

## **PACKAGE LEAFLET**

## **PACKAGE LEAFLET: INFORMATION FOR THE USER**

### **Zoledronic acid 4 mg/5 ml concentrate for solution for infusion**

**Read all of this leaflet carefully before you are given Zoledronic acid because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

#### **In this leaflet:**

1. What Zoledronic Acid is and what it is used for
2. What you need to know before you are given Zoledronic Acid
3. How Zoledronic Acid is used
4. Possible side effects
5. How to store Zoledronic Acid
6. Contents of the pack and other information

### **1. WHAT ZOLEDRONIC ACID IS AND WHAT IT IS USED FOR**

The active substance zoledronic acid 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. It is used:

- **To prevent bone complications**, e.g. fractures, in adult patients with bone metastases (this is when the cancer has spread from the primary cancer site to the bone).
- **To reduce the amount of calcium** in the blood in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

## 2. WHAT YOU NEED TO KNOW BEFORE YOU ARE GIVEN ZOLEDRONIC ACID

Follow carefully all instructions given to you by your doctor.

Your doctor will carry out blood tests before you start treatment with Zoledronic acid and will check your response to treatment at regular intervals.

### You should not be given Zoledronic acid:

- if you are breast-feeding.
- if you are allergic (hypersensitive) to zoledronic acid, another bisphosphonate (the group of substances to which Zoledronic acid belongs), or any of the other ingredients of Zoledronic acid (listed in section 6).

### Warnings and precautions

#### Talk to your doctor before you are given Zoledronic acid:

- if you have or have had a **kidney problem**.
- if 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.
- if you are having **dental treatment** or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic acid and inform your doctor about your dental treatment.

While being treated with Zoledronic acid, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or 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. Irregular heart beat (cardiac arrhythmia), seizures, spasm and twitching (tetany) have been reported as secondary to severe hypocalcaemia. In some instances the hypocalcaemia may be life-threatening. If any of these apply to you, tell your doctor straight away. If you have pre-existing hypocalcaemia, it must be corrected before initiating the first dose of Zoledronic acid. You will be given adequate calcium and vitamin D supplements.

## **Using other medicines**

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important that you tell your doctor if you are also taking:

- Aminoglycosides (medicines used to treat severe infections), calcitonin (a type of medicine used to treat post-menopausal osteoporosis and hypercalcaemia), loop diuretics (a type of medicine to treat high blood pressure or oedema) or other calcium-lowering medicines, since the combination of these with bisphosphonates may cause the calcium level in the 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 (a medicine that also 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 taken together with Zoledronic acid are unknown.
- Anti-angiogenic medicines (used to treat cancer), since the combination of these with zoledronic acid has been associated with an increased risk of osteonecrosis of the jaw (ONJ).

## **Patients aged 65 years and over**

Zoledronic acid can be given to people aged 65 years and over. There is no evidence to suggest that any extra precautions are needed.

## **Use in children and adolescents**

Zoledronic acid is not recommended for use in adolescents and children below the age of 18 years.

## **Pregnancy and breast-feeding**

You should not be given Zoledronic acid if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You must not be given Zoledronic acid 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 zoledronic acid. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

## **3. HOW ZOLEDRONIC ACID IS USED**

Zoledronic acid must only be given by healthcare professionals trained in administering bisphosphonates intravenously, i.e. through a vein.

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, nurse or pharmacist.

### **How Zoledronic acid is given**

- Zoledronic acid is given as a drip (infusion) into a vein which should take at least 15 minutes and should be administered as a single intravenous solution in a separate infusion line.

### **How much Zoledronic acid is given**

- The usual single dose given is 4 mg.
- If you have a kidney problem, your doctor will give you a lower dose depending on the severity of your kidney problem.

### **How often you will be given Zoledronic acid**

- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledronic acid every three to four weeks.
- If you are being treated to reduce the amount of calcium in your blood, you will normally only be given one infusion of Zoledronic acid.

Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day.

### **If you are given more Zoledronic acid than you should be**

If you have received doses higher than those recommended, you will be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. abnormal levels of calcium, phosphorus and magnesium in your blood) and/or changes in kidney function, including severe kidney problems. If your level of calcium falls too low, you may have to be given supplemental calcium by infusion.

## **4. POSSIBLE SIDE EFFECTS**

Like all medicines, Zoledronic acid can cause side effects, although not everybody gets them. The most common side effects are usually mild and will probably disappear after a short time.

### **Tell your doctor straight away if you get any of the following serious side effects:**

#### **Common (may affect up to 1 in 10 people):**

- Severe kidney impairment (will normally be determined by your doctor with certain specific blood tests).
- Low level of calcium in the blood.

#### **Uncommon (may affect up to 1 in 100 people):**

- 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 your doctor and dentist immediately if you experience such symptoms while being treated with Zoledronic acid or after stopping treatment.
- Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for postmenopausal osteoporosis. It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received zoledronic acid.
- Severe allergic reaction: shortness of breath, swelling mainly of the face and throat.

**Rare (may affect up to 1 in 1,000 people):**

- As a consequence of low calcium values: irregular heart beat (cardiac arrhythmia; secondary to hypocalcemia).
- A kidney function disorder called Fanconi syndrome (will normally be determined by your doctor with certain urine tests).

**Very rare (may affect up to 1 in 10,000 people):**

- As a consequence of low calcium values: seizures, numbness and tetany (secondary to hypocalcaemia).
- Talk to 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 or after stopping treatment.

**Tell your doctor about any of the following side effects as soon as possible:**

**Very common (may affect more than 1 in 10 people):**

- Low levels of phosphate in the blood.

**Common (may affect up to 1 in 10 people):**

- Headache and a flu-like syndrome consisting of 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 (couple of hours or days).
- Gastrointestinal reactions such as nausea and vomiting as well as loss of appetite.
- Conjunctivitis.
- Low levels of red blood cells (anaemia).

**Uncommon (may affect up to 1 in 100 people):**

- Hypersensitivity (allergic) 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 levels of magnesium and potassium in the blood. Your doctor will monitor this and take any necessary measures.
- Weight increase.
- Increased sweating,
- Sleepiness.

- Blurred vision, watering of the eye, eye sensitivity to light.
- Sudden coldness with fainting, limpness or collapse.
- Difficulty in breathing with wheezing or coughing.
- Urticaria ('nettle rash').

**Rare (may affect up to 1 in 1,000 people):**

- Slow heartbeat.
- Confusion.
- Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact 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
- Painfull redness and/or swelling of the eye

**Very rare (may affect up to 1 in 10,000 people):**

- Fainting due to low blood pressure.
- Severe bone, joint and/or muscle pain, occasionally incapacitating.

**Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet.

For patients in the United Kingdom

You can also report side effects directly via the Yellow Card Scheme at: [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard).

Alternatively you can call Freephone 0800 100 3352 (available from 10 a.m. to 2 p.m. Mondays to Fridays).

For patients in Ireland

You can also report side effects directly via e-mail to [medsafety@hpra.ie](mailto:medsafety@hpra.ie).

Alternatively you can call +353 1 6764971

By reporting side effects you can help provide more information on the safety of this medicine.

## **5. HOW TO STORE ZOLEDRONIC ACID**

Your doctor, nurse or pharmacist knows how to store Zoledronic acid properly (see section 6).

## **6. CONTENTS OF THE PACK AND OTHER INFORMATION**

### **What Zoledronic acid concentrate for solution for infusion contains**

- The active substance is zoledronic acid. One vial contains 4 mg of zoledronic acid, corresponding to 4.264 mg zoledronic acid monohydrate.
- The other ingredients are: mannitol (E421), sodium citrate (E331), water for injections.

### **What Zoledronic acid concentrate for solution for infusion looks like and contents of the pack**

Zoledronic acid concentrate is supplied as a liquid, clear and colourless concentrate in a vial. Each pack contains the vial with concentrate. Zoledronic acid is supplied as packs containing 1 vial.

### **Marketing Authorisation Holder**

Intrapharm Laboratories Ltd.,  
The Courtyard Barns,  
Choke Lane,  
Cookham Dean,  
Maidenhead,  
Berkshire SL6 6PT,  
United Kingdom.

### **Manufacturer**

Lisapharma S.p.A.,  
Via Licinio, 11 - 22036 Erba (Como)  
ITALY.

**This medicinal product is authorised in the United Kingdom and the Republic of Ireland under the name: Zoledronic acid 4mg/5ml concentrate for solution for infusion**

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## **INFORMATION FOR THE HEALTHCARE PROFESSIONAL**

### **How to prepare and administer Zoledronic acid 4 mg/5 ml concentrate for solution for infusion**

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

Instructions for preparing reduced doses of Zoledronic acid:

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 to ensure that they are adequately hydrated.
- Since no data are available on the compatibility of zoledronic acid with other intravenously administered substances, zoledronic acid must not be mixed with other medications/substances and should always be given through a separate infusion line.

### **How to store Zoledronic acid**

- Keep Zoledronic acid out of the reach and sight of children.
- Do not use Zoledronic acid after the expiry date stated on the pack.
- The unopened vial does not require any specific storage conditions.
- The diluted Zoledronic acid infusion solution should be used immediately in order to avoid microbial contamination.

## **PATIENT REMINDER CARD**

**This reminder card contains important safety information that you need to be aware of before and during treatment with Zoledronic acid 4 mg/5 ml concentrate for solution for infusion for cancer-related conditions.**

Your doctor has recommended that you receive zoledronic acid infusions to help prevent bone complications (e.g. fractures) caused by bone metastases (spread of cancer from primary site to the bone or to reduce the amount of calcium in the blood in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported in up to 1 in 100 people in patients receiving zoledronic acid infusions for cancer-related conditions. ONJ can also occur after stopping treatment.

In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take:

### **Before starting treatment:**

- Ask your doctor to tell you about ONJ before you start treatment.
- Check with your doctor whether a dental examination is recommended before you start treatment with zoledronic acid.
- Tell your doctor/nurse (health care professional) if you have any problems with your mouth or teeth.

Patients undergoing dental surgery (e.g. tooth extractions), who do not receive routine dental care or have gum disease, are smokers, who get different types of cancer treatments or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing ONJ.

### **While being treated:**

- You should maintain good oral hygiene, make sure your dentures fit properly and receive routine dental check-ups.
- If you are under dental treatment or will undergo dental surgery (e.g. tooth extractions), inform your doctor and tell your dentist that you are being treated with zoledronic acid.
- Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Read the package leaflet for further information.