C o m p a n y C o r e D a t a S h e e t

Product	**Pyridostigmine bromide** Date: 15.04.2015
CTD-Code:	N/A (to be used for preparation of 1.3.1 / to be attached to 5.3.6)
Title:	**Mestinon®** **Pyridostigmine bromide** - **5 mg/ml solution for injection** - **10 mg tablet** - **60 mg tablet** - **60 mg coated tablet** - **180 mg prolonged-release tablet**
Product Names:	Mestinon®
Version:	02
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NOTICE

The Company Core Data Sheet (CCDS) displays the company's current position on important characteristics of Pyridostigmine bromide, including the Core Safety Information according to ICH E2C. Because regulatory requirements and medical practices vary between countries, SPCs may differ in several respects, including but not limited to the characterisation of risks and benefits.

Document History

Version	Change/References	Valid from
01	New CCDS based on the UK SPC: Mestinon 60 mg tablets May 2007	27-01-2010

Pyridostigmine bromide
(Tablet, coated-tablet, prolonged-release tablet, solution for injection)

Version	Change/References	Valid from
02	**Section 4.2:** - Editorial changes - Subsection *Renal impairment*: wording included. Addition of method of administration of oral dosage forms **Section 4.4:** - Editorial changes - Addition of renal impairment - Information regarding thymectomy shifted to section 4.5 **Section 4.5:** - Editorial changes - Addition of thymectomy (shifted from section 4.4) - Addition of initial effect of corticosteroids **Section 4.6:** - Editorial changes - Adaption of information regarding overdose - Addition of information on fertililty **Section 4.8:** <u>New:</u> - **Immune system disorders /** Drug hypersensitivity - **Cardiac disorders /** Prinzmetal angina - **Vascular disorders** / Flushing (as symptom of an allergic reaction) - **Skin and subcutaneous tissue disorders** / Urticaria (as symptom of an allergic reaction) <u>Adapted:</u> - **SOC Nervous system disorders** has been implemented **/** Syncope has been switched from SOC Cardiac disorders - **SOC Eye disorders /** Implementation of example (blurred vision) for accommodation disorders - **Cardicac disorders /** Hypotension has been switched to SOC **Vascular disorder;** Syncope see **Nervous system disorder** - **Gastrointestinal disorders** / Abdominal cramps has been replaced by correct MedDRA code (=abdominal symptoms (e.g. discomfort pain, cramps etc.) - **Musculoskeletal and connective tissue disorders /** Fasciculation adapted by means of "(muscle twitching)" - **"** Chlorocresol may cause allergic reactions"	16-04-2015

Version	Change/References	Valid from
	(concern solution for injection only) has been shifted to SOC **Immune system disorders** **Section 4.9:** - Explicitely adressing cholinergic crisis - Convulsions and coma may also occur (added) - Addition of advice to stop treatment immediately - Diaphoresis and bronchospasm added - Further definition of impact after overdose: "…which may produce apnoea and cerebral anoxia in particularly severe cases" ... **Section 5.1:** - Editorial changes **Section 5.2:** - Editorial changes (e. g. reorganisation of text into the subsections Absorption, Distribution, Metabolism and Elimination) - Addition of concentration of pyridostigmine in breast milk; adaption of information regarding metabolism	

Pyridostigmine bromide
(Tablet, coated-tablet, prolonged-release tablet, solution for injection)

1. NAME OF THE MEDICINAL PRODUCT

Name: Mestinon® 5 mg/ml, solution for injection
Mestinon® 10 mg, tablet
Mestinon® 60 mg, tablet
Mestinon® 60 mg, coated tablet
Mestinon® retard / Mestinon® 180 mg, prolonged-release tablets

The trademark Mestinon is used throughout this CCDS.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description
[See local labelling]

2.2 Qualitative and quantitative composition
Active substance: Pyridostigmine bromide
5 mg/ml solution for injection
10 mg / tablet, 60 mg / tablet, 60 mg / coated tablet
180 mg / prolonged-release tablet

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
- Solution for injection
- Tablets, for oral use

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
[The following are representative indications. Locally approved indications may differ.]

Immediate release – oral formulation (10 mg / 60 mg)
- Myasthenia gravis
- Paralytic ileus
- Atonic constipation
- Atonic bladder
- Post-operative urinary retention

Prolonged-release
- Myasthenia gravis

Solution for injection
- Myasthenia gravis
- Antagonism of non-depolarizing muscle relaxants

4.2 Posology and method of administration

[The text in this section represents representative dosage recommendations; locally approved dosage recommendations may differ.]

Myasthenia gravis

Adults

Oral dosage forms

Multiple doses of 30 to 180 mg each are given at intervals throughout the day. The total daily dose is usually in the range of 120–1200 mg but higher doses may be needed according to dose titration.

Solution for injection

2–5 mg daily SC/IM

Newborns

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

In neonatal myasthenia, treatment with neostigmine is usually preferred. However, if this deems 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 as tablets every 4 to 6 hours 30-60 minutes before feeding, each. 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 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 of 30–360 mg.

Antagonism of non-depolarizing muscle relaxants

Adults

The usual dose is 5 mg IV

Other indications

Adults

The usual dose is 60–240 mg per day per os.

Children

The usual dose is 15–60 mg per day per os.

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

Special populations

Elderly

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

Renal impairment

Pyridostigmine is mainly excreted unchanged in the urine, therefore lower doses may be required in patients with renal impairment 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

Oral dosage forms

Mestinon should be taken with water (half-full to full glass of water).

Solution for injection

Depending on the calculated dose for a specific indication and determined body weight, the contents of one injection vial of Mestinon 5, solution for injection can be mixed with 50 ml of saline solution and/or glucose solution (5 to 10% concentrated) and then infused over a period of no more than eight hours. After this time, the properties of the active substance will change.

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

Additional for solution for injection

Mestinon is contraindicated for patients with hypersensitivity to chlorocresol.

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 diseases (COPD).

Care must 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
- Parkinsonism
- Hyperthyroidism[1]
- 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 calls for immediate discontinuation of this treatment and appropriate supportive measures, including respiratory assistance.

Tablets, 10 mg/60 mg
Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Coated-tablets, 60 mg
Patients with rare hereditary problems of fructose intolerance, glucose galactose malabsorption or sucrase isomaltase insufficiency should not take this medicine.

Solution for injection, 5 mg/ml
This medicinal product contains less than 1 mmol sodium (23 mg) per dose.

4.5 Interaction with other medicinal products and other forms of interaction

Immunosuppressant drugs
The requirement for pyridostigmine may be decreased by concomitant use with corticosteroids or immunosuppressant drugs.
Nethertheless, a new addition of corticosteroids may initially aggravate the symptoms of myasthenia gravis.[2, 3, 4]

Thymectomy
The need for Mestinon dosing may be decreased after thymectomy.

Methylcellulose
Methylcellulose and medicines containing methylcellulose as excipients can inhibit absorption of pyridostigmine bromide.

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.

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.

4.6 Fertility, pregnancy and lactation

Fertility

Nonclinical investigations in rats have not shown any negative effects on reproductive behavior. [5, 6]

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 product in pregnant patients with myasthenia gravis has revealed no untoward effect of the drug on the course of pregnancy. As the severity of myasthenia gravis often fluctuates considerably in pregnancy[7], particular care is required to avoid cholinergic crisis due to overdose. Since pyridostigmine bromide crosses the placenta barrier excessive dose of pyridostigmine should be avoided; the newborn child should be monitored to 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).

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 whereas the frequency of undesirable effect is not known:

Immune system disorders
Frequency not known: Drug hypersensitivity[8]

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

Nervous system disorders
Frequency not known: Syncope

Eye disorders
Frequency not known: Miosis[1], increased lacrimation[1], accommodation disorders (e.g. blurred vision)

Cardiac disorders
Frequency not known: Arrhythmia[1] (including bradycardia, tachycardia, AV block), Prinzmetal angina[9]

Vascular disorders
Frequency not known: Flushing , hypotension

Respiratory, thoracic and mediastinal disorders
Frequency not known: Increased bronchial secretion combined with bronchoconstriction[1]

Gastrointestinal disorders
Frequency not known: Nausea, vomiting, diarrhoea, gastrointestinal hypermotility[1], salivary hypersecretion, abdominal symptoms (e.g. discomfort pain, cramps etc.)

Skin and subcutaneous tissue disorders
Rare: Rash[1] (disappears usually soon after ceasing of medication. Bromide containing medicines should no longer be used.)
Frequency not known: Hyperhidrosis, urticaria

Musculoskeletal and connective tissue disorders
Frequency not known: Increased muscle weakness[1] fasciculation (muscle twitching)[1], tremors[1] and muscle cramps[1] or muscle hypotonia (see section 4.9)

Renal and urinary disorders
Frequency not known: Urinary urgency[1]

Because these symptoms may be an indication of cholinergic crisis[1], the physician should be notified immediately to clarify the diagnosis (see section 4.9).

4.9 Overdose

Pyridostigmine may cause cholinergic crisis. Signs of overdose due to muscarinic effects may include abdominal cramps, increased peristalsis, diarrhoea, diaphoresis, nausea and vomiting, increased bronchial secretions, bronchospasm, salivation, hyperhidrosis and miosis. Nicotinic effects consist of muscular cramps, fasciculations and general weakness up to paralysis[1], which may produce apnoea and cerebral anoxia in particularly severe cases.

Hypotension up to cardiovascular collapse, bradyarrhythmia, up to cardiac arrest[1] may occur.

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

Mestinon treatment must be stopped immediately. 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ATC Code: N07AA02

Pyridostigmine is a reversible cholinesterase inhibitor[10], 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) [11]. 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

Absorption

Peroral pyridostigmine bromide 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 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 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 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).[12]

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.[12, 13]

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 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 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
[See local labelling]

6.2 Incompatibilities
Tablets/Coated-tablets/Prolonged-release tablets
None known

Solution for injection
Compatibility studies have not been performed, therefore the solution for injection must not be mixed with other medicines (see section 4.2).

6.3 Shelf life
[See local labelling]

6.4 Special precautions for storage
[See local labelling]

6.5 Nature and contents of container <and special equipment for use, administration or implantation>
[See local labelling]

6.6 Special precautions for disposal <and other handling>
[See local labelling]

References

[1] Martindale, 34 edition

[2] Brunner NG, Namba T, & Grob D: Corticosteroids in management of severe, generalized myasthenia gravis. Effectiveness and comparison with corticotropin therapy. Neurology 1972; 22:603-610.

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[4] Warmolts JR, Engel WK, & Whitaker JN: Alternate-day prednisone in a patient with myasthenia gravis. Lancet 1970; 2:1198-1199.

[5] Hoar RM, Woo D. Reproduction Studies of Pyridostigmine Bromide in Rats. Exp Path Tox Report No. 22'291, February 11, 1970

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[7] Plauché WC. Myasthenia Gravis in Mothers and their Newborns. Clinical Obstetrics and Gynecology March 1991; 34(1):82-99.

[8] CES dated 21-Nov-2014; Update of CCDS section 4.8, additional event “Drug hypersensitivity

[9] CES dated 20-Nov-2014; Update of CCDS section 4.8, additional event “Prinzmetal angina”

[10] Taylor P. Cholinesterase agents. In: Goodman and Gilman, eds. Pharmacological Basis of Therapeutics 11th Edition 2005: 201-216.

[11] Schumm F, Gaertner HJ, Wiatr G, Dichgans J. Serumspiegel von Pyridostigmin bei Myasthenia Gravis: Methoden und Klinische Bedeutung. Fortschr. Neurol. Psychiat. 1985; 53(6): 201-11.

[12] Aquilonius SM, Hartvig P. Clinical Pharmacokinetics of Cholinesterase Inhibitors. Clinical Pharmacokinetics 1986; 11 (3):236-49

[13] Somani SM, Roberts JB, Wilson A. Pyridostigmine metabolism in man. Clin Pharmacol Ther. 1972; 13(3):393-9.