1 NAME OF THE MEDICINAL PRODUCT

Mestinon 60 mg, coated-tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: pyridostigmine bromide

3 PHARMACEUTICAL FORM

Coated tablets for oral use

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of myasthenia gravis.

4.2 Posology and method of administration

Adults
Oral dosage forms:
Multiple doses of 30 to 120 mg are given at intervals throughout the day.

The total daily dose is usually in the range of 120 – 1200 mg but doses higher than these may be needed by some patients according to dose titration.

Newborns
When this product is used in pediatric patients, the required dosage shall be determined by careful titration.

In neonatal myasthenia, usually preference will be given to treatment with Neostigmine. However, if this seems to be unsuitable (for instance, due to severe cholinergic side effects), Mestinon can be administered. As a standard value, it is recommended in these cases to give 5 mg per os in form of tablets every 4 to 6 hours, in each case 30 - 60 minutes before feeding. This dose should be gradually reduced until the medication can be discontinued. Treatment for more than eight weeks after birth will only be required in some extremely rare cases of congenital and heredofamilial infantile myasthenia.

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

Special populations
Elderly
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
There are no specific dosage recommendations for Mestinon in patients with hepatic impairment.
4.3 Contraindications

*Mestinon* is contraindicated for patients with:
- Hypersensitivity to the active substance, bromides or to any of the excipients
- Mechanical gastro-intestinal or urinary obstruction
- If you have mechanical obstruction of the gastrointestinal or urinary tract, suffer from inflammation of the peritoneum and in case of any disorders accompanied by an increased tonus of the bronchial muscles, such as spastic bronchitis and bronchial asthma.
- If you are breast-feeding

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 diseases (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 administering *Mestinon* Sugar-coated Tablets in patients with slow heart beat (bradycardia) and after gastrointestinal surgery.

If you have diabetes (the sugar content comes to 0.165 g per sugar-coated tablet, equivalent to about 0.014 bread units).

When relatively large doses of pyridostigmine bromide are taken by myasthenic patients it may be necessary to give atropine or other anticholinergic drugs to counteract the muscarinic effects.

In all patients the possibility of "cholinergic crisis", due to overdosage of pyridostigmine bromide, 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* could be decreased after thymectomy.

**Coated-tablets, 60 mg:**

Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.

**Elderly patients:**

No dose adjustment is required for the elderly; however, for treatment the possibility of age-related bradyarrhythmia (such as 2nd or 3rd-degree AV block, sick sinus syndrome), caused by the muscarinic properties of *Mestinon* Sugar-coated Tablets should be taken into consideration.

This should be diagnosed by means of an ECG before treatment is initiated and shall be checked thereafter at regular intervals. Clinical experience has shown that even in elderly patients the use of higher dosages may be required.

**Children and adolescents:**

Treatment of children younger than 6 years of age with *Mestinon*® Sugar-coated Tablets is not recommended as a dose lower than 60 mg of pyridostigmine bromide is not possible.
The initial dose for children aged 6 – 12 years is twice to four times daily one sugar-coated tablet (60 mg). For treatment of children and adolescents older than 12 years of age the same dosage as for adults is recommended.

**Patients with impaired renal function**
Reduced doses may be required for patients with impaired renal function. The dose needed should be determined according to the individual response (refer to Section "Take special care with Mestinon® Sugar-coated Tablets under the following circumstances").

**Patients with impaired liver function**
No dose adjustment is required in patients with impaired liver function.

**Method of administration**
Swallow the sugar-coated tablets with an appropriate amount of liquid.

### 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.

#### 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 bromide antagonises the effect of non-depolarising muscle relaxants (e.g. pancuronium and vecuronium). Pyridostigmine bromide may prolong the effect of depolarising muscle relaxants (e.g. suxamethonium).

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

- **Mestinon** Sugar-coated Tablets may prolong the blocking effect of succinylcholine
- Concomitant administration of **Mestinon** Sugar-coated Tablets and large-area external application of N,N-diethyl-m-toluamide (DEET), e.g. contained in Autan, should be avoided.
- Mestinon Sugar-coated Tablets may strengthen the effect of certain sleep medications and/or pain relieving drugs (such as barbiturates, opiates).
- Certain analgesic agents, cardiac stimulants (quinidine, procainamide) and other medication effecting neurotransmission may reduce the effect of Mestinon Sugar-coated Tablets.
- Some psychotropic drugs (such as tricyclic and tetracyclic anti-depressants), as well as neuroleptic agents, lithium and antihistaminic agents will antagonize (i.e. act in opposition to) the muscarinic effects of **Mestinon** Sugar-coated Tablets, while the nicotinergic effects will remain mostly unaffected.
- Oral contraceptives may weaken the effect of **Mestinon** Sugar-coated Tablets. In particular in patients with Myasthenia gravis, this may require administration of a higher dose of **Mestinon** Sugar-coated Tablets, increasing the risk of cholinergic crisis.
- Concomitant administration of **Mestinon** Sugar-coated Tablets and local anaesthetic agents (e.g. tetracaine) may lead to high concentration of the local anaesthetics in the serum possibly causing systemic effects such as arrhythmic heartbeat and central nervous system toxicity. Concomitant use of **Mestinon** Sugar-coated Tablets and other direct or indirect parasympathomimetic agents may lead to cholinergic crisis in patients with myasthenia gravis.

- In most cases, the need of **Mestinon** Sugar-coated Tablets will be clearly reduced after thymectomy (removal of the thymus gland) or in case of additional treatment (with steroids, immunosuppressive agents).
4.6 Pregnancy and lactation
The safety of pyridostigmine bromide 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 product 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 dose of pyridostigmine bromide should be avoided; newborn child should be monitored to possible effects.

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

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

Observations indicate that only negligible amounts of pyridostigmine bromide 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 inadequately treatment of Myasthenia gravis, this pharmaceutical product 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)
Not known (cannot be estimated from the available data)

The following undesirable effects were observed whereas the frequency of undesirable effect is not known:

Eye disorders:
Common: Myosis, flow of tears, disturbance of binocular vision (diplopia),
Frequency not known: Accommodation disorders

Cardiac disorders:
Frequency not known: Arrhythmia¹ (including bradycardia, tachycardia, AV block) as well syncope and hypotension¹ (see overdose section), cardiovascular effects in the postoperative phase (uncommon)
Very rare: Cardiac arrest, paradoxical reactions are possible: persistently accelerated pulse rate of more than 100 beats per minute (tachycardia), high blood pressure (hypertension).
Respiratory, thoracic and mediastinal disorders:
Uncommon: Increased bronchial secretion combined with bronchoconstriction. In patients with asthma respiratory tract complaints may occur.

Gastrointestinal disorders:
Frequency not known: Nausea, vomiting, diarrhea, abdominal cramps, gastrointestinal hypermotility, salivary hypersecretion (common), difficulty in swallowing (dysphagia) (very common)

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

Musculoskeletal, connective tissue and bone disorders:
Frequency not known: Tremors and muscle cramps or muscle hypotonia (see overdose section)
Rare: Muscular fasciculation, spasm, difficulty in swallowing, muscle weakness, in extreme cases paralysis due to neuromuscular block which shall be diagnostically differentiated from the symptoms of myasthenia gravis.

Central nervous system:
Very rare: Central nervous side effects such as irritability, anxiety, headache, sleep disorders or delirious states and convulsive seizures.
In the presence of organic brain alterations, treatment with pyridostigmine bromide may cause psychopathologic symptoms up to psychosis and/or any pre-existing symptoms may be potentiated. As these symptoms may be the first signs of cholinergic crisis, the doctor should be consulted immediately in order to clear up the cause of such symptoms. To remedy any parasympathicomimetic effects: Parenteral administration of atropine sulfate

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 overdose section).

Additional for solution for injection:
Frequency not known: Chlorocresol may cause allergic reactions.

4.9 Overdose
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 2 mg intravenously is an antidote to the muscarinic effects. Doses may be repeated every 5 to 30 minutes as needed.

Cholinergic crisis may occur following overdose of Mestinon Sugar-coated Tablets. Such state may become apparent, among others, by pronounced or increased muscle weakness. Misinterpretation of such conditions leads to life-threatening conditions due to paralysis of the respiratory muscles. Bradycardia (slow heartbeat), unwanted cardiovascular reactions, tachycardia (rapid heartbeat) as well as low blood pressure (hypotension) can be other accompanying symptoms.
Counteractive measures consist in the immediate discontinuation of Mestinon Sugar-coated Tablets and other cholinergic agents and in slow intravenous administration of 1 to 2 mg atropine sulfate. Depending on the pulse rate this dose has to be repeated after two to four hours, if needed.
5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: N07AA02

Pyridostigmine bromide is an antagonist to cholinesterase, the enzyme which normally destroys acetylcholine. The action of pyridostigmine bromide can briefly be described, therefore, as the potentiation of naturally occurring acetylcholine. Pyridostigmine bromide does not cross the blood-brain barrier except possibly in stressful conditions. Pyridostigmine bromide 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 neostigmine, it is usually much better tolerated by myasthenic patients in whom the longer action is also an advantage.

5.2 Pharmacokinetic properties

Immediate release:

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

Non-clinical data reveal no special hazard for humans with respect to conventional studies of safety pharmacology, single and repeated dose toxicity and genotoxicity. In rats an inhibition of acetylcholineserase with tremor was noted after 3 months of treatment with ≥ 15 mg/kg/60 mg/kg mortality amounted to 10% of animals treated. Treatment-related haematology'post-mortem or histopathology findings occurred in none of the dosage groups. 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 bromide.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Maize starch, Magnesium stearate, Pregelatinised starch, Povidone K30, Colloidal anhydrous silica, Talc, Acacia spary-dried gum, Iron oxide red (E172), Iron oxide yellow (E172), Light liquid paraffin, Hard paraffin, Rice starch, Sucrose crystalline, Talc

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years

May be used within 3 months after opening.

6.4 Special precautions for storage

Store under 25°C

6.5 Nature and contents of container

Amber glass bottle 20, 150 dragee

6 MANUFACTURER

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