NOVARTIS

**Package leaflet: Information for the user**

# Zometa® 4 mg/100 ml 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 Zometa is and what it is used for

The active substance in Zometa 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 Zometa

Follow carefully all instructions given to you by your doctor.

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

**You should not be given Zometa:**
- if you are breast-feeding.
- if you are allergic to zoledronic acid, another bisphosphonate (the group of substances to which Zometa 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 Zometa:**
- 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 Zometa.
- if you are having **dental treatment** or are due to undergo dental surgery, tell your dentist that you are being treated with Zometa and inform your doctor about your dental treatment.

While being treated with Zometa, 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 Zometa. 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 Zometa. You will be given adequate calcium and vitamin D supplements.

**Patients aged 65 years and over**
Zometa 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**
Zometa is not recommended for use in adolescents and children below the age of 18 years.

**Other medicines and Zometa**
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.
- 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 Zometa are unknown.
- Anti-angiogenic medicines (used to treat cancer), since the combination of these with Zometa has been associated with an increased risk of osteonecrosis of the jaw (ONJ).

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

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

## 3. How Zometa is used

- Zometa 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 Zometa 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 Zometa is given**
- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zometa 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 Zometa.

**How Zometa is given**
- Zometa 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 Zometa 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 Zometa 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.
- 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 Zometa 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 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.

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– 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 (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

| | |
|---|---|
| Ireland | HPRA Pharmacovigilance<br>Earlsfort Terrace<br>IRL - Dublin 2<br>Tel: +353 1 6764971<br>Fax: +353 1 6762517<br>Website: www.hpra.ie<br>e-mail: medsafety@hpra.ie |
| Malta | ADR Reporting<br>Website: www.medicinesauthority.gov.mt/adrportal |
| United Kingdom | Yellow Card Scheme<br>Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store |

## 5. How to store Zometa

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

After first opening, Zometa solution for infusion should preferably be used immediately. If the solution is not used immediately, it should be stored in a refrigerator at 2°C – 8°C.

## 6. Contents of the pack and other information

**What Zometa contains**
– The active substance of Zometa is zoledronic acid. One bottle contains 4 mg zoledronic acid, corresponding to 4.264 mg zoledronic acid monohydrate.
– The other ingredients are mannitol, sodium citrate and water for injections.

**What Zometa looks like and contents of the pack**
Zometa is supplied as a solution in a clear, colourless plastic bottle. One bottle contains 100 ml solution.

Zometa is supplied as a unit pack containing one bottle or as multipacks comprising 4 or 5 cartons, each containing 1 bottle. Not all pack sizes may be marketed.

**Marketing Authorisation Holder**
Novartis Europharm Limited
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**Manufacturer**
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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

## INFORMATION FOR THE HEALTHCARE PROFESSIONAL

**How to prepare and administer Zometa**
– Zometa 4 mg/100 ml solution for infusion contains 4 mg zoledronic acid in 100 ml of infusion solution for immediate use in patients with normal renal function.
– 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 solution for infusion should be used immediately, after first opening. 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 then 24 hours at 2°C – 8°C, unless dilution has taken place in controlled and validated aseptic conditions. The refrigerated solution should then be equilibrated to room temperature prior to administration.
– The solution containing zoledronic acid must not be further diluted or mixed with other infusion solutions. It 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 Zometa to assure that they are adequately hydrated.
– Zometa 4 mg/100 ml solution for infusion can be used immediately without further preparation for patients with normal renal function. In patients with mild to moderate renal impairment, reduced doses should be prepared as instructed below.

To prepare reduced doses for patients with baseline CLcr ≤ 60 ml/min, refer to Table 1 below. Remove the volume of Zometa solution indicated from the bottle and replace with an equal volume of sterile sodium chloride 9 mg/ml (0,9%) solution for injection, or 5% glucose solution for injection.

**Table 1 Preparation of reduced doses of Zometa 4 mg/100 ml solution for infusion**

| Baseline creatinine clearance (ml/min) | Remove the following amount of Zometa solution for infusion (ml) | Replace with the following volume of sterile sodium chloride 9 mg/ml (0.9%) or 5% glucose solution for injection (ml) | Adjusted dose (mg zoledronic acid in 100 ml) * |
|---|---|---|---|
| 50-60 | 12.0 | 12.0 | 3.5 |
| 40-49 | 18.0 | 18.0 | 3.3 |
| 30-39 | 25.0 | 25.0 | 3.0 |

*Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min.

– Studies with several types of infusion lines made from polyvinylchloride, polyethylene and polypropylene showed no incompatibility with Zometa.
– Since no data are available on the compatibility of Zometa with other intravenously administered substances, Zometa must not be mixed with other medications/substances and should always be given through a separate infusion line.

**How to store Zometa**
– Keep Zometa out of the reach and sight of children.
– Do not use Zometa after the expiry date stated on the pack.
– The unopened bottle does not require any special storage conditions.
– After opening the bottle, the product should be used immediately in order to avoid microbial contamination.