.25 hours oral (variable).

**Metabolism and Excretion:** Mestinon is extensively metabolised in the liver and 95% of metabolites are excreted in the urine. The chief metabolite is 3-hydroxy-N-methyl-pyridinium bromide. Neither pyridostigmine nor its metabolites are protein bound. Excretion is by filtration and secretion, or by hepatic conversion to the glucuronide. Competition for renal transport mechanisms by tertiary amines can occur.

**Indications:**
Mestinon is useful in the treatment of myasthenia gravis.

**Contraindications:**
Known hypersensitivity to anticholinesterase agents and bromide, intestinal and urinary obstruction of mechanical type.

**Precautions:**
Particular caution should be used 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.

Failure of patients to show clinical improvement may reflect over or under dosage. Overdosage may result in "cholinergic crisis" and under-dosage in "myasthenia crisis". Differentiation may require the use of edrophonium. Care should be taken in counteracting side effects with atropine, as such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis. In some patients, pyridostigmine bromide has a longer duration of action than the neostigmine salt. In such cases it is more likely to cause cholinergic crisis.
When pyridostigmine is used to treat myasthenia gravis, it should be kept in mind that individual muscle groups may respond differently to the same dose of an anticholinesterase agent, producing weakness in one muscle group while increasing strength in another. The muscles of the neck and of chewing and swallowing are usually the first muscles weakened by overdosage, followed by the muscles of the shoulder girdle and upper extremities, and finally the pelvic girdle, extraocular and leg muscles.

Vital capacity should be routinely measured whenever dosage is increased, so that the dosage of the anticholinesterase medication can be adjusted to ensure good respiratory function. Adequate facilities for cardiopulmonary resuscitation, cardiac monitoring, endotracheal intubation, and assisting respiration should be available during dosage adjustment.

Mestinon 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.

**Use in Pregnancy:** Category C. The maternal requirement for this drug in the context of myasthenia gravis may be absolute. Cholinergic effects in the neonate are rare.

The safety of Mestinon during pregnancy in humans has not been established.

Few data are available regarding the effects of cholinesterase inhibitors, including pyridostigmine, on the foetus because of the rarity of maternal conditions requiring the use of these drugs during pregnancy.

Transient muscular weakness has occurred in 10-20% of newborns whose mothers received anticholinesterase drugs for the treatment of myasthenia gravis, although similar symptoms have also been reported in infants whose mothers were not treated with these drugs.

**Use in Lactation:** The safety of Mestinon during lactation in humans has not been established.

**Paediatric use:** Use of Mestinon is not recommended in children due to the lack of adequate clinical experience in this patient population.

**Interactions with Other Medicines:**

Pyridostigmine does not antagonise, and may in fact prolong, the phase I block of depolarising muscle relaxants such as suxamethonium or decamethonium. Fully established phase II (desensitisation) block can be reversed by pyridostigmine, but the individual variation in transition time between phases I and II and difficulty in accurately determining the stage of depolarising neuromuscular block at any given time often make anticholinesterase administration ineffective or dangerous under these circumstances.

Atropine antagonises the muscarinic effects of pyridostigmine, and this interaction is utilised to counteract the muscarinic symptoms of pyridostigmine toxicity.

Anticholinesterase agents are sometimes effective in reversing neuromuscular block induced by aminoglycoside antibiotics. However, aminoglycoside antibiotics, local and some general anaesthetics, anti-arrhythmic agents, and other drugs that interfere with neuromuscular
transmission should be used cautiously, if at all, in patients with myasthenia gravis, and the dose of pyridostigmine may have to be increased accordingly.

Theoretically, drugs such as dexpanthenol, which are converted to pantothenic acid in vivo, may have additive effects with pyridostigmine by increasing production of acetylcholine.

Methocarbamol, also, should be used with caution in myasthenic patients receiving pyridostigmine bromide as impaired therapeutic response has been reported.

**Adverse Effects:**

Mestinon has a lower incidence of gastrointestinal stimulation and other muscarinic side effects seen with other anticholinesterases. However, nausea, vomiting, diarrhoea, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, myosis and diaphoresis may occur. Atropine may be used to counter these effects but not without danger, due to the difficulties in distinguishing myasthenic and cholinergic crisis.

Nicotinic effects are usually muscle cramps, fasciculation and weakness. Bradycardia and hypotension may occur. Occasionally the bromine radical may induce a rash.

**Dosage and Administration:**

*Myasthenia gravis:* 1 to 3 tablets (60 mg) two to four times daily; more in severe cases. 1 to 3 "Timespan" tablets (180 mg) once or twice daily; the needs of individuals may vary markedly from this average, but the interval between doses should be at least six hours.

The dosage and frequency of administration depend upon the clinical response of the patient and may vary from day to day, according to remissions and exacerbations of the disease and the physical and emotional stress suffered by the patient. Dosage should be adjusted so that patients take larger doses at times of greatest fatigue e.g. 30-45 minutes before meals in patients who have difficulty in eating.

Patients should be advised that the use of Mestinon may not restore the muscle strength to normal and should be cautioned not to increase their dose above the maximum response level in an attempt to relieve all symptoms.

Myasthenic patients may become refractory to Mestinon after prolonged treatment. Responsiveness may be restored, especially when resistance may have been caused by overdosage, by decreasing the dosage or withdrawing the drug for several days under medical supervision. High dosage of corticosteroids have also been used in intensive care facilities to increase responsiveness to anticholinesterase therapy.

**Overdosage:**

*For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).*

*Signs and symptoms of overdosage (cholinergic crisis):* Muscarinic effects (abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased salivation and bronchial secretions, diaphoresis and miosis) and nicotinic actions (muscle weakness, fasciculation and cramps). Bradycardia and hypotension may occur if overdosage is excessive.
In extremely high dosage, CNS symptoms of agitation and restlessness occur and death may result from cardiac arrest, respiratory paralysis or pulmonary oedema.

In patients with myasthenia gravis, in whom overdose is most likely to occur, fasciculation and parasympathomimetic side effects may be mild or absent, making "cholinergic crisis" difficult to distinguish from "myasthenic crisis".

The time of onset of weakness may sometimes indicate whether crisis is the result of overdosage of (or underdosage or resistance to) anticholinesterase drugs. Weakness that begins within 1 hour after drug administration is suggestive of overdosage while weakness occurring 3 or more hours after drug administration is suggestive of underdosage or resistance.

Edrophonium is generally used to distinguish "cholinergic crisis" from "myasthenic crisis". 2 mg by intravenous injection of this short acting anticholinergic agent should cause a brief period of exacerbation of weakness in "cholinergic crisis" or a temporary improvement of strength in "myasthenic crisis".

*Suggested treatment:* Artificial respiration may be needed if respiration is markedly depressed. (Mestinon should be discontinued immediately after diagnosis is made).

The muscarinic effects are the most serious and may be controlled by atropine (2 mg intravenously followed by intramuscular doses every 2 to 4 hours as necessary to relieve respiratory difficulty). Atropine overdosage should be avoided, as tenacious secretions and bronchial plugs may result.

It should be remembered that, unlike muscarinic effects, the skeletal muscle effects and resulting respiratory paralysis after Mestinon overdosage are not alleviated by atropine treatment.

Patients poisoned by anticholinesterases should not be given aminophylline, morphine, phenothiazine tranquillisers, reserpine, suxamethonium, theophylline or large quantities of fluids.

**Presentation and Storage Conditions:**

- **Mestinon 10 mg** Round, biconvex, white to off-white tablet with no markings.
- **Mestinon 60 mg** Round, biconvex, pale orange, sugar coated tablet with no markings.
- **Mestinon 180 mg** Round, biplanar, grey-yellow tablet with a marking ‘V M180’ on one side and scored on the other side.

Mestinon tablets are presented in coloured glass bottles in the following packs:

- 10 mg tablets - 50,100# and 250’s#
- 60 mg tablets - 150’s
- 180 mg tablets - 50 and 100’s#

# - not currently distributed in Australia

Storage Condition: Store below 25°C
Name and Address of the Sponsor:
iNova Pharmaceuticals (Australia) Pty Ltd
Level 10, 12 Help St
Chatswood NSW 2067

Poison Schedule of the medicine:
Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods:
23 August 1991

Date of most recent amendment:
16 Oct 2017