Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986
The dispensing of this medicine requires a doctor's prescription

Zoledronic Acid Taro 4 mg/5 ml
Concentrate for solution for infusion

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

Inactive ingredients and allergens in this medicine: 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, refer to 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 Taro 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 Taro 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, 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 breast-feeding.

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 Taro.
- you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic Acid Taro and inform your doctor about your dental treatment.

During treatment with the medicine
During treatment with Zoledronic Acid Taro, 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, burning sensation, have been reported in patients treated with Zoledronic Acid Taro. 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 reduced levels of blood calcium before treatment, it must be corrected before initiating treatment with Zoledronic Acid Taro. You will be given adequate calcium and vitamin D supplements.

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 special precautions are needed.

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.

Drug interactions
If you are taking, or have recently taken, other medicines including nonprescription medicines and nutritional supplements, tell your doctor or pharmacist. In particular 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 Taro has been associated with an increased risk of osteonecrosis of the jaw.

Pregnancy and breast-feeding
You should not be given Zoledronic Acid Taro 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 Taro if you are breast-feeding. Ask your doctor for advice before taking any medicine while you are pregnant or breast-feeding.

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.

Important information about some of this medicine's ingredients
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially sodium free. If your doctor uses a solution of common salt to dilute Zoledronic Acid Taro, the dose of sodium received would be larger.

3. How to use this medicine?

Always use 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 Taro 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. The dosage and treatment regimen will be determined by the doctor only.
Do not exceed the recommended dose.

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.
Persist with the treatment as recommended by the 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>each time</u> you take the medicine. Wear glasses if you need them. If you have any further questions about using this medicine, consult your doctor or the pharmacist.

4. Side effects

Like all medicines, taking Zoledronic Acid Taro may cause side effects in some people. 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.
Refer to 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 also 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, pain or stiffness while being treated with Zoledronic Acid Taro or after stopping treatment.

Side effects of unknown frequency (the frequency of these effects has not been established yet)

- Inflammation of the kidney (tubulointerstitial nephritis): signs and symptoms may include decreased volume of the urine, blood in the urine, nausea, feeling generally unwell.

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 a side effect occurs, 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 Medication' on the Ministry of Health home page (www.health.gov.il) which links you to an online form for reporting side effects, or by entering the link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! This medicine, and all other medicines, should be kept in a closed place out of the reach and sight of children and/or infants in order to prevent poisoning. Do not induce vomiting unless explicitly instructed to do so by your doctor.
- Do not use the medicine after the expiry date (exp. date) appearing on the package. The expiry date refers to the last day of that month.

Storage conditions

- Store at a temperature below 25°C. 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, sodium citrate, water for injection

What the medicine looks like and the contents of the pack:
Zoledronic Acid Taro is supplied as a clear, colourless liquid concentrate in a 5 ml 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: Taro International Ltd., 14 Hakitor St., Haifa Bay, 2624761

Manufacturer's name and address: Sun Pharmaceutical Industries Ltd., Mumbai, India.

Revised in October 2024.

Registration number of the medicine in the National Drug Registry of the Ministry of Health: 15471.34213

For further information about the medicinal product and for updated patient leaflets in Hebrew, Arabic and English, please scan the code:

https://israeldrugs.health.gov.il/#!/medDetails/154%2071%2034213%2000

For a printed copy of the patient information leaflet in English, please contact the registration holder by email Info@taro.com or by phone 1-800-464-664.

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

How to prepare and administer Zoledronic acid Taro

- To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the Zoledronic Acid Taro concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic Acid Taro is required, first withdraw the appropriate volume as indicated below and then dilute it further with 100 ml of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride or 5% w/v glucose solution.

  Do not mix Zoledronic Acid Taro concentrate with calcium-containing or other divalent cation-containing solutions such as lactated Ringer's solution.

  Instructions for preparing reduced doses of Zoledronic Acid Taro:
  Withdraw the appropriate volume of the liquid concentrate, as follows:
  - 4.4 ml for 3.5 mg dose
  - 4.1 ml for 3.3 mg dose
  - 3.8 ml for 3.0 mg dose

- For single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used. Aseptic techniques must be followed during the preparation of the infusion.
- From a microbiological point of view, the diluted solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.
- The solution containing zoledronic acid is given as a single 15-minute intravenous infusion in a separate infusion line. The hydration status of patients must be assessed prior to and following administration of Zoledronic Acid Taro to ensure that they are adequately hydrated.
- Studies with several types of infusion lines made from polyvinylchloride, polyethylene and polypropylene showed no incompatibility with Zoledronic Acid Taro.
- Since no data are available on the compatibility of Zoledronic Acid Taro with other intravenously administered substances, Zoledronic Acid Taro must not be mixed with other medications/substances and should always be given through a separate infusion line.

How to store Zoledronic Acid Taro

- Keep Zoledronic Acid Taro out of the reach and sight of children.
- Do not use Zoledronic Acid Taro after the expiry date stated on the pack.
- Store the unopened vial below 25°C.
- The diluted Zoledronic Acid Taro infusion solution should be used immediately in order to avoid microbial contamination.