SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MESTINON DRAGEES 60 MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 coated tablet (dragee) contains 60 mg pyridostigmine bromide.

Excipient(s) with known effect:
Sucrose 161.6 mg/coated tablet

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Coated tablet (dragee) for oral use
Round, biconvex, orange-white or pale orange coloured sugar coated tablet.

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. **Mestinon dragees 60 mg must not** be divided. If available, use a tablet containing 30 mg pyridostigmine bromide for 30mg dose.

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.

Children

Children under 6 years old should receive an initial dose of 30 mg of pyridostigmine bromide.

Mestinon dragees 60 mg must not be divided. If available, use a tablet containing 30 mg pyridostigmine bromide for 30 mg dose.

Children 6 – 12 years old should receive 60 mg. Dosage should be increased gradually, in increments of 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 dragees 60 mg** in elderly patients.

Renal impairment

Mestinon dragees 60 mg 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 dragees 60 mg** in patients with hepatic impairment.

4.3 Contraindications

- Hypersensitivity to the active substance, other bromides or to any of the excipients listed in section 6.1.
- Mechanical obstruction of the digestive or urinary tract

4.4 Special warnings and precautions for use

Mestinon dragees 60 mg is to be used with particular caution in
- Patients with obstructive respiratory illnesses such as bronchial asthma and chronic obstructive pulmonary disease (COPD).

Mestinon dragees 60 mg is to be used with caution in
- Patients with arrhythmias such as bradycardia and atrioventricular block (AV block). Arrhythmias tend to be more common in older patients than young adults.
- Myocardial infarction, decompensated heart failure
- Hypotension
- Vagotonia
- Peptic ulcer
- Patients who have undergone gastrointestinal surgery
- Epilepsy
- Parkinson's disease
- An overactive thyroid gland
- Renal function disorders (see section 4.2)

With these diseases, the increased risk must be carefully weighed up against the benefits of treatment.

Very high doses of pyridostigmine bromide can require the administration of atropine or other anticholinergics to specifically counteract the muscarinic effect without impairing the nicotinergic effect.

An overdose of pyridostigmine bromide can cause a cholinergic crisis. This must be

differentiated from the myasthenic crisis which can occur due to a worsening of the disease. Both cholinergic and myasthenic crises can manifest as pronounced or increased muscle weakness.
In a myasthenic crisis, intensified treatment with a cholinesterase inhibitor (e.g. **Mestinon dragees 60 mg**) may be necessary.
In a cholinergic crisis, the treatment with pyridostigmine bromide must be immediately discontinued and appropriate supportive measures, including artificial respiration, must be initiated (see section 4.9).

The active substance is mainly excreted unchanged by the kidney and should therefore be used with caution in cases of renal insufficiency. Patients with kidney disease may need lower doses (see section 4.2).

Patients with rare hereditary fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase deficiency should not take **Mestinon dragees 60 mg**.

4.5 Interaction with other medicinal products and other forms of interaction

Immunosuppressants
Concomitant therapy with immunosuppressants or corticosteroids can strengthen the effect of pyridostigmine bromide. The administration of corticosteroids may initially aggravate the symptoms of myasthenia gravis.

Thymectomy
A thymectomy can lead to a decrease in the dosage required.

Methylcellulose
Methylcellulose may prevent the absorption of pyridostigmine bromide.
Hence, the simultaneous use of medicines that contain methylcellulose as an excipient should be avoided.

Anticholinergics
Atropine and scopolamine antagonise the muscarinic effect of pyridostigmine bromide. The decreased intestinal motility caused by these medicines can inhibit the absorption of pyridostigmine bromide.

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

Other medicines
Antibiotics of the aminoglycoside group (e.g. neomycin, kanamycin), local anaesthetics and some general anaesthetics, antiarrhythmic agents and other substances that interfere with neuromuscular transmission can influence the effect of pyridostigmine bromide.

Simultaneous administration of **Mestinon dragees 60 mg** and a large-area, external application of N,N-diethyl-m-toluamide (DEET), which Autan® and other products contain, should be avoided, as pyridostigmine bromide may increase the toxicity of DEET.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are insufficient data on the administration of **Mestinon dragees 60 mg** during pregnancy.
In animal testing, pyridostigmine did not demonstrate any teratogenic effects following oral administration. However, at maternal toxic doses, foetotoxicity and effects on the offspring have been observed (see section 5.3).
Pyridostigmine crosses the placental barrier. Since the severity of the disease can vary significantly in pregnant women, particular caution is required here in order to avoid a cholinergic crisis due to overdose.
Therefore the use of **Mestinon dragees 60 mg** during pregnancy is permitted only if it is strictly indicated. The newborn should be monitored for possible effects.

The i.v. administration of cholinesterase inhibitors can cause premature contractions in pregnancy. The risk of premature contractions is highest when used towards the end of pregnancy. It is not known whether there is a risk of premature contractions with oral use.

Breastfeeding
Small amounts of pyridostigmine have been found in the plasma of breast-fed newborns/children of women treated. Based on a very limited number of cases studied, no effects have been observed on breast-fed infants/children. If treatment is required, the infant should be monitored for possible effects or weaned.

Fertility
Animal studies did not demonstrate any effect on male or female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Taking **Mestinon dragees 60 mg** may lead to accommodation disorders or contraction of the pupils and impair the ability to drive. If the underlying disease is not adequately treated or if there are cholinergic effects after a relative overdose of **Mestinon dragees 60 mg** the ability to actively participate in road traffic or to use machines can be impaired.

4.8 Undesirable effects

As with all cholinergic products, **Mestinon dragees 60 mg** may have unwanted functional effects on the autonomic nervous system.
Muscarinic-like undesirable effects may include: Nausea, vomiting, diarrhoea, abdominal cramps, gastrointestinal hypermotility as well as increased bronchial secretion, hypersalivation, bradycardia and miosis.
The primary nicotinergic effects are muscle cramps, fasciculations and muscle weakness.

The following categories are used for the frequencies of adverse reactions:
- 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 adverse reactions have been observed:

Immune system disorders
Frequency not known: Drug hypersensitivity

Psychiatric illnesses
In the presence of organic brain changes, psychopathological symptoms through to psychosis may occur during the treatment with pyridostigmine bromide; existing symptoms may intensify.

Nervous system disorders
Frequency not known: Syncope

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

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

Vascular disorders
Frequency not known: Flushing, hypotension

Respiratory, thoracic and mediastinal disorders
Frequency not known: Increased bronchial secretion combined with bronchial obstruction; asthmatics may experience respiratory symptoms.

Gastrointestinal disorders
Frequency not known: Nausea, vomiting, diarrhoea, gastrointestinal hypermotility, hypersalivation, abdominal symptoms (e.g. malaise, pain, cramps)

Skin and subcutaneous tissue disorders
Rare: Skin rash (usually subsides after the medication is discontinued. Medicines containing bromide should not be used).
Frequency not known: Hyperhidrosis, urticaria

Musculoskeletal and connective tissue disorders
Frequency not known: Increased muscle weakness, fasciculation (muscle twitching), tremor, muscle cramps or hypotonia

Renal and urinary disorders
Frequency not known: Increased urge to urinate

Side effects are generally dose-related:
In the course of treatment with **Mestinon dragees 60 mg** (mostly with oral doses exceeding 150-200 mg pyridostigmine bromide/day) the following side effects in particular may arise: attacks of sweating, salivation, lacrimation, increased bronchial secretion, nausea, vomiting, diarrhoea, abdominal cramps (due to gastrointestinal hypermotility), increased urge to urinate, muscle tremors, muscle cramps, muscle weakness or accommodation disorders (see section 4.9). After taking higher doses (500-600 mg pyridostigmine bromide/day orally), bradycardia as well as adverse cardiovascular reactions and hypotension may occur. Patients with chronic obstructive pulmonary disease (COPD) may also exhibit pulmonary obstruction in addition to increased bronchial secretion. Asthmatics may experience respiratory symptoms.

The side effects listed may also be signs of an overdose or a cholinergic crisis. The cause of the side effects must therefore be clarified (see section 4.9).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

An overdose of **Mestinon dragees 60 mg** can lead to a cholinergic crisis which necessitates intensive care monitoring. If a situation like this is not recognised, there is a risk of life-threatening respiratory muscle paralysis.

Possible symptoms of a cholinergic crisis
Muscarinic effects
Hypersalivation, lacrimation, rhinorrhoea, light to heavy sweating, increased bronchial secretion, bronchospasm, skin redness, miosis and accommodation disorders, dizziness, nausea, vomiting, increased peristalsis and diarrhoea, involuntary micturition and defecation with abdominal cramps, extreme bradycardia to the point of cardiac arrest, a drop in blood pressure through to circulatory collapse, periodic sinus tachycardia, pulmonary oedema.

Nicotinergic effects
Occasional muscle cramps, fasciculations, adynamia, general weakness through to paralysis which can lead to apnoea and cerebral anoxia in particularly serious cases.
Symptoms involving the central nervous system can be observed, including unrest, confusion, slurred speech, nervousness, irritability, and visual hallucinations.
Convulsions and coma may occur.

Treatment of a cholinergic crisis
- Immediately discontinue acetylcholinesterase inhibitors. Stop medications for 3 to 4 days
- Artificial respiration in the event of significant respiratory depression
- Slow intravenous administration of atropine (1 to 2 mg atropine sulphate) (every 5 to 30 min. if necessary) and dose reduction according to clinical factors (particularly pulse rate)
- No plasma therapy
- In the case of heavy congestion: intensive respiratory toilet, i.v. fluids, secretolytics, broncholytics if necessary.

- Careful resumption of acetylcholinesterase inhibitor therapy, e.g. start with 0.5 mg pyridostigmine bromide parenterally every 4 to 6 hours or 4 x 20 mg pyridostigmine bromide orally

Treatment in the case of accommodation disorders
Mydriatics, e.g. tropicamide (monitor pressure!).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Cholinergics, cholinesterase inhibitors
ATC code: N07AA02

Pyridostigmine is a reversible acetylcholinesterase inhibitor, the enzyme which metabolises and inactivates acetylcholine. It thus increases the concentration of acetylcholine at the neuromuscular junction of skeletal muscles. Pyridostigmine does not cross the blood-brain barrier and has a longer effect than neostigmine. The onset of effect is somewhat slower than in the case of neostigmine, generally after 30 to 60 minutes. In comparison to neostigmine, the muscarinic components and the risk of associated adverse reactions are less pronounced in the case of pyridostigmine.

5.2 Pharmacokinetic properties

Absorption
Peroral pyridostigmine bromide was poorly absorbed at 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 40-60 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. The low and highly variable bioavailability across studies is attributed to the low absorption rate of pyridostigmine bromide. In patients with myasthenia gravis, the bioavailability can 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 patients with myasthenia and 0.53 l/kg to 1.1 l/kg in surgery.

The concentration of pyridostigmine in breast milk has been found to be 36-113% compared to maternal plasma, which implies a very low dose to the nursing infant (approximately 0.1% of the dose per kilogram body weight taken by the mother).

Biotransformation
Pyridostigmine is metabolized only to a small extent. It is hydrolysed by plasma cholinesterases. The main metabolite of pyridostigmine is the hydrolysis product 3-hydroxy-N-methyl pyridinium.

Elimination
The plasma clearance occurs very quickly at 0.65 l/h/kg in healthy subjects, 0.29 to 1.0 l/h/kg in patients with myasthenia and 0.52 to 0.98 l/h/kg in patients following surgical interventions.

Intravenously administered pyridostigmine is mainly excreted by the kidney (75-90%) as parent compound and as inactive metabolites at a ratio of approximately 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.

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.

5.3 Preclinical safety data

Following oral administration of toxic doses to rats, the mortality increased due to acute respiratory failure. Damage to the neuromuscular synapses of the diaphragm could be histologically demonstrated. Longer-term oral administration to rats led to the inhibition of plasma cholinesterase and erythrocyte acetylcholinesterase.

Standard in-vitro and in-vivo tests on genetic toxicology did not indicate any clinically relevant genotoxic potential of pyridostigmine. No preclinical studies on the carcinogenicity of pyridostigmine have been performed.

Animal testing for reproductive toxicity on rats did not demonstrate any effects on male or female fertility following oral administration of pyridostigmine. In embryotoxicity tests, there was an increased absorption rate and delayed ossification of the foetuses in the maternal toxic dose range. In a peri-/postnatal study, the size and weight gain of the offspring of treated mothers were reduced.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients: Colloidal anhydrous silica , maize starch, povidone K 30, pregelatinised starch, talc, magnesium stearate
Coating components: Sucrose crystalline, rice starch, talc, acacia spray-dried gum, hard paraffin, iron oxide red (E 172), light liquid paraffin, iron oxide yellow (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

May by used within 3 months after opening.

6.4 Special precautions for storage

Do not store above 25°C.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Amber glass bottle with 20 or 150 dragees.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7.MANUFACTURER:

ICN POLFA RZESZOW S.A., POLAND

2 PRZEMYSLOWAST ST., 35-959 RZESZOW, POLAND

8. LICENSE HOLDER:

Megapharm Ltd. P.O. Box 519 Hod Hasharon 4510501

9. MARKETING AUTHORISATION NUMBER

130-84-21200

Revised in February 2022 according to MOHs guidelines.