Denk Pharma

Zoledro-Denk 4 mg/5 ml

Concentrate for solution for infusion – intravenous use
Active substance: zoledronic acid

Package leaflet: Information for the user

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, nurse or pharmacist.
- 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.

1. What Zoledro-Denk 4 mg/5 ml is and what it is used for

The active substance in Zoledro-Denk 4 mg/5 ml 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 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).
- to treat post-menopausal women and men with osteoporosis or osteoporosis caused by treatment with steroids.
- to treat Paget's disease of the bone.

2. What you need to know before you are given Zoledro-Denk 4 mg/5 ml

Follow carefully all instructions given to you by your doctor. Your doctor will carry out blood tests before you start treatment with Zoledro-Denk 4 mg/5 ml and will check your response to treatment at regular intervals.

You must not be given Zoledro-Denk 4 mg/5 ml
- if you are allergic to zoledronic acid, another bisphosphonate (the group of substances to which Zoledro-Denk 4 mg/5 ml belongs), or any of the other ingredients of this medicine (listed in section 6).
- if you have hypocalcaemia (this means that the level of calcium in your blood is too low).
- if you have severe kidney problems.
- if you are breast-feeding.
- if you are pregnant.

Warnings and precautions
Talk to your doctor before you are given Zoledro-Denk 4 mg/5 ml
- 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 Zoledro-Denk 4 mg/5 ml. For more information please refer to the patient reminder card on *http://denkpharma.de/en/therapeutic-areas/product-portfolio-of-denk-pharma/#zoledro-denk-4-mg-5-ml*.
- if you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledro-Denk 4 mg/5 ml and inform your doctor about your dental treatment.
- if you are unable to take daily calcium supplements.
- if you have had some or all of the parathyroid glands in your neck surgically removed.
- if you have had sections or your intestine removed.

While being treated with Zoledro-Denk 4 mg/5 ml, 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 Zoledro-Denk 4 mg/5 ml. You will be given adequate calcium and vitamin D supplements.

Patients aged 65 years and over
Zoledro-Denk 4 mg/5 ml 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
Zoledro-Denk 4 mg/5 ml is not recommended for use in adolescents and children below the age of 18 years.

Other medicines and Zoledro-Denk 4 mg/5 ml
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) or any other bisphosphonate, since the combined effects of these medicines taken together with Zoledro-Denk 4 mg/5 ml 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).
- Diuretics ("waterpills") that may cause dehydration.

Pregnancy and breast-feeding
You should not be given Zoledro-Denk 4 mg/5 ml if you are pregnant. Tell your doctor if you are or think that you may be pregnant or are planning to have a baby.

You must not be given Zoledro-Denk 4 mg/5 ml 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.

Zoledro-Denk 4 mg/5 ml contains sodium
This medicine contains less than 1 mmol (23 mg) sodium per dose, i.e. it is essentially "sodium free".

3. How Zoledro-Denk 4 mg/5 ml is used
- Zoledro-Denk 4 mg/5 ml 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 much Zoledro-Denk 4 mg/5 ml 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 Zoledro-Denk 4 mg/5 ml is given
- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledro-Denk 4 mg/5 ml 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 Zoledro-Denk 4 mg/5 ml.
- For osteoporosis, one infusion of Zoledro-Denk 4 mg/5 ml works for one year. Your doctor will let you know when to return for your next dose. In case you recently broke your hip, it is recommended that Zoledro-Denk 4 mg/5ml is administered two or more weeks after your hip repair surgery. It is important to take calcium and vitamin D supplements (for example tablets) as directed by your doctor.
- For Paget's disease, one infusion of Zoledro-Denk 4 mg/5 ml may work for longer than one year, and your doctor will let you know if you need to be treated again. Your doctor may advise you to take calcium and vitamin D supplements (e.g. tablets) for at least the first ten days after being given Zoledro-Denk 4 mg/5 ml. It is important that you follow this advice carefully so that the level of calcium in your blood does not become too low in the period after the infusion. Your doctor will inform you regarding the symptoms associated with hypocalcaemia.

How Zoledro-Denk 4 mg/5 ml is given
- Zoledro-Denk 4 mg/5 ml 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.

Using Zoledro-Denk 4 mg/5 ml with food and drink
Make sure you drink enough fluids (at least one or two glasses) before and after the treatment with Zoledro-Denk 4 mg/5 ml, as directed by your doctor. This will help to prevent dehydration. You may eat normally on the day you are treated with Zoledro-Denk 4 mg/5 ml. This is especially important in patients who take diuretics and in elderly patients.

If a dose of Zoledro-Denk 4 mg/5 ml is missed
Contact your doctor or hospital as soon as possible to reschedule your appointment.

Before stopping Zoledro-Denk 4 mg/5 ml therapy
If you are considering stopping Zoledro-Denk 4 mg/5 ml treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Zoledro-Denk 4 mg/5 ml.

If you are given more Zoledro-Denk 4 mg/5 ml 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.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects
Like all medicines, this medicine can cause side effects, although not everybody gets them.
The following side effects were observed when zoledronic acid was administered to prevent bone complications in patients with bone metastases or tumour-induced hypercalcaemia:

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): Severe kidney impairment (will normally be determined by your doctor with certain specific blood tests); low level of calcium in the blood. 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): 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 Zoledro-Denk 4 mg/5 ml 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. 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): 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). 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): 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 Zoledro-Denk 4mg/5ml or after stopping treatment. Fainting due to low blood pressure. Severe bone, joint and/or muscle pain, occasionally incapacitating.
The following side effects were observed when zoledronic acid was administered to treat osteoporosis or Paget's disease:

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

Common (may affect up to 1 in 10 people): Headache, dizziness, sickness, vomiting, diarrhoea, pain in the muscles, pain in the bones and/or joints, pain in the back, arms or legs, flu-like symptoms (e.g. tiredness, chills, joint and muscle pain), chills, feeling of tiredness and lack of interest, weakness, pain, feeling unwell, swelling and/or pain at the infusion site.

In patients with Paget's disease: symptoms due to low blood calcium, such as muscle spasms, or numbness, or a tingling sensation especially in the area around the mouth.

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.

Uncommon (may affect up to 1 in 100 people): Flu, upper respiratory tract infections, decreased red cell count, loss of appetite, sleeplessness, sleepiness which may include reduced alertness and awareness, tingling sensation or numbness, extreme tiredness, trembling, temporary loss of consciousness, eye infection or irritation or inflammation with pain and redness, eye sensitivity to light, spinning sensation, increased blood pressure, flushing, cough, shortness of breath, upset stomach, abdominal pain, constipation, dry mouth, heartburn, skin rash, excessive sweating, itching, skin reddening, neck pain, stiffness in muscles, bones and/or joints, joint swelling, muscle spasms, shoulder pain, pain in your chest muscles and rib cage, joint inflammation, muscular weakness, abnormal kidney test results, abnormal frequent urination, swelling of hands, ankles or feet, thirst, toothache, taste disturbances.

Rare (may affect up to 1 in 1,000 people): Unusual fracture of the thigh bone particularly in patients on long-term treatment 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.

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

Frequency not known (frequency cannot be estimated from the available data): Severe allergic reactions including dizziness and difficulty breathing, swelling mainly of the face and throat, decreased blood pressure, dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea; pain in the mouth and/or jaw, swelling or non-healing sores in 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 Zoledro-Denk 4mg/5ml or after stopping treatment.

Kidney disorder (e.g. decreased urine output) may occur. Your doctor should do a blood test to check your kidney function before each dose of Zoledro-Denk 4mg/5ml. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving this medicine, as directed by your healthcare provider.

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

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

5. How to store Zoledro-Denk 4 mg/5 ml
- Keep this medicine out of the reach and sight of children.
- Do not use this medicine after the expiry date which is stated on the carton after "Exp". The expiry date refers to the last day of that month.
- Store below 25°C. Do not freeze.
- **Shelf-life:**
  - Unopended vial: 3 years
  - After opening: immediate use.
  - After dilution: refer to "The following information is intended for healthcare professionals only".

6. Contents of the pack and other information

What Zoledro-Denk 4 mg/5 ml contains
- The active substance is zoledronic acid. One 5 ml vial Zoledro-Denk 4 mg/5 ml contains 4 mg of zoledronic acid.
- The other ingredients are: mannitol, sodium citrate, water for injections.

General classification for supply
Medicinal product subject to medical prescription.

What Zoledro-Denk 4 mg/5 ml looks like and contents of the pack
Zoledro-Denk 4 mg/5 ml is a clear and colourless concentrate for solution for infusion.

It is available in colourless, transparent plastic vials each filled with 5 ml solution.

Zoledro-Denk 4 mg/5 ml is supplied as packs containing 1 vial.

Marketing Authorisation Holder
DENK PHARMA GmbH & Co. KG
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Manufacturer
Siegfried Hameln GmbH
Langes Feld 13, 31789 Hameln, Germany

This leaflet was last revised in 11/2017.

The following information is intended for healthcare professionals only:

Preparation guide for Zoledro-Denk 4 mg/5 ml

Concentrate for solution for infusion
Active substance: zoledronic acid

How to prepare and administer Zoledro-Denk 4 mg/5 ml
To prepare an infusion solution containing 4 mg zoledronic acid, dilute the Zoledro-Denk 4 mg/5 ml concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution.

If a lower dose of Zoledro-Denk 4 mg/5 ml 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 this medicinal product with calcium-containing or other divalent cation-containing solutions such as lactated Ringer's solution.

Instructions for preparing reduced doses of Zoledro-Denk 4 mg/5 ml:

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.
- Chemical and physical in-use stability after dilution of Zoledro-Denk 4 mg/5 ml with sodium chloride 9 mg/ml (0.9 %) solution for injection and glucose 50 mg/ml (5%) solution for injection has been demonstrated for 48 hours at room temperature (20 - 24°C) or when stored in a refrigerator at 2-8°C.
- 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 Zoledro-Denk 4 mg/5 ml to ensure that they are adequately hydrated.
- Since no data are available on the compatibility of Zoledro-Denk 4 mg/5 ml with other intravenously administered substances, Zoledro-Denk 4 mg/5 ml must not be mixed with other medications/substances and should always be given through a separate infusion line.

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