Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
This medicine is dispensed with a doctor's prescription only

Zoledronic Acid Fresenius 4 mg/5 ml

Concentrate for solution for infusion

Active ingredient
One 5 ml vial contains 4 mg zoledronic acid.

Inactive ingredients and allergens: see section 2 under 'Important information about some of this medicine's ingredients', and section 6 'Additional Information'.

Read the entire leaflet carefully before using this medicine. This leaflet contains concise information about this medicine. If you have further questions, consult your doctor or pharmacist. This medicine has been prescribed to treat 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 this medicine intended for?

Zoledronic Acid Fresenius 4 mg/5 ml is used to:
- Treat patients with multiple myeloma and patients with documented bone metastases from solid tumours (where cancer spreads from the primary site to the bone), together with standard anticancer therapy.
- For prostate cancer, treatment is given if there is progression after at least one hormonal treatment.
- Reduce the amount of calcium in the blood in patients where the level is too high due to presence of a tumour.

Therapeutic group:
Bisphosphonates

The active substance in Zoledronic Acid Fresenius 4 mg/5 ml is zoledronic acid, which belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change.

2. Before using this medicine

- Carefully follow all the instructions given to you by the doctor.

Do not use this medicine if:

- you are sensitive (allergic) to zoledronic acid, to another bisphosphonate (the group of substances to which zoledronic acid belongs) or to any of the other ingredients that this medicine contains (listed in section 6, in the list of inactive ingredients).
- you are breastfeeding.

Special warnings about using this medicine

Before treatment with the medicine, tell your doctor if:
- you have or have had a kidney problem.
- you have or have had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Your doctor may recommend a dental examination before you start treatment with Zoledronic Acid Fresenius 4 mg/5 ml.

- you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic Acid Fresenius 4 mg/5 ml and inform your doctor about your dental treatment.

During treatment with the medicine
During treatment with Zoledronic Acid Fresenius 4 mg/5 ml, you should maintain good oral hygiene (including regular tooth brushing) and have routine dental check-ups.
Consult a doctor and a dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain, swelling, non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw.
Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing osteonecrosis of the jaw.
Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin and burning sensation have been reported in patients treated with zoledronic acid. Irregular heart beat (cardiac arrhythmia), seizures, spasms, and twitching (tetany) have been reported following severely reduced levels of blood calcium. In some instances, reduced levels of blood calcium may be life-threatening. If any of the symptoms apply to you, tell your doctor immediately. If you have a reduced level of blood calcium before treatment, it must be corrected before initiating treatment with Zoledronic Acid Fresenius 4 mg/5 ml. You will be given adequate calcium and vitamin D supplements.

Drug interactions
If you are taking or have recently taken, other medicines including nonprescription medicines and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
- Aminoglycosides (medicines used to treat severe infections), calcitonin (a medicine used to treat postmenopausal osteoporosis and high levels of blood calcium), loop diuretics (medicines to treat high blood pressure or edema) or other calcium-lowering medicines. The combination of these medicines with bisphosphonates may cause the calcium level in your blood to become too low.
- Thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.
- Aclasta (an additional medicine that contains zoledronic acid and is used to treat osteoporosis and other non-cancer diseases of the bone), or any other bisphosphonate, since the combined effects of these medicines are unknown.
- Anti-angiogenic medicines (used to treat cancer). The combination of these medicines with Zoledronic Acid Fresenius 4 mg/5 ml has been associated with an increased risk of osteonecrosis of the jaw.

Pregnancy and breastfeeding
You should not be given Zoledronic Acid Fresenius 4 mg/5 ml if you are pregnant. Tell your doctor if you are pregnant or think that you may be pregnant.
You must not be given Zoledronic Acid Fresenius 4 mg/5 ml if you are breast-feeding. Ask your doctor for advice before taking any medicine while you are pregnant or breastfeeding.

Driving and using machines
There have been very rare cases of drowsiness and sleepiness with the use of this medicine. Therefore, caution must be exercised when driving, using machinery, or performing other activities that require full attention.

Children and adolescents
This medicine is not recommended for use in adolescents and children under 18 years of age.

Patients aged 65 years and older

This medicine can be used in patients aged 65 years and older. There is no evidence to suggest that any extra precautions are needed.

Important information about some of this medicine's ingredients
The medicine contains less than 1 mmol (23 mg) sodium per dose; therefore, it is considered 'sodium-free'.

3. How to use this medicine?
Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.
Zoledronic Acid Fresenius 4 mg/5 ml can only be given by a healthcare professional trained to administer bisphosphonates intravenously.
Your doctor will recommend that you drink enough water before each treatment to help prevent dehydration.
Carefully follow all the other instructions given to you by your doctor, pharmacist or nurse.
Only your doctor will determine your dose and how you should take this medicine.

Do not exceed the recommended dose.

Tests and follow up
The doctor will perform blood tests before starting treatment with this medicine and will check your response to treatment at regular intervals.

If you have received a higher dosage than recommended, you must be carefully monitored by your doctor. This is because you may develop blood electrolyte abnormalities (such as abnormal levels of calcium, phosphorus, and magnesium) and/or changes in kidney function, including severely impaired kidney function. If your blood level of calcium is too low, you may have to be given supplemental calcium by infusion.

Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop taking this medicine without consulting your doctor.

Do not take medicines in the dark! Check the label and the dose <u>every time</u> you take a medicine. Wear glasses if you need them. If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. Side effects
Like with all medicines, using Zoledronic Acid Fresenius 4 mg/5 ml may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them. The most common side effects are usually mild and will probably disappear after a short time.

Contact a doctor immediately if you have one or more of the following severe side effects:

Common side effects (may affect up to 1 in 10 patients):
- Severe kidney function impairment (will normally be determined by specific blood tests).
- Low level of calcium in the blood.

Uncommon side effects (may affect up to 1 in 100 patients):
- Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell the doctor and dentist immediately if you experience these symptoms while being treated with this medicine or after stopping treatment.
- Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for treatment of postmenopausal osteoporosis. It is unknown whether zoledronic acid causes

irregular heart rhythm, but you must tell the doctor if you experience these symptoms while being treated with zoledronic acid.
- Severe allergic reaction: shortness of breath, swelling mainly of the face and throat.

Rare side effects (may affect up to 1 in 1,000 patients):
- As a consequence of low calcium levels: irregular heart beat (cardiac arrhythmia, secondary to hypocalcaemia).
- Impaired kidney function known as Fanconi syndrome (usually diagnosed by the doctor by certain urine tests).

Very rare side effects (may affect up to 1 in 10,000 patients):
- As a consequence of low calcium levels: seizures, numbness and tetany (secondary to hypocalcaemia).
- Tell your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- Osteonecrosis has very rarely been seen occurring with other bones than the jaw, especially the hip or thigh. Tell your doctor immediately if you experience symptoms such as new onset or worsening of aches or stiffness while being treated with Zoledronic Acid Fresenius 4 mg/5 ml or after stopping treatment.

Consult a doctor as soon as possible if you have one or more of the following side effects:

Very common side effects (may affect more than 1 in 10 patients):
- Low level of phosphorus in the blood.

Common side effects (may affect up to 1 in 10 patients):
- Headache and a flu-like syndrome, including fever, fatigue, weakness, drowsiness, chills, and bone, joint and/or muscle ache. In most cases, no specific treatment is required and the symptoms disappear after a short time (a few hours or days).
- Gastrointestinal reactions such as nausea and vomiting, as well as loss of appetite.
- Conjunctivitis.
- Low level of red blood cells (anemia).

Uncommon side effects (may affect up to 1 in 100 patients):
- Hypersensitivity reactions.
- Low blood pressure.
- Chest pain.
- Skin reactions (redness and swelling) at the infusion site, rash, itching.
- High blood pressure, shortness of breath, dizziness, anxiety, sleep disturbances, taste disturbances, trembling, tingling or numbness of the hands or feet, diarrhea, constipation, abdominal pain, dry mouth.
- Low counts of white blood cells and blood platelets.
- Low level of magnesium and potassium in the blood. Your doctor will monitor this and act accordingly.
- Weight gain.
- Increased sweating.
- Sleepiness.
- Blurred vision, tearing of the eyes, eye sensitivity to light.
- Sudden coldness with fainting, limpness, or collapse.
- Difficulty in breathing, with wheezing or coughing.
- Urticaria.

Rare side effects (may affect up to 1 in 1,000 patients):
- Slow heartbeat.
- Confusion.

- Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis. Consult your doctor if you experience pain, weakness or discomfort in your thigh, hip, or groin as this may be an early indication of a possible fracture of the thigh bone.
- Interstitial lung disease (inflammation of the tissue around the air sacs of the lungs).
- Flu-like symptoms including arthritis and joint swelling.
- Painful redness and/or swelling of the eye.

Very rare side effects (may affect up to 1 in 10,000 patients):
- Fainting due to low blood pressure.
- Severe bone, joint, and/or muscle pain, occasionally incapacitating.

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.
You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il
In addition, you can report by sending an email to the Registration Holder's patient safety unit: drugsafety@neopharmgroup.com

5. How to store the medicine?
- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.

- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:
Store below 25°C. Store the vial in its outer package to protect from light. Use the solution immediately after preparing it according to the instructions.
If it is not used immediately, storage prior to use is the responsibility of the user and it should be kept in a refrigerator (2-8°C). The total time between preparing the solution, storage in the refrigerator and end of administration must not exceed 24 hours. If the medicine is refrigerated, it should be brought to room temperature before administration.

6. Additional information
In addition to the active ingredient, this medicine also contains:
Mannitol (E421), sodium citrate dihydrate, water for injection

What the medicine looks like and the contents of the pack:
A clear, colourless solution in a vial. One vial contains 4 mg zoledronic acid. Each pack contains 1, 4 or 10 vials. Not all pack sizes may be marketed.

Registration holder's name and address:
Neopharm (Israel) 1996 Ltd., Hashiloach 6, P.O. Box 7063, Petach Tiqva, 4917001.

Manufacturer's name and address:
Fresenius Kabi Austria GmbH, Graz, Austria

Revised in January 2023 according to MOH guidelines.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 156-91-34402