PACKAGE INSERT - INSTRUCTIONS FOR USE - READ CAREFULLY!

Zoledronic acid Fresenius Kabi 4 mg/5 ml concentrate for solution for infusion

Composition

One vial with 5 ml concentrate contains 4 mg of zoledronic acid (as monohydrate).
One ml concentrate contains 0.8 mg of zoledronic acid (as monohydrate)
Also contains Mannitol, Sodium citrate and water for injections.

Pharmaceutical form

Concentrate for solution for infusion (sterile concentrate)

Clear and colourless solution

Address of the pharmaceutical company

Fresenius Kabi Deutschland GmbH
D-61346 Bad Homburg v.d.H.
Germany

Manufacturers:
Fresenius Kabi Austria GmbH
Hafnerstraße 36
A-8055 Graz
Austria

Therapeutic indications

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone.
- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

Contraindications

Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients listed in section Composition.
Breast-feeding (see section Fertility, pregnancy and lactation).

Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity. The potential risk for humans is unknown. Zoledronic acid Fresenius Kabi should not be used during pregnancy.

Breast-feeding
It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid Fresenius Kabi is contraindicated in breast-feeding women (see section Contraindications).

Fertility
Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in peripartrient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans.

Special warnings and precautions for use

General
Patients must be assessed prior to administration of Zoledronic acid Fresenius Kabi to ensure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating Zoledronic acid Fresenius Kabi therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Other products containing zoledronic acid as active substances are available for osteoporosis indications and treatment of Paget´s disease of the bone. Patients being treated with Zoledronic acid Fresenius Kabi should not be treated with any other medicines containing zoledronic acid or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Renal insufficiency
Patients with TIH with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zoledronic acid Fresenius Kabi outweighs the possible risk.

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months.

Zoledronic acid, used as indicated in sections Therapeutic indications and Posology and method of administration, has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid Fresenius Kabi and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.

Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic acid Fresenius Kabi. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of Zoledronic acid Fresenius Kabi are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic acid Fresenius Kabi should be withheld. Zoledronic acid Fresenius Kabi should only be resumed when serum creatinine returns to within 10% of baseline.

Zoledronic acid Fresenius Kabi treatment should be resumed at the same dose as that given prior to treatment interruption.

In view of the potential impact of zoledronic acid, on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of Zoledronic acid Fresenius Kabi is not recommended in patients with severe renal impairment.

Hepatic insufficiency
As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients that were given zoledronic acid as indicated in section Therapeutic Indications and Posology and method of administration. However, such reports have been infrequent. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the zoledronic acid or another bisphosphonate.

Atypical fractures of the femur
Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.
During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is essentially "sodium-free".

Effects on ability to drive and use machines

Adverse reactions, such as dizziness and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of Zoledronic acid Fresenius Kabi along with driving and operating of machinery.

Interaction with other medicinal products and other forms of interaction

In clinical studies, zoledronic acid, used as indicated in section Therapeutic Indications and Posology and method of administration, has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro, but no formal clinical interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Caution is indicated when Zoledronic acid Fresenius Kabi is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when Zoledronic acid Fresenius Kabi is used in combination with thalidomide.

Reports of ONJ have been received in patients treated with zoledronic acid (as indicated in sections Therapeutic Indications and Posology and method of administration) and concomitant anti-angiogenic medicinal products.

Incompatibilities

To avoid potential incompatibilities, Zoledronic acid concentrate is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Zoledronic acid concentrate must not be mixed with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution, and should be administered as a single intravenous solution in a separate infusion line.

Posology and method of administration

Zoledronic acid Fresenius Kabi must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

Posology
Prevention of skeletal related events in patients with advanced malignancies involving bone
Adults and elderly
The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.

Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

Treatment of TIH
Adults and elderly
The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment
TIH:
Zoledronic acid Fresenius Kabi treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl (see section Special warnings and precautions for use).

Prevention of skeletal related events in patients with advanced malignancies involving bone:
When initiating treatment with Zoledronic acid Fresenius Kabi in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid Fresenius Kabi is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with Zoledronic acid, pa-

tients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, the following Zoledronic acid Fresenius Kabi dose is recommended (see also section Special warnings and precautions for use):

Baseline Creatinine Clearance (ml/min)	Zoledronic acid Fresenius Kabi Recommended Dose *
>60	4.0 mg zoledronic acid
50–60	3.5 mg* zoledronic acid
40–49	3.3 mg* zoledronic acid
30–39	3.0 mg* zoledronic acid

* 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.

Following initiation of therapy, serum creatinine should be measured prior to each dose of Zoledronic acid and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:

- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l.
- For patients with an abnormal baseline creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l.

In the clinical studies, Zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section Special warnings and precautions for use). Zoledronic acid Fresenius Kabi treatment should be resumed at the same dose as that given prior to treatment interruption.

Paediatric population
The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established. Currently available data are described in section Special warnings and precautions for use but no recommendation on a posology can be made.

Method of administration

Intravenous use.
Zoledronic acid Fresenius Kabi 4 mg/5 ml concentrate for solution for infusion, further diluted in 100 ml (see section Special precautions for disposal), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced Zoledronic acid Fresenius Kabi doses are recommended (see section Posology and section Special warnings and precautions for use).

Instructions for preparing reduced doses of Zoledronic acid Fresenius Kabi
Withdraw an appropriate volume of the concentrate needed, 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

The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zoledronic acid Fresenius Kabi concentrate must not be mixed with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution, and should be administered as a single intravenous solution in a separate infusion line.

Patients must be maintained well hydrated prior to and following administration of Zoledronic acid Fresenius Kabi.

Overdose

Clinical experience with acute overdose of zoledronic acid is limited. The administration of doses up to 48 mg of zoledronic acid in error has been reported. Patients who have received doses higher than those recommended (see section Posology and method of administration) should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

Undesirable effects

Summary of the safety profile
Within three days after zoledronic acid administration, used as indicated in section Therapeutic indications and Posology and method of administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia and rigors; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following are the important identified risks with Zoledronic acid in the approved indications:
Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1.

Tabulated list of adverse reactions
The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid:

Table 1
Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Common: Anaemia
Uncommon: Thrombocytopenia, leukopenia
Rare: Pancytopenia

Immune system disorders
Uncommon: Hypersensitivity reaction
Rare: Angioneurotic oedema

Psychiatric disorders
Uncommon: Anxiety, sleep disturbance
Rare: Confusion

Nervours system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence

Eye disorders
Common: Conjunctivitis
Uncommon: Blurred vision, scleritis and orbital inflammation
Very rare: Uveitis, episcleritis

Cardiac disorders
Uncommon: Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare: Bradycardia

Respiratory, thoracic and mediastinal disorders
Uncommon: Dyspnoea, cough, bronchoconstriction

Gastrointestinal disorders
Common: Nausea, vomiting, anorexia
Uncommon: Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth

Skin and subcutaneous tissue disorders
Uncommon: Pruritus, rash (including erythematous and macular rash), increased sweating

Musculoskeletal and connective tissue disorders
Common: Bone pain, myalgia, arthralgia, generalised pain
Uncommon: Muscle cramps, osteonecrosis of the jaw*

Renal and urinary disorders
Common: Renal impairment
Uncommon: Acute renal failure, haematuria, proteinuria

General disorders and administration site conditions
Common: Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Uncommon: Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria

Investigations
Very common: Hypophosphataemia
Common: Blood creatinine and blood urea increased, hypocalcaemia
Uncommon: Hypomagnesaemia, hypokalaemia
Rare: Hyperkalaemia, hypernatraemia

*Based on clinical trials with adjudication of possible cases of osteonecrosis of the jaw. Since these reports are subject to confounding factors, it is not possible to reliably establish a causal relationship to exposure to the medicinal product.

Description of selected adverse reactions
Renal function impairment
Zoledronic acid, used as indicated in sections Therapeutic indications and Posology and method of administration, has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section Special warnings and precautions for use).

Osteonecrosis of the jaw
Cases of osteonecrosis (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged (see section Special warnings and precautions for use).

Atrial fibrillation
In one 3-year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs. placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with zoledronic acid 4 mg every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

Acute phase reaction
This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-zoledronic acid infusion, (used as indicated in section Posology and method of administration), and the reaction is also referred to using the terms "flu-like" or "post-dose" symptoms.

Atypical fractures of the femur
During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Pharmaceutical precautions

Prior to administration, 5.0 ml concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 ml of calcium-free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution).

Studies with glass bottles, as well as several containers types made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with Zoledronic acid Fresenius Kabi.

Additional information on handling of Zoledronic acid Fresenius Kabi, including guidance on preparation of reduced doses, is provided in section Posology and method of administration.

Aseptic techniques must be followed during the preparation of the infusion. For single use only.

Only clear solution free from particles and discolouration should be used.

Healthcare professionals are advised not to dispose of unused Zoledronic acid Fresenius Kabi via the domestic sewage system.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Special precautions for storage

This medicinal product does not require any special storage condition.

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-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. Any refrigerated solution should then be equilibrated to room temperature prior to administration.

Presentation

Plastic vial made of colourless polypropylene closed with bromobutyl rubber stopper and aluminium cap with plastic flip-off component.

Packs containing 1, 4 or 10 vials.

Not all pack sizes may be marketed.

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FRESENIUS KABI