Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Mestinon 60mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Tablet contains 60.0mg pyridostigmine bromide.

Each Tablet contains 60.75mg lactose monohydrate.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet

White to off-white, round, biplanar, bevel-edged tablets imprinted with "V" M60 across one face and with two break marks forming a cross on the other.

The tablet can be divided into equal halves.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Myasthenia gravis, paralytic ileus and post-operative urinary retention.

4.2 Posology and method of administration

Myasthenia gravis
Adults
Doses of 30 to 120mg are given at intervals throughout the day when maximum strength is needed (for example, on rising and before mealtimes). The usual duration of action of a dose is 3 to 4 hours in the daytime but a longer effect (6 hours) is often obtained with a dose taken on retiring for bed.
The total daily dose is usually in the range of 5 - 20 tablets but doses higher than these may be needed by some patients.

Children
Children under 6 years old should receive an initial dose of half a tablet (30mg) of Mestinon; children 6-12 years old should receive one tablet (60mg). Dosage should be increased gradually, in increments of 15-30mg daily, until maximum improvement is obtained. Total daily requirements are usually in the range of 30 - 360mg

Other Indications (paralytic ileus)
Adults
The usual dose is 1 to 4 tablets (60 to 240mg) per day.

Children
The usual dose is 15 to 60mg per day.
The frequency of these doses may be varied according to the needs of the patient.

Special Populations

Elderly patients
There are no specific dosage recommendations for Mestinon in elderly patients.

Renal impairment
Pyridostigmine bromide 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
No specific dosage recommendations for Mestinon in patients with hepatic impairment.

Method of administration
For oral use.
Mestinon should be taken with water (half full to full glass of water).

4.3 Contraindications

Mestinon should not be given to patients with mechanical gastro-intestinal or urinary obstruction. Mestinon is contraindicated in patients with known hypersensitivity to the drug and to bromides or any of the excipients.

4.4 Special warnings and precautions for use

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

Care must be taken in patients with:

- Arrhythmias such as bradycardia and atrioventricular block (elderly patients may be more susceptible to dysrhythmias than the young adult),
- Recent coronary occlusion,
- Hypotension,
- Vagotonia,
- Peptic ulcer,
- Epilepsy,
- Parkinsonism,
- Hyperthyroidism,
- Renal impairment.

When relatively large doses of pyridostigmine are taken by myasthenic patients it may be necessary to give atropine or other anticholinergic drugs to specifically counteract the muscarinic effects of pyridostigmine while maintaining its nicotinergic effect.

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

In impaired kidney function, prolonged dosage intervals or lower subsequent doses may be indicated.

Lactose intolerance: Mestinon tablets contain 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 interactions

Antimuscarinics:

Atropine and hyoscine antagonise the muscarinic effects of pyridostigmine. The slower gastro-intestinal motility caused by these drugs may affect the absorption of pyridostigmine.

Immunosuppressant drugs:

The requirement for pyridostigmine bromide may be decreased by concomitant use with corticosteroids or immunosuppressant drugs. Nevertheless, a new addition of corticosteroids may initially aggravate the symptoms of myasthenia gravis.

Thymectomy:

The need for Mestinon dosing may be decreased after thymectomy.

Methylcellulose:

Methylcellulose and medicines containing methylcellulose as an excipient can inhibit 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. suxarnethonium).

Others:

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

4.6 Fertility, pregnancy and lactation

Fertility
Nonclinical investigations in rats have not shown any negative effects on reproductive behaviour.

Pregnancy
The safety of pyridostigmine during pregnancy has not been established. Although the possible hazards to mother and child must be weighed against the potential benefits in every case, experience with Mestinon in pregnant patients with myasthenia gravis has revealed no untoward effect of the drug on the course of pregnancy. Isolated reports of stillbirth or miscarriage have been reported; however, a causal association to the use of pyridostigmine could not be established.

As the severity of myasthenia gravis often fluctuates considerably in pregnancy, particular care is required to avoid cholinergic crisis due to overdose of the drug, but otherwise management is no different from that in non-pregnant patients.
Since pyridostigmine bromide crosses the placenta barrier. Since pyridostigmine crosses the placenta barrier excessive doses of pyridostigmine should be avoided; the newborn child should be monitored for possible effects.

Reproductive studies in rabbits and rats showed no teratogenic but embryo-/foetotoxic effects at doses toxic to the dam (see section 5.3).

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

Experience with Mestinon in pregnant patients with myasthenia gravis has revealed no untoward effect of the drug on the course of pregnancy.

Lactation
The safety of pyridostigmine during lactation has not been established. 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-fed infant.

4.7 Effects on ability to drive and use machines

Miosis and accommodation disorders caused by pyridostigmine or an inadequately treatment of myasthenia gravis may impair visual acuity and, consequently, the ability to react as well as the ability to drive and use machinery.

4.8 Undesirable effects

As with all cholinergic products, Mestinon 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.

Within the system organ classes, adverse reactions are listed under headings of frequency (number of patients expected to experience the reaction), using the following categories:
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)
Frequency Not known (cannot be estimated from the available data)

The following undesirable effects were observed
Immune system disorders
Frequency not known: Drug hypersensitivity

Nervous system disorders
Frequency not known: Syncope

Eye disorders
Frequency not known: Miosis, increased lacrimation, accommodation disorders (e.g. blurred vision)

Cardiac disorders
Frequency not known: Arrhythmia (including bradycardia, tachycardia, AV block, Prinzmetal angina

Vascular disorders
Frequency not known: Flushing, hypotension

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

Gastrointestinal disorders
Frequency not known: Nausea, vomiting, diarrhea, gastrointestinal hypermotility , salivary hypersecretion, abdominal symptoms (e.g. discomfort pain, cramps, etc.)

Skin and subcutaneous tissue disorders
Rare: Rash (disappears usually soon after ceasing of medication. Bromide containing medicines should no longer be used.)
Frequency not known: Hyperhydrosis, urticaria

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 Overdose)

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 Overdose).

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. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Website: www.hpra.ie.

4.9 Overdose

Overdosage may lead to cholinergic crisis characterised severe muscurinic 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, diaphoresis, nausea and vomiting, increased bronchial secretions, salivation, hyperhydrosis, and miosis. Nicotinic effects consist of muscular cramps, fasciculations and general weakness up to paralysis which may produce apnoea and cerebral anoxia in particularly severe cases.

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

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

Mestinon treatment must be stopped immediately. Artificial ventilation should be instituted if respiration is severely depressed. Atropine sulphate 1 to 2mg intravenously is an antidote to the muscarinic effects. Doses may be repeated every 5 to 30 minutes as needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Anticholinesterases

ATC code: N07AA02

Pyridostigmine is reversible cholinesterase inhibitor which enzyme inactivates acetylcholine. Pyridostigmine prolongs the acetylcholine effect at the synaptic cleft. It does not cross the blood-brain barrier. Pyridostigmine has a more prolonged action than neostigmine (Prostigmin) 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 its longer duration of action is also an advantage.

5.2 Pharmacokinetic properties

Absorption
Oral pyridostigmine was poorly absorbed by about 22-25%. The rate and extent of absorption show wide inter-individual differences.

When administered in healthy volunteers at oral daily doses of 120 mg, 120-370 mg, and 180-1440 mg the oral bioavailability of pyridostigmine bromide was 7.6%, 18.9%, and 3-4% with Cmax of 40-80 µg/L, 20-100 µg/L, and 180 µg/L at tmax of 3-4 h, 1.5-6 h, and 1.5 h, respectively. This low and highly variable bioavailability across studies is attributed to the low absorption rate of pyridostigmine. In patients with myasthenia gravis, oral bioavailability may decrease to 3.3%.

Distribution
Pyridostigmine is not bound to plasma proteins. The apparent volume of distribution after intravenous administration was 1.03 L/kg to 1.43 L/Kg in healthy patients, 1.76 L/Kg in myasthenia gravis patients and 0.53 to 1.1 L/Kg in surgery.

The concentration of pyridostigmine in breast milk has been found to be 36 to 113% compared to maternal plasma, which implies a very low dose to the nursing infant (about 0.1% of the dose per kilogram bodyweight taken by the mother).

Metabolism

Pyridostigmine is metabolized only to a small extent. It is hydrolised by plasma cholinesterases. The main metabolite of pyridostigmine is the hydrolysis product 3-hydroxy-N-methyl-pyridinium.

Elimination
Systemic (intravenous) pyridostigmine is mainly excreted by the kidneys (75 – 90%) as parent compound and as inactive metabolites at a ratio of about 4:1. A total of 5-15% of oral doses are dose-dependently excreted by the kidneys as parent compound, thus reflecting the low degree of oral pyridostigmine absorption.

The total plasma clearance was very rapid with 0.65 L/h/kg in healthy subjects, 0.29-1.0 L/h/kg in myasthenic patients, and 0.52- 0.98 L/h/kg in patients with surgery, respectively.

After intravenous administration the apparent terminal elimination half-life was 1.51-1.74 h in healthy volunteers, 1.05 h in myasthenic patients, and 0.38-1.86 h in surgical patients, respectively. With oral administration, this was 3 to 4 h.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans with respect to conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. Reproductive study results in rabbits and rats showed no teratogenic but embryo-/foetotoxic effects with increased resorptions, reduced litter size and body weight reduction as well as a slight increase in delayed ossification at doses toxic to the dam. No carcinogenicity studies have been conducted with pyridostigmine.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:

Lactose Monohydrate
Maize Starch
Colloidal Hydrated Silica
Talc
Magnesium stearate

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 25°C. Store in the original package. Keep the bottle tightly closed.

6.5 Nature and contents of container

Amber glass bottles with aluminium screw or low density polyethylene caps and desiccant containing 200 tablets.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Mylan IRE Healthcare Limited
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8 MARKETING AUTHORISATION NUMBER

PA2010/052/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 01 April 1979

Date of last renewal: 01 April 2009

10 DATE OF REVISION OF THE TEXT

February 2020