AMONZITRA CONCENTRATE FOR SOLUTION FOR INFUSION 0.8MG/ML

Zoledronic Acid Concentrate for Solution for Infusion 0.8mg/mL

COMPOSITION AND PHARMACEUTICAL FORM
One vial with 5ml concentrate contains 4mg zoledronic acid anhydrous, corresponding to 4.25mg zoledronic acid monohydrate.
Liquid Concentrate for solution for infusion.

INDICATIONS
- Treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumours and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
- Treatment of hypercalcaemia of malignancy (HCM).

DOSAGE AND ADMINISTRATION
Zoledronic Acid 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 line separate from all other drugs.
Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy
Adults and elderly
The recommended dose in the treatment of bone metastases and treatment of osteolytic lesions is 4 mg zoledronic acid. The concentrate must be further diluted with 100 mL 0.9 % w/v sodium chloride or 5 % w/v glucose solution and given as an intravenous infusion lasting no less than 15 minutes every 3 to 4 weeks.
Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

Treatment of HCM
Adults and elderly
The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dL or 3.0 mmol/L) is 4 mg zoledronic acid. The concentrate must be further diluted with 100 mL 0.9 % w/v sodium chloride or 5 % w/v glucose solution, given as a single intravenous infusion of no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of zoledronic acid.

Renal impairment
HCM:
Zoledronic Acid treatment in patients with hypercalcaemia of malignancy (HCM) and who have severe renal impairment should be considered only after evaluating the risks and benefit 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.

Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy.
When initiating treatment with zoledronic acid in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CrCl) should be determined. CrCl is calculated from serum creatinine levels using the Cockcroft-Gault formula. Zoledronic Acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CrCl < 30 mL/min. In clinical trials with zoledronic Acid, patients with serum creatinine > 265 micromol/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 CrCl 30 to 60 mL/min, the following zoledronic acid dose is recommended.

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid Recommended Dose
>60	4.0 mg
50 - 60	3.5 mg*
40 - 49	3.3 mg*
30 - 39	3.0 mg*

*Doses have been calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=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 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), an increase of ≥ 0.5 mg/dL;
• For patients with an abnormal baseline creatinine (> 1.4 mg/dL), an increase of ≥ 1.0 mg/dL.
In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value. Zoledronic acid should be resumed at the same dose as that prior to treatment interruption.

Instructions on preparing reduced doses of Zoledronic Acid
Withdraw an appropriate volume of the liquid 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
For information on the reconstitution and dilution of Zoledronic acid, see section 'instructions for use and handling' and 'information for healthcare professionals'. The withdrawn amount of liquid 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 of no less than 15 minutes.

CONTRAINDICATIONS
Zoledronic acid concentrate is contraindicated in pregnancy, in breast-feeding women, patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of zoledronic acid.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
General
Patients must be assessed prior to administration of zoledronic acid to assure that they are adequately hydrated. Overhydration should be avoided in patients at risk of cardiac failure.
Standard hypercalcaemia-related metabolic parameters, such as albumin-corrected serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, 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.
Amonzitra (zoledronic acid) concentrate for solution for infusion 0.8mg/ml contains the same active ingredient as found in Zoledronic acid 5mg/100ml solution for infusion. Patients being treated with Zoledronic Acid Concentrate for Infusion should not be treated with Zoledronic acid 5mg/100ml solution for infusion concomitantly.
Zoledronic acid should also not be given together with other bisphosphonates since the combined effects of these agents are unknown.
While not observed in clinical trials with Zoledronic acid, there have been reports of bronchoconstriction in acetylsalicylic acid sensitive asthmatic patients receiving bisphosphonates.
The safety and efficacy of zoledronic acid in paediatric patients have not been established.
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 continued treatment with zoledronic acid 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 ≥ to 3 months.
Bisphosphonates have 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 or other bisphosphonates as well as use of nephrotoxic drugs or using a shorter infusion time than currently recommended.
While the risk is reduced with a dose of zoledronic acid 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. 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. Upon initiation of treatment in all adult patients except patients with HCM with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should only be resumed when creatinine level returns to within 10% of baseline value.
In view of the potential risk of renal function deterioration in patients treated with bisphosphonates, including zoledronic acid, on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 micromol/L or ≥ 4.5 mg/dL for patients with HCM and ≥ 265 micromol/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 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 predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.
Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).
Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.
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 judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of other anatomical sites
Cases of osteonecrosis of other anatomical sites including the hip, femur and external auditory canal have been reported predominantly in adult cancer patients treated with bisphosphonates, including Zoledronic acid.

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 Zoledronic acid-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of Zoledronic acid 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. Reports of atypical femoral fracture have been received in patients treated with Zoledronic acid; however causality with Zoledronic acid therapy has not been established.
During 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.

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking bisphosphonates. This category of drugs includes zoledronic acid. 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 re-challenged with the same drug or another bisphosphonate.

Hypocalcaemia
Hypocalcaemia has been reported in patients treated with Zoledronic acid. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcaemia. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when Zoledronic acid is administered with other hypocalcaemia causing drugs, as they may have synergistic effect resulting in severe hypocalcaemia. Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

INTERACTIONS
In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics except for loop 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 like zoledronic acid 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 is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.
No dose adjustment for Zoledronic acid 4 mg is needed when coadministered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zoledronic acid 4 mg given as a 15-minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28). Coadministration of thalidomide with Zoledronic acid did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

WOMEN OF CHILD-BEARING POTENTIAL, PREGNANCY, LACTATION AND FERTILITY
Women of child-bearing potential
Women of child-bearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the fetus while receiving Zoledronic acid. There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section CONTRAINDICATION) while receiving bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk has not been established.

Pregnancy
Studies in rats have shown reproductive toxicological effects. The potential risk in humans is unknown. Zoledronic acid should not be used during pregnancy (see section CONTRAINDICATIONS).

Lactation
It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid should not be used by breast-feeding women.

Fertility
The fertility was decreased in rats dosed subcutaneously with 0.01 mg/kg/day of zoledronic acid with systemic exposures of 0.12 times the human systemic exposure following an intravenous dose of 4 mg (based on AUC). The effects observed included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses. There are no data available in humans.

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES
No studies on the effects on the ability to drive and use machines have been performed.

ADVERSE DRUG REACTIONS
Summary of the safety profile
The most serious adverse drug reactions reported in patients receiving Zoledronic Acid in the approved indications are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute phase reaction, and hypocalcaemia. The frequencies of these adverse reactions are shown in Table 1 or shown as adverse reactions from 'Spontaneous reports and literature cases' with 'not known' frequency.
Frequencies of adverse reactions for Zoledronic Acid 4 mg are mainly based on data collected from chronic treatment. Adverse reactions to Zoledronic Acid are usually mild and transient and similar to those reported for other bisphosphonates. Those reactions can be expected to occur in approximately one third of patients treated with Zoledronic Acid.
Within three days after Zoledronic Acid administration, an acute phase reaction has commonly been reported, with symptoms including pyrexia, fatigue, bone pain, chills, influenza-like illness, arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection Description of selected adverse reaction). Cases of arthralgia and myalgia have been reported.
Very commonly, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels, which is asymptomatic not requiring treatment. Commonly, the serum calcium may fall to asymptomatic hypocalcaemic levels. Gastrointestinal reactions, such as nausea and vomiting have been commonly reported following intravenous infusion of Zoledronic Acid. Uncommonly, local reactions at the infusion site such as redness or swelling and/or pain were also observed.
Anorexia was commonly reported in patients treated with Zoledronic Acid 4 mg.
Rash or pruritus has been uncommonly observed.
As with other bisphosphonates, cases of conjunctivitis have been commonly reported.
Based on pooled analysis of placebo controlled studies, severe anaemia (Hb < 8.0 g/dL) was commonly reported in patients receiving Zoledronic Acid 4 mg.
Adverse reactions (Table 1) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000).

Table 1

Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
Immune system disorders	
Uncommon:	Hypersensitivity reaction
Rare:	Angioedema
Nervous system disorders	
Common:	Headache, paraesthesia
Uncommon:	Dizziness, dysgeusia, hypoaesthesia, hyperaesthesia, tremor
Very rare:	Convulsion, hypoesthesia and tetany (secondary to hypocalcaemia)
Psychiatric disorders	
Common:	Sleep disorder
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusional state
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision
Rare:	Uveitis, episcleritis
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite, constipation
Uncommon:	Diarrhoea , abdominal pain, dyspepsia, stomatitis, dry mouth
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough
Rare:	Interstitial lung disease (ILD)
Skin and subcutaneous tissue disorders	
Common:	Hyperhidrosis
Uncommon:	Pruritus, rash (including erythematous and macular rash)
Musculoskeletal and connective tissue disorders	
Common:	Bone pain, myalgia, arthralgia, generalised body pain, joint stiffness
Uncommon:	Osteonecrosis of jaw (ONJ), muscle spasms
Cardiac disorders	
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcemia)
Vascular disorders	
Common:	Hypertension
Uncommon:	Hypotension
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
General disorders and administration site conditions	
Common:	Acute phase reaction, pyrexia, influenza-like illness (including: fatigue, chills, malaise and flushing), peripheral edema, asthenia
Uncommon:	Injection site reactions (including: pain, irritation, swelling, induration, redness), chest pain, weight increased
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

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)
The following adverse reactions have been reported during post-marketing experience with Zoledronic Acid via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency (which is therefore categorized as not known) or establish a causal relationship to drug exposure.
Immune system disorders: anaphylactic reaction/shock
Nervous system disorders: somnolence
Eye disorders: episcleritis, scleritis and orbital inflammation
Cardiac disorders: atrial fibrillation
Vascular disorders: hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors
Respiratory, thoracic and mediastinal disorders: bronchospasm
Skin and subcutaneous tissue disorders: urticaria
Musculoskeletal and connective tissue disorders: severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including Zoledronic Acid).
Description of selected adverse reactions

Renal function impairment
Zoledronic Acid has been associated with reports of renal function impairment. In a pooled analysis of safety data from Zoledronic Acid registration trials for the prevention of skeletal-related events in patients with advanced malignancy involving bone, the frequency of renal function 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 tumors (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 Zoledronic Acid (see section WARNINGS AND PRECAUTIONS, see section INTERACTIONS).

Osteonecrosis of the jaw
Cases of osteonecrosis (primarily of the jaw) but also of other anatomical sites including hip, femur and external auditory canal, have been reported predominantly in cancer patients treated with bisphosphonates, including 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 well documented

GLUE AREA
NO PRINTING

60 mm

GLUE AREA
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5 mm
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OPTICAL CODE
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PHARMA CODE

2.5 mm

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OPTICAL CODE
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3 mm
AMONZITRA CONCENTRATE FOR SOLUTION FOR INFUSION 0.8MG/ML
Zoledronic Acid Concentrate for Solution for Infusion 0.8mg/mL
AAA00047
3 mm
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3 mm

GLUE AREA
NO PRINTING

risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic drugs, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section WARNINGS AND PRECAUTIONS). Data suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

Acute phase reaction
This adverse drug reaction consists of a constellation of symptoms that includes pyrexia, fatigue, bone pain, chills, influenza-like illness, 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; these symptoms usually resolve within a few days.

Atrial fibrillation
In one 3 year, randomized, 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 to 4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

OVERDOSE
Clinical experience with acute overdosage of zoledronic acid is limited. 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.

PHARMACODYNAMICS
Zoledronic acid belongs to a new highly potent class of bisphosphonates which act primarily on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date.
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, mineralization or mechanical properties of bone.
In addition to being a very 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 preclinical studies:

- *In vivo*: Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment making it less conducive to tumour cell growth, anti-angiogenic activity, anti-pain activity.
- *In vivo*: 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.

Clinical trial results in the treatment of osteolytic, osteoblastic and mixed bone metastases and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy
Zoledronic acid was compared to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients with 214 men receiving zoledronic acid 4 mg versus 208 receiving placebo. After the initial 15 months of treatment, 186 patients continued for up to an additional 9 months, giving a total duration of double-blind therapy up to 24 months. Zoledronic acid 4 mg demonstrated a significant advantage over placebo for the proportion of patients experiencing at least one skeletal related event (SRE) (38% for zoledronic acid 4 mg versus 49% for placebo, p=0.028), delayed the median time to first SRE (488 days for zoledronic acid 4 mg versus 321 days for placebo, p=0.009), and reduced the annual incidence of event per patient - skeletal morbidity rate (0.77 for zoledronic acid 4 mg versus 1.47 for placebo, p=0.005). Multiple event analysis showed 36% risk reduction in developing skeletal related events in the zoledronic acid group compared with placebo (p=0.002). Pain was measured at baseline and periodically throughout the trial. Patients receiving zoledronic acid reported less increase in pain than those receiving placebo, and the differences reached significance at months 3, 9, 21 and 24. Fewer zoledronic acid patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 2.
In a second study, zoledronic acid reduced the number of SREs and extended the median time to an SRE by over two months in the population of patients who had other solid tumours involving bone, which had a median survival of only six months (134 patients with non-small-cell lung cancer (NSCLC), 123 with other solid tumours treated with zoledronic acid vs 130 patients with NSCLC, 120 with other solid tumours treated with placebo). After initial 9 months of treatment, 101 patients entered the 12 month extension study, and 26 completed the full 21 months. Zoledronic acid 4 mg reduced the proportion of patients with SREs (39% for zoledronic acid 4 mg versus 48% for placebo, p=0.039), delayed the median time to first SRE (236 days for zoledronic acid 4 mg versus 155 days for placebo, p=0.009), and reduced the annual incidence of events per patient - skeletal morbidity rate (1.74 for zoledronic acid 4 mg versus 2.71 for placebo, p=0.012). Multiple event analysis showed 30.7% risk reduction in developing skeletal related events in the zoledronic acid group compared with placebo (p=0.003). The treatment effect in non- small cell lung cancer patients appeared to be smaller than in patients with other solid tumours. Efficacy results are provided in Table 3.

Table 2: Efficacy results (prostate cancer patients receiving hormonal therapy)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
N	214	208	214	208	214	208
Proportion of patients with SREs(%)	38	49	17	25	26	33
p-value	0.028		0.052		0.119	
Median time to SRE (days)	488	321	NR	NR	NR	640
p-value	0.009		0.020		0.055	
Skeletal morbidity rate	0.77	1.47	0.20	0.45	0.42	0.89
p-value	0.005		0.023		0.060	
Risk reduction of suffering from multiple events** (%)	36	-	NA	NA	NA	NA
p-value	0.002		NA		NA	

* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable

Table 3: Efficacy results (solid tumours other than breast or prostate cancer)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
N	257	250	257	250	257	250
Proportion of patients with SREs(%)	39	48	16	22	29	34
p-value	0.039		0.064		0.173	
Median time to SRE (days)	236	155	NR	NR	424	307
p-value	0.009		0.020		0.079	
Skeletal morbidity rate	1.74	2.71	0.39	0.63	1.24	1.89
p-value	0.012		0.066		0.099	
Risk reduction of suffering from multiple Events** (%)	30.7	-	NA	NA	NA	NA
p-value	0.003		NA		NA	

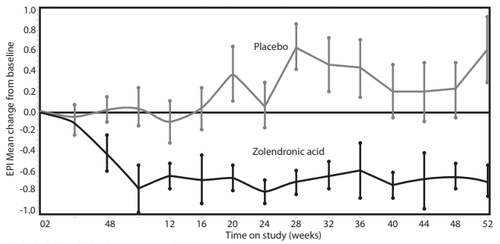
* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable
In a third phase III randomised, double-blind trial comparing zoledronic acid 4 mg to pamidronate 90 mg, 1,122 patients (564 zoledronic acid 4 mg, 558 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg zoledronic acid or 90 mg pamidronate every 3 to 4 weeks. Eight patients were excluded from the efficacy analysis because of good clinical practice non-compliance. 606 patients entered the 12-month, double-blind extension phase. Total therapy lasted up to 24 months. The results demonstrated that zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of skeletal related events. The multiple event analyses revealed a significant risk reduction of 16% (p=0.030) in patients treated with zoledronic acid 4 mg. Efficacy results are provided in Table 4.

Table 4: Efficacy results (breast cancer and multiple myeloma patients)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
N	561	555	561	555	561	555
Proportion of patients with SREs(%)	48	52	37	39	19	24
p-value	0.198		0.653		0.037	
Median time to SRE (days)	376	356	NR	714	NR	NR
p-value	0.151		0.672		0.026	
Skeletal morbidity rate	1.04	1.39	0.53	0.60	0.47	0.71
p-value	0.084		0.614		0.015	
Risk reduction of suffering from multiple events** (%)	16	-	NA	NA	NA	NA
p-value	0.030		NA		NA	

* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable
In clinical trials performed in patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity.
Zoledronic Acid was also studied in a double blind, randomized, placebo- controlled trial in 228 adult patients with documented bone metastases from breast cancer to evaluate the effect of Zoledronic acid on skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcaemia and adjusted prior fracture), divided by the total risk period. Patients received either 4 mg Zoledronic Acid or placebo every four weeks for one year. Patients were evenly distributed between Zoledronic Acid -treated and placebo groups. The SRE rate ratio at one year was 0.61, indicating that treatment with Zoledronic Acid reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the Zoledronic Acid -treated group versus 49.6% in the placebo group (p=0.003). Median time to onset of the first SRE was not reached in the Zoledronic Acid -treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic Acid reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo. In the Zoledronic Acid -treated group, decreases in pain scores from baseline (using the Brief Pain Inventory, BPI) occurred from 4 weeks onwards and at every subsequent time point during the study, while the pain score in the placebo group remained unchanged or increased from baseline (Figure 1). Zoledronic Acid inhibited the worsening of the analgesic score more than placebo. In addition, 71.8% of Zoledronic Acid -treated patients versus 63.1% of placebo patients showed improvement or no change in the ECOG performance score at the final observation.

Figure 1:
Mean change from baseline in Brief Pain Inventory (BPI) pain scores by treatment group and time on study.



Clinical trial results in the treatment of HCM
Clinical studies in hypercalcaemia of malignancy (HCM) demonstrated that the effect of zoledronic acid is characterized by decreases in serum calcium and urinary calcium excretion.
To assess the effects of zoledronic acid versus pamidronate 90 mg, the results of two pivotal multicentre studies in patients with HCM were combined in a pre-planned analysis. The results showed that zoledronic acid 4 mg and 8 mg were statistically superior to pamidronate 90 mg for the proportion of complete responders at day 7 and day 10. There was faster normalisation of corrected serum calcium at day 4 for zoledronic acid 8 mg and at day 7 for zoledronic acid 4 mg and 8 mg. The following response rates were observed:

Table 5: Proportion of complete responders by day in the combined HCM studies:

	Day 4	Day 7	Day 10
Zoledronic acid 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zoledronic acid 8 mg (N=90)	55.6% (p=0.021)*	83.3% (p=0.010)*	86.7% (p=0.015)*
Pamidronate 90 mg (N=99)	33.3%	63.6%	69.7%

*p-values denote statistical superiority over pamidronate.
Median time to normocalcaemia was 4 days. By day 10 the response rate was 87 to 88 % for the zoledronic acid treatment groups versus 70 % for pamidronate 90 mg. Median time to relapse (re-increase of albumin-corrected serum calcium ≥ 2.9 mmol/L) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg. The results showed that both zoledronic acid doses were statistically superior to pamidronate 90 mg for time to relapse. There were no statistically significant differences between the two zoledronic acid doses.
In clinical trials performed in patients with hypercalcaemia of malignancy (HCM), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

PHARMACOKINETICS
Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 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 drug 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 drug on day 28.
Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2}$ alpha 0.24 and $t_{1/2}$ beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2}$ gamma 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug 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.
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 significantly positively 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 64 cancer patients studied. Population analysis showed that for a patient with creatinine clearance of 50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 72% 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). The use of zoledronic acid is not recommended in patients with severe renal impairment.
Zoledronic acid shows 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.

NON-CLINICAL SAFETY DATA
Toxicity studies
In the bolus parenteral studies, Zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2 to 3 days in dogs for up to 52 weeks was also well tolerated.
The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphysis of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.
The kidney was identified as a major target organ for toxicity in parenteral studies with zoledronic acid. In the intravenous infusion studies, renal tolerability was observed in rats given six infusions at doses of up to 0.6 mg/kg at 3-day intervals, while five infusions of 0.25 mg/kg administered at 3-week intervals were well tolerated in dogs.
Reproduction toxicity
Teratogenicity studies were performed in two species, both via subcutaneous administration of zoledronic acid. Teratogenicity was observed in the rat at doses ≥0.2 mg/kg/day and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats.
No teratogenic or embryo/fetal effects were observed in the rabbit, although maternal toxicity was marked at 0.1 mg/kg/day. Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcaemia
Mutagenicity
Zoledronic acid was not mutagenic in vitro and in vivo in the mutagenicity tests performed.
Carcinogenicity
In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential.

EXCIPIENTS
Mannitol, Sodium citrate, water for injections.

INCOMPATIBILITIES
Studies with glass bottles, as well as several types of infusion bags and infusion lines 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.
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 line separate from all other drugs.

STORAGE
Store below 30°C

Reconstituted solution:
After aseptic dilution, it is preferable to use the diluted product immediately. If not used immediately, the diluted solution should be stored at 2 to 8°C. The duration and conditions of storage prior to use are under the healthcare provider's responsibility. The total time between dilution, storage in a refrigerator at 2-8°C and end of administration must not exceed 24 hours.

INSTRUCTIONS FOR USE AND HANDLING
Zoledronic acid 4 mg/5 mL concentrate for solution for infusion is for intravenous use only. 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). If refrigerated, the solution must be allowed to reach room temperature before administration.
Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.
Zoledronic acid should be kept out of the reach and sight of children.

INFORMATION FOR THE HEALTHCARE PROFESSIONALS
How to prepare and administer zoledronic acid

- To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the zoledronic acid concentrate (5.0 mL) with 100 mL of calcium-free or other divalent cation-free infusion solution. If a lower dose of zoledronic acid is required, first withdraw the appropriate volume and 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 zoledronic acid concentrate with calcium-containing or other divalent cation-containing solutions such as Lactated Ringer's solution.
Instructions on preparing reduced doses of zoledronic acid
Withdraw an appropriate volume of the liquid 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

- After preparation, zoledronic acid infusion solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the care provider and should be in a refrigerator at 2° to 8°C. Allow the refrigerated solution to reach room temperature before administration.
- The total time between dilution, storage in the refrigerator and end of administration must not exceed 24 hours.
- The solution containing zoledronic acid is given as a single intravenous infusion of no less than 15 minutes. The hydration status of patients must be assessed prior to and following administration of zoledronic acid to assure that they are adequately hydrated.
- Studies with glass bottles, several types of infusion bags and infusion lines 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.
- Since no data are available on the compatibility of zoledronic acid with other intravenously administered substances, zoledronic acid must not be mixed with other medications/substances and should always be given through a separate infusion line.

Manufacturer:
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10 000 Zagreb
Croatia

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GLUE AREA NO PRINTING

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2,5 mm