1.3.1.1 Professional Information for medicines for human use

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

MESTINON® 10 mg (tablets)

MESTINON® 60 mg (tablets)

2 QUALITIVE AND QUANTITIVE COMPOSITION

MESTINON® tablets contain 10 mg or 60 mg of the dimethylcarbamic-ester of 1-methyl-3-hydroxypyridinium bromide (pyridostigmine bromide)

Excipients with known effect:

MESTINON® 10 mg (tablets):

Contains sugar: Lactose 30,00 mg

MESTINON® 60 mg (tablets):

Contains sugar: Sucrose 161,569 mg

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

MESTINON®10 mg tablets:

White to off-white round and biconvex tablets.

Diameter approximately 8,0mm.

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.

Diameter approximately 9,6 mm.

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.
- MESTINON® is contraindicated in mechanical intestinal 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 cholinergeic crisis:*

o 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.

- 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 e.g. galactosaemia, the Lapp 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 conditions such as fructose intolerance, glucose-galactose mal-absorption or sucrase-isomaltase insufficiency should not take MESTINON 60 mg.

4.5 Interaction with other medicines and other forms of Interaction

Immunosuppressant ~~drugs~~ 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 gastro-intestinal 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

- Nicotinic side effects are comprised chiefly of muscle cramps, fasciculation and weakness. Skin rash may occur.
- As with all cholinergic products, MESTINON® may have unwanted functional effects on the autonomic nervous system.
- Muscarinic-like adverse effects may be exhibited as nausea, vomiting, diarrhoea, abdominal cramps, increased peristaltic and increased bronchial secretion, salivation, bradycardia and miosis and diaphoresis.

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, Prinz metal 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "Report Drug Reaction Process", found online under SAHPRA's safety publications: https://www.sahpra.org.za/

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.
- Its muscarinic effects consist of abdominal cramps, increased peristalsis, diarrhoea, nausea and vomiting, increased bronchial secretions, salivation, hyperhidrosis and miosis.

- Nicotinic increased effects are 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.
- Nicotinic effects may be treated symptomatically.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

PHARMACOLOGICAL CLASSIFICATION:

A.5.3 Cholinergics

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

Pharmacodynamic effects:

Pyridostigmine bromide is an orally reversible cholinesterase inhibitor. It has a slower onset and longer duration of action than neostigmine.

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 and 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 into amber glass bottles, closed with screw caps with or without a 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

Viatris Healthcare (Pty) Ltd

4 Brewery Street

Isando

1600

Republic of South Africa

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

12 July 1994

10 DATE OF REVISION OF TEXT

29 September 2023