Package Leaflet: Information for the user

Zoledronic acid Mylan 4 mg/5 ml concentrate for solution for infusion
Zoledronic acid

Read all of this leaflet carefully before you are given this medicine 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, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Zoledronic acid Mylan is and what it is used for

The active substance in Zoledronic acid Mylan 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. It is used:
- **To prevent bone complications**, e.g. fractures, in adult patients with bone metastases (spread of cancer from primary 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 Mylan

Follow carefully all instructions given to you by your doctor.
Your doctor will carry out blood tests before you start treatment with Zoledronic acid Mylan and will check your response to treatment at regular intervals.

You must not be given Zoledronic acid Mylan:
- if you are breast-feeding.
- if you are allergic to zoledronic acid, another bisphosphonate (the group of substances to which zoledronic acid belongs), or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Zoledronic acid Mylan:
- 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 Mylan.
- if you are having **dental treatment** or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic acid Mylan and inform your doctor about your dental treatment.

While being treated with Zoledronic acid Mylan, 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.

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

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

Other medicines and Zoledronic acid Mylan
Tell your doctor if you are taking, have recently taken or might take any other medicines. 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.
- Other medicines that also contain zoledronic acid and which are 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 Mylan 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).

Pregnancy and breast-feeding
You should not be given Zoledronic acid Mylan if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You must not be given Zoledronic acid Mylan 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.

Zoledronic acid Mylan contains sodium.
This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

3. How Zoledronic acid Mylan is used

- Zoledronic acid Mylan 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, pharmacist or nurse.

How much Zoledronic acid Mylan is given
- The usual single dose given is 4 mg zoledronic acid.
- 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 Mylan
- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledronic acid Mylan 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 Mylan.

How Zoledronic acid Mylan is given
- Zoledronic acid Mylan 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.

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 Mylan than you should be
If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. abnormal levels of calcium, phosphorus and magnesium) and/or changes in kidney function, including severe kidney impairment. 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, this medicine can cause side effects, although not everybody gets them. The most common ones are usually mild and will probably disappear after a short time.

Tell your doctor about any of the following serious side effects straight away:

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 Mylan 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 hypocalcaemia).
- 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.

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 level 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 level of red blood cells (anaemia).

Uncommon (may affect up to 1 in 100 people):
- 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. Your doctor will monitor this and take any necessary measures.
- Weight increase.
- Increased sweating.
- Sleepiness.
- Blurred vision, tearing of the eye, eye sensitivity to light.
- Sudden coldness with fainting, limpness or collapse.
- Difficulty in breathing with wheezing or coughing.
- Urticaria.

Rare (may affect up to 1 in 1,000 people):
- Slow heart beat.
- 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 sacks of the lungs).
- Flu-like symptoms including arthritis and joint swelling.

- Painful 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. You can also report side effects directly via:

UK
The Yellow Card Scheme, at www.mhra.gov.uk/yellowcard

IRELAND
HPRA
Pharmacovigilance
Earlsfort Terrace
IRL – Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
email: medsafety@hpra.ie

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

5. How to store Zoledronic acid Mylan

Your doctor, pharmacist or nurse knows how to store Zoledronic acid Mylan properly.

6. Contents of the pack and other information

What Zoledronic acid Mylan contains
- The active substance is zoledronic acid. One vial contains 4 mg zoledronic acid (as monohydrate).
- The other ingredients are: sodium citrate, sodium hydroxide, hydrochloric acid and water for injections.

What Zoledronic acid Mylan looks like and contents of the pack
Zoledronic acid Mylan is a clear and colourless concentrate for solution for infusion. The concentrate is supplied in a clear and colourless glass vial with a rubber stopper and a plastic flip-off cap.
One vial contains 5 ml of concentrate.
Zoledronic acid Mylan is supplied as packs containing 1, 4 or 10 vials or as multipacks comprising 4 packs, each containing 1 vial.
Not all pack sizes may be marketed.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

The following information is intended for healthcare professionals only:

How to prepare and administer Zoledronic acid Mylan

- To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the concentrate (5 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic acid Mylan 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 sodium chloride 9 mg/ml (0.9%) solution for injection or 5% w/v glucose solution.

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

Instructions for preparing reduced doses of Zoledronic acid Mylan:
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. Chemical and physical in-use stability has been demonstrated for 48 hours at 2°C-8°C and at 25°C after dilution in 100 ml sodium chloride 9 mg/ml (0.9%) solution for injection or 5% w/v glucose solution (minimal concentration: 3 mg/100 ml; maximal concentration: 4 mg/100 ml).

- 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 Mylan to ensure that they are adequately hydrated.

- Studies with polyolefin bags (prefilled with sodium chloride 9 mg/ml (0.9%) solution for injection or 5% w/v glucose solution), showed no incompatibility with Zoledronic acid Mylan.

- Since no data are available on the compatibility of Zoledronic acid Mylan with other intravenously administered substances, Zoledronic acid Mylan must not be mixed with other medicinal products/substances and should always be given through a separate infusion line.

How to store Zoledronic acid Mylan

- Keep Zoledronic acid Mylan out of the sight and reach of children.
- Do not use Zoledronic acid Mylan after the expiry date stated on the vial and carton after EXP.
- The unopened vial does not require any specific storage conditions.
- Storage conditions of the diluted solution are described in the above paragraph (See "How to prepare and administer Zoledronic acid Mylan").