

1 NAME OF THE MEDICINAL PRODUCT

Mestinon 60 mg Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 60 mg pyridostigmine bromide.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Tablet for oral administration.

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.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

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.

Paediatric population

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 to 30 – 360mg.

Other Indications (paralytic ileus, post-operative urinary retention)

Adults

The usual dose is 1 to 4 tablets (60 – 240mg) per day.

Paediatric population

The usual dose is 15 – 60mg per day.

The frequency of these doses may be varied according to the needs of the patient.

Special populations

Elderly

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

Renal impairment

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.

Hepatic impairment

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

Method of administration

For oral use

4.3 Contraindications

Mestinon is contra-indicated in 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 Mestinon 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
- Epilepsy or Parkinsonism
- Hyperthyroidism

When relatively large doses of Mestinon 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 gastro-intestinal motility caused by these drugs may affect the absorption of Mestinon.

In all patients the possibility of "cholinergic crisis", due to overdosage of Mestinon , 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 Mestinon is usually markedly decreased after thymectomy or when additional therapy (steroids, immunosuppressant drugs) is given.

Patients with rare hereditary problems of galactose intolerance, the Lapp 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 decrease 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

The safety of Mestinon 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 Mestinon 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 non-pregnant patients.

Observations indicate that only negligible amounts of Mestinon 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, Mestinon 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, 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.

Adverse reactions are listed below according to system organ class and frequency. Frequencies are defined according to the following convention:

Very common ($\geq 1/10$), Common ($\geq 1/100$ to $< 1/10$), Uncommon ($\geq 1/1,000$ to $< 1/100$), Rare ($\geq 1/10,000$ 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, 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. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

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. Doses may be repeated every 5 to 30 minutes as needed.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Nervous system, parasymphomimetics, anticholinesterases, pyridostigmine , ATC code: N07AA02

Mestinon is an antagonist to cholinesterase, the enzyme which normally destroys acetylcholine. The action of Mestinon can briefly be described, therefore, as the potentiation of naturally occurring acetylcholine. Mestinon has a more prolonged action than Prostigmin (neostigmine) although it is somewhat slower to take effect (generally taking 30 – 60 minutes). Because it has a weaker "muscarinic" action than Prostigmin, 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.

5.3 Preclinical safety data

There are no preclinical data of relevance to the prescriber, which are additional to those already included in other sections of the SmPC.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains:

Lactose

Starch

Precipitated Silica

Talc

Magnesium Stearate

Purified Water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store below 25°C. Store in the original package in order to protect from light and moisture.

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

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Mylan Products Ltd,
Station Close,
Potters Bar,
Hertfordshire,
EN6 1TL,
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 46302/0133

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT

13/04/2018