SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

MESTINON® 10 mg (tablets)

MESTINON® 60 mg (tablets)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

MESTINON® 10 mg tablets:

Each tablet contains 10 mg pyridostigmine bromide.

Contains sugar: Lactose 30,00 mg

MESTINON® 60 mg tablets:

Each tablet contains 60 mg pyridostigmine bromide.

Contains sugar: Sucrose 161,569 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Tablet for oral use.

MESTINON®10 mg tablets: White to off-white round and biconvex tablets.

MESTINON® 60 mg tablets: Round, biconvex, orange-white to pale orange, sugar-coated tablets. In cross-section the sugar-coated tablets are white to off-white in colour.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Myasthenia gravis.

4.2 Posology and method of administration

Posology

Adults: 1-3 60 mg tablets two to four times daily, or higher doses if required.

Children: 7 mg/kg body-mass daily at four hourly intervals.

It is important to remember that the dosage must be individually titrated.

No response to a specific dosage could be due to underdosage or overdosage.

Usually in the case of too large a dose given too frequently, side effects of the muscarinic and/or nicotinic type will manifest *(see section 4.8)*.

Method of administration

For oral use.

4.3 Contraindications

- Hypersensitivity to the active substance pyridostigmine and to bromides or to any of the excipients listed in section 6.1.
- Mechanical gastrointestinal or urinary obstruction.

4.4 Special warnings and precautions for use

Although failure of patients to show clinical improvement may reflect underdosage, it can also be indicative of overdosage. Overdosage may result in cholinergic crisis, a state characterised by increasing muscle which, through involvement of the muscles of respiration, my lead to 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. Differential diagnosis can be aided by the Tensilon (edrophonium chloride) test. If 0,1 mL (1 mg) or at most 0,2 mL (2 mg) of Tensilon (edrophonium chloride) is given intravenously, a marked improvement indicates myasthenic crisis. Any other response, whether equivocal or exacerbation of symptoms, must be considered to be cholinergic. The treatment of the two conditions obviously differs radically. Whereas the presence of myasthenic crisis suggests the need for more intensive anticholinesterase therapy, the diagnosis of cholinergic crisis calls for the prompt withdrawal of all medicines of this type and institution of appropriate supportive measures, including respiratory assistance. The immediate use of atropine in cholinergic crisis is also recommended. Atropine may

also be used to abolish or obtund gastrointestinal side effects or other muscarinic reactions. Care should be observed in the use of atropine for counteracting side effects; such use, by masking signs of overdosage, can lead to inadvertent induction of cholinergic crisis.

Differentiation of myasthenic and cholinergic crisis:

- The patient with myasthenic crisis will often have a history of intervening infection, emotional trauma, perhaps a relationship to the menstrual cycle or cessation of medication. The usual dose of the medicine becomes ineffective and increased weakness or side reactions do not occur after taking medication.
- A cholinergic crisis may begin in a similar manner but the patient keeps increasing the amount and frequency of medication, with less effect and more side reactions, especially increased secretions with gastrointestinal activity. The patient in cholinergic crisis is weak, as in myasthenic crisis, but there is usually pallor (a cold clammy skin) often accompanied by hypertension, bradycardia, miosis, excessive salivation and perspiration and muscular fasciculation.

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 medicine dosage effect.

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

Care should be taken in patients with:

- Arrythmias such as bradycardia and AV block (eldery 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 MESTINON® are taken by myasthenic patients it may be necessary to give atropine or other anti-cholinergic medicines to specifically counteract the muscarinic effects of MESTINON® while maintaining its nicotinergic effect.

The requirement for MESTINON® is usually markedly decreased after thymectomy or when additional therapy (steroids, immunosuppressant medicines) is given (see section 4.5).

MESTINON® should be given with caution to elderly patients and to patients with pre-existing conduction disturbances.

Safety in pregnancy has not been established.

Note: certain antibiotics, especially neomycin, streptomycin and kanamycin have a mild definite non-depolarizing blocking action which may accentuate neuromuscular block. These antibiotics should only be used in the myasthenic patient when definitely indicated and then with careful observation to adjust anticholinesterase dosage.

Lactose/Sucrose warning:

MESTINON® 10 mg

Lactose warning:

MESTINON® 10 mg contains lactose that may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take MESTINON® 10 mg.

MESTINON® 60 mg

Sucrose warning:

MESTINON® 60 mg contains sucrose that may have an effect on the glycaemic control of patients with diabetes mellitus. Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take MESTINON® 60 mg.

4.5 Interaction with other medicines and other forms of Interaction

Immunosuppressant medicines:

The requirement for MESTINON® may be decreased by concomitant use when additional therapy (corticosteroids or immune-suppressant medicines) is given. 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:

Methycellulose and medicines containing methycellulose as excipients can completely inhibit absorption of pyridostigmine bromide as contained in MESTINON®.

Antimuscarinics:

Atropine and hyoscine antagonise the muscarinic effects of MESTINON®. It should be noted that the slower gastrointestinal motility caused by these medicines may affect the absorption of MESTINON®.

Muscle relaxants:

MESTINON® antagonises the effect of non-polarising muscle relaxants e.g. pancuronium and vecuronium). MESTINON® may prolong the effect of depolarising muscle relaxants (e.g. suxamethonium).

Others:

Aminoglycoside antibiotics, local and some general anaesthetics, antiarrhythmic medicines, and other medicines that interfere with neuromuscular transmission may interact with MESTINON®.

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of MESTINON® during pregnancy has not been established.

Breastfeeding

The safety of MESTINON® during breastfeeding has not been established.

4.7 Effects on ability to drive and use machines

MESTINON® may cause miosis and accommodation disorders and an inadequate treatment of myasthenia gravis may impair visual acuity and may have minor influence on mental and/or physical

abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

Summary of the safety profile

As with all cholinergic medicines, 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, miosis and diaphoresis. The primary nicotinic effects are muscle cramps, fasciculation and weakness. Skin rash may occur.

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).

Tabulated list of adverse reactions

Body System	**Rare**	**Frequency not known**
Immune system disorders:		Hypersensitivity (*see section 4.3*).
Nervous system disorders:		Syncope.
Eye disorders:		Miosis, increased lacrimation, accommodation disorders (e.g. blurred vision).
Cardiac disorders:		Dysrhythmia (incl. bradycardia, tachycardia, AV block) as well as

		syncope and hypotension, Prinzmetal angina.
Vascular disorders:		Flushing, hypotension.
Respiratory, thoracic and mediastinal disorders:		Increased bronchial secretion combined with bronchoconstriction.
Gastrointestinal disorders:		Nausea, vomiting, diarrhoea, gastrointestinal (GI) hypermotility, salivary hypersecretion, abdominal symptoms (e.g. discomfort, pain, cramps).
Skin and subcutaneous tissue disorders:	Rash (disappears usually soon after ceasing of medication. Bromide containing medicines should no longer be used).	Hyperhydrosis, urticarial.
Musculoskeletal, connective tissue and bone disorders:		Increased muscle weakness, fasciculation (muscle twitching), tremors and muscle cramps or muscle hypotonia (*see section 4.9*).
Renal and urinary disorders:		Urinary urgency.

Because these symptoms may be an indication of cholinergic crisis, the doctor 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested

to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In the event of an overdose, side effects can be precipitated and/or be of increased severity (*see section 4.8)*.

As MESTINON® is excreted mainly by the kidneys, caution is advised in cases of renal function impairment.

Overdosage may lead to “cholinergic crisis”. The signs and symptoms of overdosage are due to muscuranic and nicotinic actions. Cardiovascular and respiratory failure may occur.

MESTINON® may cause cholinergic crisis. Signs of overdosage due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretions, salivation, hyperhidrosis 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.

Bradycardia ranging up to cardiac arrest, hypotension ranging up to cardiovascular collapse may occur if overdosage is excessive.

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

Skin rashes due to sensitivity to bromide ion have been reported.

Overdosage with decreased therapeutic effect must be differentiated from myasthenia gravis.

Suggested treatment of overdosage:

MESTINON® treatment must be stopped immediately.

Artificial ventilation should be instituted if respiration is severely depressed.

The muscarinic effects are the most serious and may be controlled by atropine.

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.

Nicotinic effects may be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A.5.3 Cholinergics

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

Pyridostigmine is a reversible cholinesterase inhibitor, which an enzyme inactivates acetylcholine. Pyridostigmine prolongs the acetylcholine effect at the synaptic cleft. It does not cross the blood-brain barrier at non-toxic doses. Pyridostigmine has a more prolonged action than neostigmine although it is somewhat slower to take effect (generally taking 30-60 minutes). Because it has a weaker muscarinic effect 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

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

Administered in healthy volunteers at oral daily doses of 120 mg, 120-370 mg, and 180-1440 mg, the oral absolute bioavailability of pyridostigmine bromide was 7,6 %, 18,9 %, and 3-4 % with C_{max} of 40-80 µg/L, 20-100 µg/L, and 180 µg/L at t_{max} 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 absolute 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 subjects, 1,76 L/kg in myasthenia gravis patients, and 0,53 to 1,1 L/kg in surgical patients.

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

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. With oral use, a total of 5-15 % of oral doses is 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 surgical patients, 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

MESTINON® 10 mg:

Colloidal anhydrous silica,

Lactose monohydrate,

Magnesium stearate,

Maize starch,

Pregelatinized starch,

Talc.

MESTINON® 60 mg:

Colloidal anhydrous silica,

Magnesium stearate,

Maize starch,

Povidone,

Pregelatinized starch.

Coating components:

Acacia spray-dried gum,

Hard paraffin,

Iron oxide red (E172),

Iron oxide yellow (E172),

Light liquid paraffin,

Rice starch,

Sucrose crystalline,

Talc.

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

MESTINON® 10 mg:

36 months

MESTINON® 60 mg:

48 months

6.4 Special precautions for storage

Store at or below 25 °C.

Protect from light.

Store in the original package/container.

6.5 Nature and contents of container

MESTINON® 10 mg:

50, 100, 250 tablets are packaged in amber glass bottles closed with high-density (HD) polyethylene screw caps with bellows.

MESTINON® 60 mg:

20, 100, 150 tablets are packed in amber glass bottles, closed with screw caps with or without bellows and a tamper evident ring.

20 tablets in glass bottle with screw cap with bellows.

100 tablets in glass bottle with screw cap without bellows.

150 tablets in glass bottle with screw cap without bellows.

Not all pack sizes may be marketed.

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

No special requirements for disposal.

7 THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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8 REGISTRATION NUMBER(S)

MESTINON® 10 mg tablets: UX/5.3/179

MESTINON® 60 mg tablets: C/5.3/610

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

MESTINON® 10 mg tablets: 22 July 1987

MESTINON® 60 mg tablets: 02 December 1991

10 DATE OF REVISION OF TEXT

09 April 2026