V-02

Zoledronic Dexcel 4mg/5ml
Concentrate for solution for infusion

זולדרוניק דקסל 4מ"ג/5מ"ל
תרכיז להכנת תמיסה לעירוי

زولدرونيك ديكسل ٤ ملغ/٥ ملل
محلول مركز لتحضير محلول للتسريب

Patient package insert according to Pharmacists' Regulations (Preparations), 1986.

This medicine can be sold with a physician's prescription only.

Zoledronic Dexcel 4mg/5ml
Concentrate for solution for infusion

Zoledronic acid 4 mg in 5 ml vial

Excipients – see section 6 "Additional Information".

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

1. What is the Medicine Intended for?

Zoledronic Dexcel is used to:
— treat patients with multiple myeloma and patients with documented bone metastases (spreading of cancer from the primary site to the bone), together with standard anticancer therapy.
For prostate cancer, the treatment is given if there is progression after at least one hormonal treatment.
— reduce the amount of calcium in the blood in patients whose level is too high due to the presence of a tumor.

Therapeutic group: Bisphosphonates.
Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change.

2. Before Using the Medicine

Carefully follow all the instructions given to you by the physician.

Do not use the medicine if:
- you are hypersensitive (allergic) to zoledronic acid, to another bisphosphonate (the group of substances to which zoledronic acid belongs) or to any of the other ingredients contained in the medicine (see section 6).
- you are breastfeeding.

Special warnings regarding the use of this medicine:

○ **Before treatment with Zoledronic Dexcel, tell the physician if:**
- you have or have had a kidney problem.
- you have or have had pain, swelling or numbness in the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Your physician may recommend a dental examination before you start treatment with **Zoledronic Dexcel**.
- you are receiving dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with **Zoledronic Dexcel** and tell your physician about your dental treatment.

○ **While being treated with Zoledronic Dexcel**
While being treated with **Zoledronic Dexcel**, you should maintain good oral hygiene (including regular tooth brushing) and receive routine dental examinations.
Refer to the physician and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing or discharging sores, as these may 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 a gum problem, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may be at higher risk of developing osteonecrosis of the jaw.
Low levels of calcium in the blood (hypocalcaemia), which sometimes lead to muscle cramps, dry skin, burning sensation, have been reported in patients treated with zoledronic acid.
Irregular heartbeat (cardiac arrhythmia), seizures, spasms and shaking have been reported as a result of severe hypocalcaemia.
In some instances, hypocalcaemia may be life-threatening. If any of these symptoms apply to you, tell the physician immediately. If you have hypocalcaemia before treatment, your calcium levels must be corrected before starting treatment with **Zoledronic Dexcel**. You will be given sufficient calcium and vitamin D supplements.

Other medicines and Zoledronic Dexcel
If you are taking or have recently taken other medicines, including non-prescription medicines and nutritional supplements, tell the physician or pharmacist. Especially if you are taking:
- aminoglycosides (medicines used to treat severe infections), calcitonin (a medicine used to treat postmenopausal osteoporosis and hypercalcaemia), loop diuretics (medicine for the treatment of high blood pressure or oedema) or other calcium-lowering medicines. The combination of these medicines with bisphosphonates may cause the blood calcium level to become too low.
- thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicine that might harm your kidneys.
- other medicines that contain zoledronic acid and are 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 Dexcel** is associated with an increased risk of osteonecrosis of the jaw.

Pregnancy and Breastfeeding
You should not be treated with **Zoledronic Dexcel** if you are pregnant. Tell the physician if you are or think that you might be pregnant.
You must not be treated with **Zoledronic Dexcel** if you are breastfeeding.

Driving and use of machinery
There have been cases of drowsiness and sleepiness during treatment with zoledronic acid.
Therefore caution must be exercised when driving, using machinery or performing other activities that require full attention.

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

Patients aged 65 years and over
This medicine can be used for patients aged 65 years and older. There is no evidence to suggest that special precautions are necessary.

Important information regarding some of the ingredients of this medicine
Each vial (before dilution) contains approximately 5.6 mg sodium.

3. How Should You Use This Medicine?

Always use according to the physician's instructions. Check with the physician or pharmacist if you are not sure.
Zoledronic Dexcel is to be administered only by a healthcare professional trained in intravenous administration of bisphosphonates.
Your physician will recommend that you drink enough water before each treatment to help prevent dehydration.

The dosage and treatment regimen will be determined by the physician only.

Do not exceed the recommended dose.

Tests and Follow up
The physician will perform blood tests before starting treatment with **Zoledronic Dexcel** and will check your response to treatment at regular intervals.

If you have received a higher dosage than recommended, you must be strictly monitored by your physician. This is because you may develop blood electrolyte abnormalities (e.g., abnormal calcium, phosphorus and magnesium levels) and/or changes in kidney function, including severe kidney function impairment. If your blood calcium level is too low, you may need to receive supplemental calcium by infusion.

Adhere to the treatment regimen as recommended by the physician.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting the physician.

Do not take medicines in the dark! Check the label and the dose each time you take a medicine. Wear glasses if you need them.

If you have any further questions regarding the use of this medicine, consult the physician or pharmacist.

4. Side Effects

As with any medicine, the use of **Zoledronic Dexcel** may cause side effects in some users. Do not be alarmed while reading the list of side effects. You might not suffer from any of them.

Refer to a physician immediately if you have one or more of the following severe side effects:
Common side effects (effects that appear in 1-10 users out of 100):
- Severe kidney malfunction (will normally be determined by the physician using specific blood tests).
- Low level of calcium in the blood.

Uncommon side effects (effects that appear in 1-10 users out of 1,000):
- 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 physician and dentist immediately if you experience these symptoms while being treated with **Zoledronic Dexcel** or after stopping treatment.
- Irregular heart rhythm (atrial fibrillation) has been observed in patients receiving zoledronic acid for the treatment of postmenopausal osteoporosis. It is unknown whether zoledronic acid causes irregular heart rhythm, but you must tell the physician 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 (effects that appear in 1-10 users out of 10,000):
- As a consequence of low calcium levels: irregular heart rhythm (cardiac arrhythmia, secondary to hypocalcaemia).
- Disturbance in kidney function called Fanconi syndrome (will normally be diagnosed by the physician using specific urine tests).

Very rare side effects (effects that appear in less than one user out of 10,000):
- As a consequence of low calcium levels: seizures, numbness and cramps (secondary to hypocalcaemia).
- Tell your physician if you have ear pain, discharge from the ear and/or an ear infection. These may be signs of osteonecrosis of the ear.

Refer to a physician as soon as possible if you have one or more of the following side effects:
Very common side effects (effects that appear in more than one user out of ten):
- Low level of phosphorus in the blood.

Common side effects (effects that appear in 1-10 users out of 100):
- Headache and a flu-like syndrome, including fever, fatigue, weakness, drowsiness, chills and pain in the bone, joints and/or muscles. 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 (anaemia).

Uncommon side effects (effects that appear in 1-10 users out of 1,000):
- 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, diarrhoea, constipation, abdominal pain, dry mouth.
- Low counts of white blood cells and blood platelets.
- Low level of magnesium and potassium in the blood. The physician will monitor this and act accordingly.
- Weight gain.
- Excessive sweating.
- Sleepiness.
- Blurred vision, watery eyes, sensitivity of the eye to light.
- Sudden feeling of cold with fainting, exhaustion or collapse.
- Difficulty breathing with wheezing or coughing.
- Urticaria.

Rare side effects (effects that appear in 1-10 users out of 10,000):
- Slow heartbeat.
- Confusion.
- Unusual fracture of the thigh bone, particularly in patients receiving long-term treatment for osteoporosis. Refer to the physician if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early sign 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.
- Redness and/or swelling accompanied by pain in the eye.

Very rare side effects (effects that appear in less than one user out of 10,000):
- Fainting due to low blood pressure.
- Severe bone, joint and/or muscle pain, occasionally incapacitating.

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

Side effects can be reported to the Ministry of Health by clicking on the link "דיווח על תופעות לוואי עקב טיפול תרופתי" found on the home page of the Ministry of Health's website (www.health.gov.il), which directs to the online form for reporting side effects or via the link:
https://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

5. How Should You Store the Medicine?

- Avoid poisoning! This medicine and all other medicines must be stored in a safe place out of the reach of children and/or infants, to avoid poisoning. Do not induce vomiting unless explicitly instructed to do so by the physician.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- **Storage conditions:** Store at a temperature below 30°C.
Use the solution immediately after preparing it according to the instructions. If it is not used immediately, its storage prior to use is the responsibility of the user and should be in a refrigerator (2-8°C). The solution that was stored in the refrigerator must reach room temperature before administration.
The total time between the preparation of the solution, its storage in the refrigerator and the end of administration must be no longer than 24 hours.

6. Additional Information

In addition to the active ingredient, the medicine also contains:
Mannitol, Sodium citrate, Water for injection.

What the medicine looks like and contents of the package:
Zoledronic Dexcel 4 mg/5 ml comes as a liquid concentrate in a vial. One vial contains 4 mg zoledronic acid.
Approved pack sizes: Each pack contains 1, 4, 10 vials. Some pack sizes might not be marketed.

Manufacturer and address: Actavis Italy S.P.A. Milano, Italy.

Drug registration number at the national medicines registry of the Ministry of Health:
151 83 34036 00

This leaflet was checked and approved by the Ministry of Health in: November 2016

Zoledronic Dexcel PIL PB1216-06

Registration holder: Dexcel® Ltd.
1 Dexcel St., Or-Akiva 3060000, Israel

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

How to prepare and administer Zoledronic Dexcel

— To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the **Zoledronic Dexcel** concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of **Zoledronic Dexcel** 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 Dexcel concentrate with calcium-containing or other divalent cation-containing solutions such as lactated Ringer's solution.

Instructions for preparing reduced doses of **Zoledronic Dexcel**
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.

— After aseptic addition of **Zoledronic Dexcel** 4mg/5ml concentrate for solution for infusion to the infusion media (sodium chloride 0.9% w/v or glucose 5% w/v), the **Zoledronic Dexcel** solution for infusion should be used immediately. If the solution is not used immediately, storage prior to use is responsibility of the user and should be at 2°C – 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration. The cumulated time between dilution with infusion media, storage in a refrigerator and end of administration must not be longer than 24 hours.

— 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 Dexcel** to ensure that they are adequately hydrated.

— Since no data are available on the compatibility of **Zoledronic Dexcel** with other intravenously administered substances, **Zoledronic Dexcel** must not be mixed with other medications/substances and should always be given through a separate infusion line.

How to store Zoledronic Dexcel

— Keep **Zoledronic Dexcel** out of the reach and sight of children.
— Do not use **Zoledronic Dexcel** after the expiry date stated on the pack.
— Store below 30°C.
— The diluted **Zoledronic Dexcel** infusion solution should be used immediately in order to avoid microbial contamination.