PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986

The medicine is dispensed with a doctor's prescription only

Pyridostigmine 30
Pyridostigmine 60

Tablets

Active ingredient:
Each tablet of Pyridostigmine 30 contains: pyridostigmine bromide 30 mg
Each tablet of Pyridostigmine 60 contains: pyridostigmine bromide 60 mg

For the list of the additional ingredients, see section 6.
See also 'Important information about some of the medicine's ingredients' in section 2.

Read the entire leaflet carefully before using the medicine.
This leaflet contains concise information about the medicine. If you have any further questions, please refer to the doctor or pharmacist.
This medicine has been prescribed for the treatment of your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is the medicine intended for?

The medicine is intended for treatment of myasthenia gravis.

Therapeutic Group: cholinesterase enzyme inhibitors.

The tablets contain the active ingredient pyridostigmine bromide that acts as a cholinesterase enzyme inhibitor, thus preventing the increased breakdown of acetylcholine, a substance that transmits pulses from the nerve to the muscle.
Patients suffering from myasthenia gravis feel that the muscles weaken and tire easily. In severe cases, they even reach a state of muscle paralysis.

2. Before using the medicine

Do not use the medicine if:

- You are sensitive (allergic) to the active ingredient pyridostigmine bromide, to other bromides, or to any of the additional ingredients the medicine contains (for the list of the additional ingredients, see section 6).
- You suffer from mechanical obstruction of the digestive system or urinary tract.

Special warnings regarding the use of the medicine:

- If you are about to undergo surgery, inform the medical staff that you are taking this medicine.

Before starting treatment with Pyridostigmine tell your doctor if:

- You suffer from respiratory diseases, such as asthma, bronchospasm or chronic obstructive pulmonary disease (COPD).
- You suffer from heart diseases such as: worsening of heart failure (symptoms when at rest), cardiac conduction system disorders (AV block) or heart rhythm disorders such as slow heart rate or you have recently had a heart attack (heart rhythm disorders are more widespread in the older population).
- You suffer from low blood pressure.
- You suffer from a stomach ulcer.
- You have had gastrointestinal surgery.
- You suffer from epilepsy.
- You suffer from Parkinson's disease.
- You suffer from kidney problems.

- You suffer from vagotonia, which is a state of hyperactivity of the vagus nerve, that causes symptoms such as: slowing of the heart rate, constriction of pupils.
- You suffer from over active thyroid gland.
- You have had surgery to remove the thymus gland.

If you are taking very high dosages of Pyridostigmine, you may need atropine or other anticholinergics in order to specifically neutralize the muscarinic effect without impairing the nicotinergic effect.

Drug interactions:

If you are taking, or if you have recently taken any other medicines, including non-prescription medicines and nutritional supplements, please tell the doctor or pharmacist.
Especially inform the doctor or pharmacist if you are taking the following medicines (it should be noted that the following list indicates the active ingredients in the medicines. If you are not sure whether you are using one of these medicines, please consult with the doctor or pharmacist):

- Steroids or other medicines that suppress the immune system.
- Anticholinergic medicines; atropine and scopolamine inhibit the muscarinic effect of pyridostigmine bromide. These medicines reduce bowel motility, and thus may affect pyridostigmine bromide absorption in the body.
- Medicines containing methyl-cellulose may interfere with Pyridostigmine absorption. Avoid using medicines containing methyl-cellulose concurrently with Pyridostigmine.
- Certain antibiotics, such as antibiotics of the aminoglycoside group (e.g. neomycin, kanamycin)
- Medicines to treat heart rhythm disorders.
- Anesthetics used for general anesthesia in surgeries, local anesthetics.
- Additional medicines affecting the conduction between nerve and muscle.
- Medicines for muscle relaxation during surgery, such as pancuronium or vecuronium: if you are about to undergo surgery, inform the doctor that you are taking Pyridostigmine. In addition, Pyridostigmine may cause prolonging of the time for the effect of other muscle relaxants such as suxamethonium.
- Medicines containing N,N-diethyl-m-toluamide (DEET) - avoid applying to large skin areas when Pyridostigmine is being used.

Pregnancy, breastfeeding and fertility:

Consult the doctor if you are pregnant, breastfeeding, think you are pregnant or are planning a pregnancy.

Pregnancy

The active ingredient in Pyridostigmine crosses the placental barrier. Use the medicine during pregnancy only if the doctor decides that the treatment is necessary. In particular, avoid taking high dosages of the medicine.

Intravenous administration of cholinesterase enzyme inhibitors - the group to which the medicine Pyridostigmine belongs - may cause premature labor in pregnancy. The risk of premature labor increases towards the end of the pregnancy. It is not known whether oral administration of the medicine may cause premature labor.

Breastfeeding

The active ingredient in Pyridostigmine passes into the breastmilk in small quantities. In a very small number of cases investigated, no influence on the breastfed babies/children was observed. If treatment with Pyridostigmine is necessary, possible side effects in the baby/child need to be monitored or they need to be weaned off breastfeeding.

Fertility

Pyridostigmine was not found to have any effect on male or female fertility in animal studies.

Driving and use of machinery: The medicine may cause a reduction in vision sharpness and constriction of pupils, thereby impairing your ability to drive or operate machinery. If the medicine

impairs your vision, do not drive or operate machinery. As for children, they should be warned against riding a bicycle or playing near roads.

Important information about some of the medicine's ingredients:
The tablets contain lactose. If you are sensitive to lactose or have intolerance to certain sugars, inform the doctor before taking the medicine (see section 6).

3. How to use the medicine?

Always use according to the doctor's instructions. Check with the doctor or pharmacist if you are not sure about the dosage and the manner of treatment with the medicine. The dosage and manner of treatment will be determined by the doctor only.
Use this medicine at set times as determined by the attending doctor.
The standard dosage is usually:
The dosage will be determined by the doctor.
From the moment you take the determined dose, it takes 30 to 60 minutes for the medicine to start having an effect. Its effect continues for between 4 and 6 hours. Therefore, consult with the doctor on the optimal times for taking it, so that it will have an effect when you need to use the muscles, for instance 30 to 60 minutes before the meal.

Adults:
Doses of 30-120 mg given at intervals throughout the day. Pyridostigmine 60 mg cannot be halved. For a dose of 30 mg use a tablet containing 30 mg pyridostigmine bromide.
The total daily dosage is usually in the range of 120-1200 mg, but higher dosages than these may be required for some patients according to the dosage titration.
Children:
The starting dose for children under the age of 6 is 30 mg pyridostigmine bromide. Pyridostigmine 60 mg cannot be halved. For a dose of 30 mg use a tablet containing 30 mg pyridostigmine bromide.
The dosage for children age 6-12 years is 60 mg. The dosage should be increased gradually, an addition of 30 mg per day, until maximum improvement is obtained. The total daily dosage is usually in the range of 30-360 mg.

Special population groups
Elderly
There are no specific dosage recommendations for elderly patients.

Patients with impaired kidney function
Pyridostigmine is mostly excreted unchanged through the kidneys, and therefore lower dosages and adjustment of the dosage based on the patient's individual response may be required, in patients suffering from kidney problems.

Patients with impaired liver function
There are no specific dosage recommendations for patients with liver failure.

Do not exceed the recommended dose.
There is no information on crushing or chewing the tablets.
Do not halve the tablet since there is no scored line. (If it is necessary to split the tablet in order to make it easier to swallow, make sure to take all the parts of the tablet).
Swallow the medicine with water.

If you have accidentally taken a higher dosage: If you have taken an overdose or if a child or any person has accidentally swallowed the medicine, refer immediately to a doctor or a hospital emergency room and bring the package of the medicine with you.
Taking an overdose of this medicine may cause a cholinergic crisis, which could lead amongst others to pronounced or increased muscle weakness up to paralysis.
Additional symptoms that may manifest are extreme slowing of the heart rate or even cardiac arrest;

cyclical heart rate acceleration, drop in blood pressure up to collapse of the blood system; dizziness, nausea and vomiting, urinary incontinence, defecation accompanied by cramps, diarrhea, increased bronchial secretion, bronchial muscles contraction combined with possible constriction of the airways, pulmonary edema, increased tear and saliva secretion, increased nasal discharge, light to heavy sweating, reddish skin, constriction of the pupils and impaired vision sharpness, random muscle contractions, involuntary muscle spasms and general weakness.
Symptoms that involve the central nervous system may occur, including restlessness, confusion, slurred speech, nervousness, irritability, hallucinations, as well as seizures and coma (see section 4 - Side effects).

If you forgot to take the medicine at the set time, take a dose as soon as you remember. Take the next dose at the usual time. Do not take a double dose to make up for the forgotten dose. If you forgot more than one dose, consult with the doctor.
Adhere to the treatment as recommended by the doctor. Even if your state of health improves, do not stop the treatment with the medicine without consulting the doctor.

Do not take medicines in the dark! Check the label and the dose <u>each time</u> you take a medicine. Wear glasses if you need them.
If you have further questions concerning the use of the medicine, consult the doctor or pharmacist.

4. Side effects
As with any medicine, the use of Pyridostigmine may cause side effects in some users. Do not be alarmed while reading the list of side effects, you may not suffer from any of them.

Rare side effects (effects that appear in 1-10 users out of 10,000):
Skin rash (usually disappears after discontinuing use of the medicine. Do not use medicines containing bromide.)

Side effects of unknown frequency (effects whose frequency has not yet been determined):
<u>Immune system disorders</u>
Hypersensitivity to the medicine (allergy)

<u>Psychiatric disorders</u>
In the presence of organic brain changes, under use of Pyridostigmine, psychopathological symptoms up to psychosis may appear, existing symptoms may intensify.

<u>Nervous system disorders</u>
Temporary loss of consciousness due to a decrease in the blood flow to the brain (fainting)

<u>Eyes</u>
Constriction of pupils (miosis)
Increased tear secretion
Impaired ability of the eye to adjust to near/far vision (e.g. blurred vision)

<u>Cardiovascular system</u>
Arrhythmia (e.g. heart palpitations), rapid heartbeat (tachycardia), slow heartbeat (bradycardia), heart conduction disorders (AV block), coronary arteries spasms (Prinzmetal angina)

<u>Vascular disorders</u>
Flushing
Low blood pressure

<u>Respiratory system</u>

Increased bronchial secretion combined with constriction of the airways, asthma patients may experience respiratory symptoms.

Digestive system
Nausea, vomiting, diarrhea
Increased activity of the digestive system, abdominal discomfort (e.g. weakness, pain, cramps)
Increased saliva secretion

Skin
Increased sweating
Urticaria (hives)

Muscles
Muscle weakness
Decreased muscle tone
Involuntary muscle twitching
Muscle tremor
Muscle cramps

Kidneys and urinary system
Sudden and strong urge to urinate

The side effects are usually dependent on dosage.

During the treatment with Pyridostigmine (mainly with an oral dosage exceeding 150-200 mg pyridostigmine bromide per day), the following side effects may occur: sweating episodes, increased saliva secretion, increased tear secretion, increased bronchial secretion, nausea, vomiting, diarrhea, abdominal cramps (due to increased activity of the digestive system), increased urge to urinate, muscle tremor, muscle cramps, muscle weakness and impairment of the eye's ability to adjust to near/far vision.
After taking higher dosages (500-600 mg pyridostigmine bromide per day orally), the heart rate may slow and cardiovascular side effects may occur together with excessively low blood pressure (see section 3 - How to use the medicine).
The side effects listed may also be symptoms of overdose or a cholinergic crisis. It is important to check the cause of the side effects with your doctor.

If a side effect appears, if one of the side effects worsens, or when you suffer from a side effect not mentioned in this leaflet, consult with the doctor.

Side effects may be reported to the Ministry of Health by clicking on the link "Report on side effects following medicinal treatment" on the homepage of the Ministry of Health website (www.health.gov.il) which leads to an online form for reporting side effects, or by entering the link:
https://sideeffects.health.gov.il/

5. How to store the medicine?

- Avoid poisoning! This medicine, and any other medicine, must be stored in a closed place out of the reach and sight of children and/or babies, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the doctor.
- Do not use the medicine after the expiry date (exp. date) stated on the package. The expiry date refers to the last day of that month.
- Storage conditions: Store in the original package below 25°C.

6. Additional information

In addition to the active ingredient, the medicine also contains the following ingredients:

Lactose, maize starch, stearic acid, silicon dioxide colloidal, ethyl cellulose, magnesium stearate.

Each tablet of Pyridostigmine 30 contains approximately 50 mg lactose.
Each tablet of Pyridostigmine 60 contains approximately 100 mg lactose.

What does the medicine look like and what does the package contain?
Pyridostigmine 30: round white tablets, in blister packs of 21 tablets.
Pyridostigmine 60: round white tablets, in blister packs of 30 tablets.

Manufacturer and Registration Holder: Rafa Laboratories Ltd., P.O.B.405, Jerusalem 9100301.

Medicine registration number in the National Medicines Registry of the Ministry of Health:
Pyridostigmine 30: 051-77-25053
Pyridostigmine 60: 145-41-31869

Revised in November 2023 according to MOH's guidelines.