SEACROSS ZOLEDRONIC ACID 4MG/5ML CONCENTRATE FOR SOLUTION FOR INFUSION

QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 5 ml concentrate contains 4 mg zoledronic acid, corresponding to 4.264 mg zoledronic acid monohydrate.
One ml concentrate contains 0.8 mg zoledronic acid (as monohydrate).

DESCRIPTION

Before dilution: Zoledronic Acid 4 mg/ 5 ml is a sterile clear, colourless to yellowish solution for parenteral use available in 5 ml colourless cycloolefine copolymer (CoP) vials.
After dilution: clear colourless solution

CLINICAL PARTICULARS

Therapeutic indications

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

Posology and method of administration

Zoledronic acid 4mg/5ml 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 hypercalcemia of malignancy (HCM)

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

Hypercalcemia of malignancy (HCM) : Zoledronic acid 4mg/5ml treatment in patients with hypercalcaemia of malignancy (HCM) and 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 micromol/L or > 4.5 mg/dL were excluded. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL.

Prevention of skeletal related events in patients with advanced malignancies involving bone:

When initiating treatment with Zoledronic acid 4mg/5ml 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 4mg/5ml 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 Injection , patients 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 these populations as CLcr 30 to 60 mL/min, reduced Zoledronic acid 4mg/5ml dose is recommended:

Baseline creatinine clearance (ml/min)	Zoledronic acid 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=75mL/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 4mg/5ml 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 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 4mg/5ml treatment was resumed only when the creatinine level returned to within 10% of the baseline value. Zoledronic acid 4mg/5ml treatment should be resumed at the same dose as that given prior to treatment interruption.

Method of administration
Intravenous use.
Zoledronic acid 4mg/5ml, further diluted in 100ml, 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 4mg/5ml doses are recommended.

Instructions for preparing reduced doses of Zoledronic acid 4mg/5ml
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.
Patients must be maintained well hydrated prior to and following administration of Zoledronic acid 4mg/5ml.

Contraindications

- Hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of Zoledronic acid 4mg/5ml.
- Pregnancy and breast-feeding women

Warnings and precautions
General
Patients must be assessed prior to administration of Zoledronic acid injection to assure that they are adequately hydrated.

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

Standard hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium should be carefully monitored after initiating Zoledronic acid 4mg/5ml therapy. If hypocalcaemia, hypophosphatemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary.
Untreated hypercalcemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Zoledronic acid 4mg/5ml contains the same active substance as found in Aclasta (zoledronic acid). Patients being treated with Zoledronic acid 4mg/5ml should not be treated with Aclasta concomitantly, since the combined effects of these agents are unknown.

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 Injection is not recommended in patients with severe renal impairment.

Renal insufficiency
Patients with HCM 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 4mg/5ml 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.

As with other bisphosphonates, Zoledronic acid 4mg/5ml 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 4mg/5ml and other bisphosphonates as well as use of other nephrotoxic drugs, or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of Zoledronic Acid Injection 4 mg administered over no less than 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 Zoledronic acid 4mg/5ml.

Increases in serum creatinine also occur in some patients with chronic administration of Zoledronic Acid Injection 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 4mg/5ml. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of Zoledronic acid 4mg/5ml are recommended. In patients who show evidence of renal deterioration during treatment, Zoledronic acid 4mg/5ml should be withheld. Zoledronic acid 4mg/5ml should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid 4mg/5ml treatment should be resumed at the same dose as that given prior to treatment interruption.

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 has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as Zoledronic acid 4mg/5ml. 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.

The following risk factors should be considered when evaluating an individual's risk of developing osteonecrosis of the jaw:
- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose
- Cancer, chemotherapy, radiotherapy, corticosteroids, smoking
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors.

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.

Musculoskeletal pain
Severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking Zoledronic acid 4mg/5ml. 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 Zoledronic acid 4mg/5ml 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.

Hypocalcaemia
Hypocalcaemia has been reported in patients treated with Zoledronic acid 4mg/5ml. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when Zoledronic acid 4mg/5ml is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia. Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zoledronic acid

4mg/5ml therapy. Patients should be adequately supplemented with calcium and vitamin D.

Osteonecrosis of the external auditory canal
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Interaction with other medicinal products and other forms of interaction
Caution is advised when bisphosphonates are administered with aminoglycosides or calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.
Caution is indicated when Zoledronic Acid 4 mg/ 5 ml is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.
Caution is advised when Zoledronic Acid 4 mg/ 5 ml is administered with anti-angiogenic medicinal products, as an increase in the incidence of Osteonecrosis of the jaw has been observed in patients treated concomitantly with these medicinal products.

Zoledronic Acid 4 mg/5ml 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 enzyme in vitro, but no formal clinical interaction studies have been performed.

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

Pregnancy and lactation
Pregnancy
There are no adequate data on the use of zoledronic acid in pregnant women. The potential risk for humans is unknown. Zoledronic Acid 4mg/5ml should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.
Lactation
It is not known whether zoledronic acid is excreted into human milk. Zoledronic Acid 4mg/5ml is contraindicated in breast-feeding women.

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 along with driving and operating of machinery.

Undesirable effects
Within three days after Zoledronic Acid 4 mg/5ml administration, an acute phase reaction has commonly been reported, with symptoms including, bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection Description of selected adverse reactions).
The following are the important identified risks with Zoledronic Acid 4 mg/5ml in the approved indications:
Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 1

Table 1

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
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision, scleritis and orbital inflammation
Rare:	Uveitis
Very rare:	Episcleritis
Cardiac disorders	
Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough, bronchoconstriction
Rare:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite
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 spasms, osteonecrosis of the jaw
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi Syndrome.
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
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
Investigations	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia

Description of selected adverse reactions

Renal function impairment

Zoledronic Acid has been associated with reports of renal dysfunction in the prevention of skeletal-related events in patients with advanced malignancies involving bone. 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.

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.

Acute phase reaction
This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post Zoledronic Acid infusion, and the reaction is also referred to using the terms 'flu-like' or 'post-dose' symptoms.

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with Zoledronic Acid in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an association between Zoledronic Acid therapy, the reported event of hypocalcaemia, and the secondary development of cardiac arrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including; convulsions, hypoaesthesia and tetany.

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 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.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08

Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.
The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated:
- *In vivo:* Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment, making it less conducive to tumour cell growth, anti-angiogenic activity and anti-pain activity.
- *In vitro:* Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

Pharmacokinetic properties
Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in patients with bone metastases yielded the following pharmacokinetic data, which were found to be dose independent.

After initiating the infusion of zoledronic acid, the plasma concentrations of zoledronic acid rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of zoledronic acid on day 28.

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½\alpha}$ 0.24 and $t_{½\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½\gamma}$ 146 hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue.

From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 l/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

The interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as seen with other bisphosphonates.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the cancer patients. Population analysis showed that for a patient with creatinine clearance of 20 ml/min (severe renal impairment), or 50 ml/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37% or 72%, respectively, of that of a patient showing creatinine clearance of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

Zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

Special populations

Paediatric patients

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure.

PHARMACEUTICAL PARTICULARS

List of excipients

Mannitol
Sodium citrate
Water for injections

Incompatibilities

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

This medicinal product 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.

Storage condition
Before dilution: Store below 30°C.

After dilution: Chemical and physical in-use stability after dilution has been demonstrated for 30 hours at 2-8°C and 25°C. From a microbiological point of view, the diluted solution for infusion should be used immediately. The refrigerated solution should then be equilibrated to room temperature prior to administration.

Nature and contents of container
5ml plastic vial made of clear transparent Resin CZ cycloolefine polymer with 20mm Type I Teflon coated chlorobutyl rubber stopper. Each vial of the finished product is sealed with aluminium flip-off seal caps (20mm, clear outside and unlacquered inside or equivalent) with green polypropylene disks.
Pack size: 1 x 5ml/vial

Special precautions for disposal and other handling
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).

Additional information on handling of Zoledronic acid, 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 via the domestic sewage system.

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

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