PRODUCT MONOGRAPH

ZOLEDRONIC ACID CONCENTRATE FOR
INJECTION (Zoledronic Acid for Injection)

4 mg Zoledronic acid/5 mL incorporated as the monohydrate

Sterile liquid concentrate must be diluted before use

Bone Metabolism Regulator

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Control # 198168

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[Pr]Zoledronic Acid for Injection

For Intravenous Infusion

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	• Concentrate: 4 mg zoledronic acid/5 mL[†]	• Concentrate: mannitol, sodium citrate and water. *For a complete listing see*

[†] This corresponds to 4.264 mg zoledronic acid monohydrate

INDICATIONS AND CLINICAL USE

Tumour-Induced Hypercalcaemia (TIH)

Zoledronic Acid for Injection is indicated for the treatment of Tumour-Induced Hypercalcaemia, defined as albumin-corrected serum calcium (cCa) ≥ 12.0 mg/dL (3.0 mmol/L), following adequate saline rehydration. Prior to treatment with Zoledronic Acid for Injection, renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.

Bone Metastases of Solid Tumours and Osteolytic Lesions of Multiple Myeloma

Zoledronic Acid for Injection is indicated for the treatment of patients with documented bone metastases from solid tumours (including prostate cancer, breast cancer, lung cancer, renal cell carcinoma and other solid tumours) and patients with osteolytic lesions of multiple myeloma in conjunction with standard care in order to prevent or delay potential complications from the bone lesions (see **WARNINGS AND PRECAUTIONS, Deterioration in renal function**).

Zoledronic Acid for Injection must only be administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

CONTRAINDICATIONS

- Hypersensitivity to zoledronic acid or other bisphosphonates, or any of the excipients in the formulation of Zoledronic Acid for Injection (see **DOSAGE FORMS, COMPOSITION AND PACKAGING**).

- Non-corrected hypocalcaemia at the time of infusion (see **WARNINGS AND PRECAUTIONS, Hypocalcaemia**)

- Pregnancy and breastfeeding women (see **WARNINGS AND PRECAUTIONS, Special populations**)

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- **Osteonecrosis of the jaw** (ONJ), (See, **Musculoskeletal, Osteonecrosis of the Jaw** below)
- **Deterioration in renal function** (See **Renal** below)
- The use of Zoledronic Acid for Injection is **not recommended in patients with severe renal impairment** (See **Special Populations** below)
- **Hypocalcaemia** (See **General, Hypocalcaemia** below**)**
- Single doses of Zoledronic Acid for Injection should not exceed 4 mg and the duration of the infusion should be no less than 15 minutes. **(**See **Renal** and **DOSAGE AND ADMINISTRATION** below**)**

General

Drug Interactions

Zoledronic Acid for Injection contains the same active ingredient that is contained in ACLASTA® (zoledronic acid). Patients being treated with Zoledronic Acid for Injection should not be treated with ACLASTA concomitantly.

Zoledronic Acid for Injection should not be given together with other bisphosphonates since the combined effects of these agents are unknown.

Zoledronic Acid for Injection is eliminated by renal excretion. Caution is indicated when zoledronic acid is administered in conjunction with drugs that are potentially nephrotoxic (e.g. aminoglycosides, other antineoplastic agents, ASA, NSAIDs), or that can significantly impact renal function (e.g. diuretics, ACE inhibitors, leading to dehydration).

Caution is advised when zoledronic acid for injection is administered with anti-angiogenic drugs, as the incidence of ONJ is increased when these drugs are used concomitantly (see **Osteonecrosis of the Jaw**, **DRUG INTERACTIONS, Drug-Drug Interactions**).

Caution is advised when Zoledronic Acid for Injection is administered with loop diuretics (particularly in patients treated for TIH), with aminoglycosides, or with calcitonin, since there may be an additive effect on the risk of developing hypocalcaemia.

Zoledronic Acid for Injection should be used with extreme caution in conjunction with other antineoplastic agents that are known to produce renal dysfunction (it is advised that renal function be monitored) or where the dose depends upon renal function (for example platinum- containing agents).

Zoledronic Acid for Injection should not be mixed with calcium-containing intravenous infusions.

Effects on ability to drive or use machines

In rare cases, somnolence and/or dizziness may occur, in which case the patient should not drive, operate potentially dangerous machinery or engage in other activities that may be hazardous.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with zoledronic acid for injection. QTc prolongation and neurologic adverse events (tonic-clonic seizures, tetany and numbness) have been reported secondary to cases of severe hypocalcaemia. In some instances, the hypocalcaemia required hospitalization and/or was life-threatening.

Caution is advised when Zoledronic Acid for Injection is administered with other hypocalcaemia-causing drugs (including aminoglycosides, calcitonin, or loop diuretics), as they may have an additive effect resulting in severe hypocalcaemia (see also **DRUG INTERACTIONS**).

Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

Serum albumin-corrected calcium should be measured prior to each dose and during therapy with Zoledronic Acid for Injection (see **Monitoring and Laboratory Tests**). Zoledronic Acid for Injection is contraindicated in patients who have non-corrected hypocalcaemia at the time of infusion (see **CONTRAINDICATIONS**).

Tumour-Induced Hypercalcaemia

It is essential in the initial treatment of tumour-induced hypercalcaemia that intravenous rehydration be instituted to restore urine output. All patients, including patients with mild to moderate renal impairment, should be hydrated adequately throughout treatment, but overhydration must be avoided.

In patients with cardiac disease, especially in the elderly, additional saline overload may precipitate cardiac failure (left ventricular failure or congestive heart failure). Fever (influenza-like symptoms) may also contribute to this deterioration.

Carcinogenesis and Mutagenesis

In carcinogenicity studies, zoledronic acid was administered orally (gavage) to rats and mice for at least 104 weeks without evidence of carcinogenic potential. Chronic parenteral administration was not feasible given the potential of the compound to cause severe local irritation. The pharmacological bone changes (nonproliferative hyperostosis) typically observed following long term bisphosphonate administration to young animals with growing skeletons gave clear evidence of systemic exposure to zoledronic acid in both species at all doses.

Six mutagenicity studies were conducted with zoledronic acid: three Ames Assays (using E. coli and/or S. typhimurium), a gene mutation assay using V79 hamster cells, a cytogenetics test with Chinese hamster cells and an *in vivo* micronucleus assay in rats. There was no evidence of

mutagenic potential.

Cardiovascular

In a 3-year, randomized, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg dose once yearly vs. placebo in the treatment of post menopausal 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 for injection 4 mg administered every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

As only limited clinical data are available for patients with hepatic impairment, dosage recommendations cannot be given for this group.

Musculoskeletal

Atypical Fractures of the Femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. Reports of atypical femoral fracture have also been received in patients treated with zoledronic acid for injection. 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 for Injection -treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of Zoledronic Acid for Injection 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 Zoledronic Acid for Injection 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, including zoledronic acid for injection (see **ADVERSE REACTIONS**). The time to onset of symptoms varied from one day to several months after starting treatment. Zoledronic Acid for Injection should be discontinued if symptoms are severe. 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.

Osteonecrosis

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported in cancer patients treated with zoledronic acid for injection or with other bisphosphonates. Although no causal relationship has been established, there is an association between bisphosphonate use and the development of ONJ. Post-marketing experience suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma) and dental status (dental extractions, periodontal disease, and local trauma including poorly fitting dentures); these are associated with a greater risk of developing ONJ. Cancer patients also receive other treatments that may play a role in the development of ONJ, such as chemotherapy and glucocorticosteroids. Many patients reporting ONJ had signs of local infection including osteomyelitis (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Presentation of ONJ may include altered local sensation (hyperaesthesia or numbness), maxillofacial pain, "toothaches", denture sore spots, loose teeth, exposed bone in the oral cavity, impaired healing, recurrent or persistent soft tissue infection in the oral cavity, and marked oral odour. The onset can be from months to years after commencing bisphosphonate therapy. Cancer patients should maintain good oral hygiene. It is recommended that cancer patients be encouraged to have an oral examination of both hard and soft tissues, with appropriate preventive dentistry performed prior to treatment with Zoledronic Acid for Injection. These oral assessments are recommended to be continued at regularly scheduled intervals after Zoledronic Acid for Injection therapy is initiated and during treatment with Zoledronic Acid for Injection (see Monitoring and Laboratory Tests). While receiving Zoledronic Acid for Injection therapy, patients should immediately report any oral symptoms. It is advisable that patients undergo routine dental check-ups during their treatment with Zoledronic Acid for Injection. Patients should avoid invasive dental procedures if possible, but should continue with regular dental cleaning and oral hygiene. Biopsies are not recommended unless metastasis to the jaw is suspected. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there is no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

The start of treatment, or of a new course of treatment, should be delayed in patients with unhealed open soft tissue lesions in the mouth.

The following should be considered when evaluating a patient's risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds)
- Route of administration (higher risk for parenteral administration)
- Cumulative dose of bone resorption therapy
- Co-morbid conditions (e.g. anaemia, coagulopathies) and smoking
- Periodontal disease, poorly fitting dentures, history of dental disease.

Temporary interruption of Zoledronic Acid for Injection treatment should be considered until the condition resolves and contributing factors are mitigated where possible.

Caution is advised when Zoledronic Acid for Injection is administered with anti-angiogenic

drugs, as the incidence of ONJ is increased when these drugs are used concomitantly **(see DRUG INTERACTIONS, Drug-Drug Interactions)**.

Osteonecrosis of Other Anatomical Sites

Cases of osteonecrosis of other anatomical sites including the femur, hip, humerus, external auditory canal, tibia, ribs, spine, knee, and metatarsal bones have been reported in patients treated with zoledronic acid for injection (see **ADVERSE REACTIONS, Post-Market Adverse Drug Reactions**).

Ophthalmologic

Ocular disturbances (conjunctivitis, uveitis, episcleritis, scleritis and orbital inflammation) have been reported with zoledronic acid for injection therapy. Patients with ocular events other than uncomplicated conjunctivitis should be referred to an ophthalmologist for evaluation. Treatment may need to be discontinued.

Peri-Operative Considerations

Patients treated with Zoledronic Acid for Injection should avoid invasive dental procedures if possible. Biopsies are not recommended unless metastasis to the jaw is suspected. For patients who develop ONJ while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there is no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment. (See also **Musculoskeletal, Osteonecrosis**, **Osteonecrosis of the Jaw)**

Renal

Assessment of renal function is recommended in all patients prior to the administration of each dose and during therapy with Zoledronic Acid for Injection.

Deterioration in Renal Function

DUE TO THE RISK OF CLINICALLY SIGNIFICANT DETERIORATION IN RENAL FUNCTION, WHICH MAY PROGRESS TO RENAL FAILURE, SINGLE DOSES OF ZOLEDRONIC ACID FOR INJECTION SHOULD NOT EXCEED 4 MG AND THE DURATION OF THE INFUSION SHOULD BE NO LESS THAN 15 MINUTES. (See also **DOSAGE AND ADMINISTRATION)**

Bisphosphonates, including zoledronic acid for injection, have been associated with reports of renal function deterioration. **Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic Acid For Injection or other bisphosphonates, or using a shorter infusion time than currently recommended (the 4 mg dose is given as a single dose intravenous infusion over not less than 15 minutes in not less than 100 mL diluent). Concomitant use of potentially nephrotoxic drugs (i.e. ASA, NSAIDS, diuretics, ACE inhibitors etc.) may also increase the potential for renal function deterioration. Renal function should be assessed prior to the administration of each dose of Zoledronic Acid for Injection and should be monitored appropriately during therapy with Zoledronic Acid for Injection**. Renal

deterioration, progression to renal failure (some with fatal outcome) and dialysis have been reported very rarely in cancer patients (e.g., those with hypercalcaemia of malignancy and/or pre-existing renal disease) after the initial dose or a single dose of zoledronic acid for injection. Increases in serum creatinine may occur in some patients with chronic administration of zoledronic acid for injection at recommended doses. Patients 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 for Injection outweighs the possible risk (see also **DOSAGE AND ADMINISTRATION**).

In clinical trials and from post-marketing surveillance, serious cases of acquired Fanconi syndrome have been reported in patients treated with zoledronic acid for injection. If acquired Fanconi syndrome is detected (hyperaminoaciduria, glucosuria in the presence of normal serum glucose, phosphate wasting, among other clinical features), treatment with Zoledronic Acid for Injection should be discontinued and appropriate treatment should be instated.

Zoledronic Acid for Injection should be used with extreme caution in conjunction with other antineoplastic agents that are either known to produce renal impairment (it is advised that renal function be monitored); **or where the dose depends upon renal function (for example platinum- containing agents).**

Respiratory

Patients with Asthma

While not observed in clinical trials with zoledronic acid for injection, administration of other bisphosphonates has been associated with bronchoconstriction in acetylsalicylic acid (ASA)-sensitive asthmatic patients. Zoledronic Acid for Injection should be used with caution in patients with aspirin-sensitive asthma.

Special Populations

Renal Impairment: Zoledronic acid for injection is excreted exclusively via the kidney and the risk of adverse reactions may be greater in patients with impaired renal function. **The use of Zoledronic Acid for Injection is not recommended in patients with severe renal impairment** due to the potential impact of bisphosphonates, including zoledronic acid for injection, on renal function and the lack of extensive clinical safety data in these patients. Patients with severe renal impairment were excluded from clinical trials (defined as serum creatinine > 400 μmol/L or > 4.5 mg/dL in patients with tumour-induced hypercalcaemia and serum creatinine > 265 μmol/L or > 3.0 mg/dL in patients with bone metastases of solid tumours and osteolytic lesions of multiple myeloma) and from limited pharmacokinetic studies (defined as creatinine clearance [CrCl] < 30 mL/min) with zoledronic acid for injection.

Close monitoring of renal function is necessary in patients who are receiving concomitant drugs with nephrotoxic potential.

Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic Acid for Injection.

Upon initiation of treatment in patients with bone metastases of solid tumours and osteolytic lesions of multiple myeloma, with mild-to-moderate renal impairment, lower doses of Zoledronic Acid for Injection are recommended. In patients who show evidence of renal deterioration during treatment, appropriate evaluation should be carried out and consideration should be given

as to whether the potential benefit outweighs the possible risk. If Zoledronic Acid for Injection treatment is to be continued in these patients, Zoledronic Acid for Injection should only be resumed when serum creatinine returns to within 10% of baseline (see **DOSAGE AND ADMINISTRATION).**

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 foetus while receiving Zoledronic Acid for Injection. There may be a risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant while receiving Zoledronic Acid for Injection (see **CONTRAINDICATIONS**). The impact of variables such as time between cessation of zoledronic acid for injection therapy to conception on this risk has not been established.

Pregnant Women: Zoledronic Acid for Injection is contraindicated during pregnancy (see **CONTRAINDICATIONS**). There is no clinical evidence to support the use of zoledronic acid for injection in pregnant women, and animal studies suggest zoledronic acid for injection may cause foetal harm when administered to a pregnant woman.

In animal reproduction studies, zoledronic acid was administered subcutaneously to rats and rabbits. Teratogenicity manifested by external, visceral and skeletal malformations was observed in the rat at doses ≥ 0.2 mg/kg (2.4 fold the systemic human exposure at 4 mg based on AUC comparison). There was also evidence of maternal toxicity at ≥ 0.2 mg/kg as well as foetal toxicity at 0.4 mg/kg (2.4 and 4.8 fold the human exposure, respectively). In the rabbit, maternal toxicity was marked at ≥ 0.1 mg/kg due to decreased serum calcium. Zoledronic acid readily crosses the placental barrier and is taken up into the developing foetal skeleton. The potential risk in humans is unknown (see also **DETAILED PHARMACOLOGY, Reproductive Toxicity Studies**).

Nursing Women: Zoledronic Acid for Injection is contraindicated in breast-feeding women (see **CONTRAINDICATIONS**). There is no clinical experience with zoledronic acid for injection in lactating women and it is not known whether zoledronic acid for injection passes into breast milk. A study in lactating rats has shown that another bisphosphonate AREDIA® (pamidronate) passes into the milk. Mothers treated with Zoledronic Acid for Injection should therefore not breast feed their infants.

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 foetuses. There are no data available in humans.

Paediatrics (< 18 years of age): The safety and efficacy of zoledronic acid for injection in paediatric patients have not been established. No toxicology studies have been conducted in juvenile animals. The most frequent finding in growing animals during repeat-dose studies consisted of increased primary spongiosa (non-proliferative hyperostosis) in the metaphysis of long bones. Zoledronic Acid for Injection is not recommended for use in paediatric patients.

Paediatric Osteogenesis Imperfecta (OI)
In a one-year, active-controlled trial which compared zoledronic acid for injection and pamidronate in osteogenesis imperfecta (OI), zoledronic acid for injection was studied in 74 children aged 1 year to 17 years. Of the patients with type I OI, fracture adverse events of long bones in the lower extremities were reported in approximately 26% (femur) and 11% (tibia) of patients treated with zoledronic acid vs. 0% and 3%, respectively, of patients treated with pamidronate.

Geriatrics (> 65 years of age): Controlled clinical studies of zoledronic acid for injection in TIH do not provide a sufficient number of geriatric subjects to determine whether patients 65 years and older respond differently. The median age in the two controlled clinical trials in patients with tumour-induced hypercalcaemia was 61 years old (range: 21-87 years old).

Controlled clinical studies of zoledronic acid for injection in the treatment of bone metastases of solid tumours and osteolytic lesions of multiple myeloma in patients over age 65 revealed similar efficacy and safety compared to younger patients. The proportion of patients experiencing SREs is lower in the zoledronic acid for injection treatment group when compared to placebo and similar to AREDIA (pamidronate) 90 mg. Older patients generally had adverse events similar to those of the overall population. However, because of the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in elderly patients, Zoledronic Acid for Injection should be administered with caution in this patient population.

Race: Japanese female subjects had substantially higher systemic exposure, i.e., 47% higher AUC0-24h and 39% higher Cmax than the North American population (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions, Race**).

Monitoring and Laboratory Tests

Serum electrolytes, creatinine, phosphate, magnesium and calcium, and CBC with differential must be closely monitored in all patients treated with zoledronic acid for injection. Renal function should be assessed prior to the administration of each dose and should be monitored appropriately during therapy with of Zoledronic Acid for Injection (see **WARNINGS AND PRECAUTIONS, Renal**). Serum albumin- corrected calcium should be measured prior to each dose and should be monitored during therapy with Zoledronic Acid for Injection (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, General, Hypocalcaemia**).

Patients with anaemia, leukopenia or thrombocytopenia should have regular haematology assessments.

In tumour-induced hypercalcaemia, either ionized calcium or total serum calcium corrected (adjusted) for albumin should be monitored during treatment with Zoledronic Acid for Injection. Serum calcium levels in patients who have hypercalcaemia of malignancy may not reflect the severity of hypercalcaemia, since hypoalbuminaemia is commonly present. Corrected serum calcium values should be calculated using established algorithms, such as: Albumin-corrected serum calcium (CSC, mmol/L) = tCa + 0.02 (mid-range albumin-measured albumin).

Prior to treatment with Zoledronic Acid for Injection, an oral examination of both hard and soft tissues, with appropriate preventive dentistry is recommended. These careful oral examinations are recommended to be continued at regularly scheduled intervals after Zoledronic Acid for

Injection therapy is initiated and during treatment with Zoledronic Acid for Injection (see **WARNINGS AND PRECAUTIONS, Musculoskeletal, Osteonecrosis, Osteonecrosis of the Jaw**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most serious adverse drug reactions reported in patients receiving zoledronic acid for injection are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function deterioration, acute phase reaction, and hypocalcaemia.

Adverse reactions to zoledronic acid for injection are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with fever. Within three days after zoledronic acid for injection administration, an acute phase reaction has been reported commonly, with symptoms including pyrexia, fatigue, bone pain and/or arthralgias, myalgias, chills, influenza-like illness, arthritis and joint swelling; these symptoms usually resolve within a few days.

Gastrointestinal reactions such as nausea and vomiting have been reported commonly following intravenous infusion of zoledronic acid for injection. Local reactions at the infusion site, such as redness or swelling and/or pain, were observed infrequently.

Rash or pruritis and chest pain have been reported uncommonly following treatment with zoledronic acid for injection.

As with other bisphosphonates, isolated cases of hypomagnesaemia have been reported. Isolated cases of episcleritis have been reported, uveitis has been reported rarely, blurred vision has been reported uncommonly and cases of conjunctivitis have been reported commonly.

Cardiac arrhythmias associated with hypocalcaemia have been reported rarely following treatment with zoledronic acid for injection. Atrial fibrillation not associated with hypocalcaemia has been reported following treatment with zoledronic acid.

Cases of interstitial lung disease have been reported rarely following treatment with zoledronic acid for injection.

Clinical Trial Adverse Drug Reactions

Tumour-Induced Hypercalcaemia Clinical Trials

Patients with tumour-induced hypercalcaemia may have numerous confounding medical conditions that make causality of adverse events difficult to assess due to the prevalence and wide variety of symptoms related to the underlying disease, its progression and the side effects of cytotoxic chemotherapy.

In patients treated with zoledronic acid for injection, serum calcium may fall to asymptomatic hypocalcaemic levels. This frequently leads to a reduction in renal calcium excretion which is accompanied by a fall in serum phosphate levels that does not require treatment.

Grade 3 [Common Toxicity Criteria (CTC)] serum creatinine was reported in 2.3% and 3.0% of patients receiving zoledronic acid for injection 4mg and AREDIA (pamidronate) 90 mg, respectively, in the clinical trials in tumour-induced hypercalcaemia. Grade 4 (CTC) serum creatinine was reported in 0% and 1.0% in patients receiving zoledronic acid for injection 4 mg and AREDIA (pamidronate) 90 mg, respectively.

Table 1 lists the adverse events considered to be treatment-related in the tumour-induced hypercalcaemia trials.

Table 1 Treatment-Related Adverse Events Reported in Tumour-Induced Hypercalcaemia Clinical Trials

	ZOLEDRONIC ACID FOR INJECTION 4 mg % (N= 86)	**AREDIA 90 mg % (N=103)**
Fever	7.0	9.7
Hypocalcaemia	5.8	1.9
Hypophosphataemia	3.5	1.0
Nausea	1.2	1.0
Pruritus	1.2	0
Skeletal pain	1.2	1.0
Hypomagnesaemia	1.2	0
Taste perversion	1.2	0
Thirst	1.2	0
Pancytopenia	1.2	0
Arthralgia	1.2	0
Bradycardia	1.2	0
Confusion	1.2	0
Fatigue	1.2	0
Hallucination	1.2	0
Vomiting	1.2	0
Chest pain	1.2	0

Bone Metastases of Solid Tumours and Osteolytic Lesions of Multiple Myeloma Clinical Trials

The adverse event data pertaining to bone metastases of solid tumours and osteolytic lesions of multiple myeloma are based upon the core and extension phases of the three pivotal controlled trials in this indication (see **DETAILED PHARMACOLOGY** and **CLINICAL STUDIES**). These trials included 2042 safety evaluable patients treated with either zoledronic acid for injection 4 mg, AREDIA 90 mg, or placebo. Of these 2042 patients who entered the core phase of the trials, 969 completed the core phase, 619 entered the safety extension phase, and 347 completed the extension phase. The median duration of exposure to zoledronic acid for injection 4 mg (core plus extension phases) was 10.5 months for patients with prostate cancer, 12.8 months for patients with breast cancer and multiple myeloma, and 4.0 months for patients with lung cancer and other solid tumours. The mean duration of exposure to zoledronic acid for injection 4 mg (core plus extension phases) was 11.8 months for patients with prostate cancer, 13.9 months for patients with breast cancer and multiple myeloma, and 5.7 months for patients

with lung cancer and other solid tumours (see **CLINICAL STUDIES**).

In general, zoledronic acid for injection was well tolerated across all studies for various tumour types in patients with bone metastases and in patients with multiple myeloma. The proportion of patients experiencing Grade 3 and Grade 4 laboratory abnormalities and adverse events were similar in patients treated with zoledronic acid for injection and AREDIA (pamidronate).

Grade 3 [Common Toxicity Criteria (CTC)] serum creatinine was reported in 1.3%, 1.5% and 1.7% of patients receiving zoledronic acid for injection 4 mg, AREDIA 90 mg and placebo, respectively. Grade 4 (CTC) serum creatinine was reported in 0.4%, 0.4% and 0% of patients receiving zoledronic acid for injection 4 mg, AREDIA 90 mg and placebo, respectively.

The most commonly reported (>15%) adverse events occurred with similar frequencies in the zoledronic acid for injection, AREDIA and placebo treatment groups, and most of these events may have been related to the underlying disease state or cancer therapy. Table 2 lists the events which occurred in ≥ 15% of patients regardless of study drug relationship by preferred term and treatment group, in the bone metastases trials.

Table 2 Commonly Reported Events in Three Bone Metastases Clinical Trials

	zoledronic acid for injection 4 mg n (%)	AREDIA 90 mg n (%)	Placebo n (%)
Patients studied			
Total no. of patients studied	1031 (100)	556 (100)	455 (100)
Total no. of patients with an AE	1015 (98.4)	548 (98.6)	445 (97.8)
Adverse events (preferred term)			
Bone pain	55.2%	56.8%	62.4%
Nausea	46.2%	47.8%	37.6%
Fatigue	38.6%	43.2%	28.6%
Anaemia	33.4%	31.5%	28.1%
Vomiting	32.3%	32.9%	26.8%
Pyrexia	31.8%	30.9%	19.6%
Constipation	31.0%	29.1%	38.2%
Dyspnoea NOS	27.4%	27.9%	23.5%
Weakness	24.4%	19.4%	25.1%
Diarrhoea NOS	24.2%	29.1%	18.2%
Myalgia	23.2%	25.7%	16.3%
Anorexia	22.4%	14.6%	23.1%
Cough	21.7%	23.2%	14.3%
Arthralgia	21.0%	23.6%	16.0%
Oedema lower limb	20.9%	22.7%	18.5%
Malignant neoplasm aggravated	19.9%	17.4%	19.6%
Headache NOS	18.5%	26.8%	11.0%
Dizziness (excl. vertigo)	17.5%	16.4%	12.7%
Insomnia NEC	16.1%	20.0%	16.0%
Weight decreased	15.9%	9.0%	13.4%
Back pain	15.1%	19.1%	8.8%
Paresthesia NEC	14.5%	15.3%	7.7%
Depression NEC	14.2%	17.1%	10.8%
Pain in limb	13.9%	15.1%	11.4%

NOS: Not otherwise specified NEC: Not elsewhere classified

The adverse events occurring during the studies were generally of a type and frequency expected in patients with cancer and bone metastases, many of whom were undergoing antineoplastic therapy. Except for pyrexia, the absolute difference in the proportions of patients in the ZOLEDRONIC ACID FOR INJECTION 4 mg group compared with the placebo group for any of the common adverse events did not exceed 10%. Pyrexia, or fever, may occur as part of an acute phase reaction with bisphosphonate administration.

Among less commonly occurring adverse events (<15% of patients in any group), hypocalcaemia was reported in 4.7%, 2.5%, and 0.7% of patients in the zoledronic acid for injection 4 mg, AREDIA and placebo groups, respectively. Hypokalaemia was reported in 9.7%, 9.0%, and 4.8% of patients in the zoledronic acid for injection 4 mg, AREDIA and placebo groups, respectively. Arthritis was reported in 2.42%, 4.32% and 3.08% of patients and joint swelling was reported in 1.55%, 2.88% and 1.32% of patients in the zoledronic acid for injection 4 mg, AREDIA and placebo groups, respectively.

Hypotension

Based on the clinical trial experience, the frequency of non-serious hypotensive events is uncommon (between 0.1% and 1.0%).

Deterioration in Renal Function

In a pooled analysis of the laboratory data from the three registration trials of zoledronic acid for injection for the treatment of multiple myeloma and bone metastases from breast, prostate, lung and other solid tumours, renal deterioration was defined as an increase of 44.2 μmol/L (0.5 mg/dL) for patients with normal baseline creatinine (< 123.76 μmol/L or < 1.4 mg/dL) or an increase of 88.4 μmol/L (1.0 mg/dL) for patients with an abnormal baseline creatinine (≥ 123.76 μmol/L or ≥ 1.4 mg/dL). The following are data on the incidence of renal deterioration in patients receiving zoledronic acid for injection 4 mg over 15 minutes in these trials (see Table 3).

Table 3 Percentage of Patients with Renal Function Deterioration Who Were Randomized Following the 15-Minute Infusion Amendment

Patient Population/Baseline Creatinine				
Multiple Myeloma and Breast Cancer	**zoledronic acid for injection 4 mg**		**AREDIA 90 mg**	
	n/N	(%)	n/N	(%)
Normal	27/246	(11.0%)	23/246	(9.3%)
Abnormal	2/26	(7.7%)	2/22	(9.1%)
Total	29/272	(10.7%)	25/268	(9.3%)
Solid Tumours	**zoledronic acid for injection 4 mg**		**Placebo**	
	n/N	(%)	n/N	(%)
Normal	17/154	(11%)	10/143	(7%)
Abnormal	1/11	(9.1%)	1/20	(5%)
Total	18/165	(10.9%)	11/163	(6.7%)
Prostate Cancer	**zoledronic acid for injection 4 mg**		**Placebo**	
	n/N	(%)	n/N	(%)
Normal	12/82	(14.6%)	8/68	(11.8%)
Abnormal	4/10	(40%)	2/10	(20%)
Total	16/92	(17.4%)	10/78	(12.8%)

The risk of deterioration in renal function appeared to be related to time on study, whether

patients were receiving zoledronic acid for injection (4 mg over 15 minutes), placebo, or AREDIA.

In a pooled analysis of safety data from the three registration trials of zoledronic acid for injection for the treatment of multiple myeloma and bone metastases from breast, prostate, lung and other solid tumours, the frequency of renal function adverse events (adverse reactions) suspected to be related to zoledronic acid for injection was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%).

The frequency distribution of chemotherapy-associated adverse events by chemotherapy, renal involvement and treatment group for patients in the primary safety population is provided in Table 4. This includes patients who were administered at least one chemotherapeutic agent during the study (i.e., patients treated with only hormonal agents are not included). Each chemotherapeutic agent is classified in one of the three categories: renally excreted, nephrotoxic, or no renal involvement (see Tables 4-1 and 4-2). For a chemotherapy that is both renally excreted and nephrotoxic, the agent is classified as nephrotoxic.

Patients receiving renally excreted drugs that were not nephrotoxic had a similar incidence of nausea for the zoledronic acid for injection and placebo treatment groups when compared to the nephrotoxic agents. Nausea was higher for the AREDIA treatment group for the nephrotoxic agents when compared to the agents that were not nephrotoxic and renally excreted. Vomiting, stomatitis and anorexia were similar for all of the treatment groups whether or not the agent was renally excreted or nephrotoxic. Alopecia was higher in all groups treated with nephrotoxic drugs when compared to renally excreted drugs.

Table 4 Frequency distribution of chemotoxicities (>1%) by renal involvement and treatment group for patients who were treated with at least one chemotherapy agent (Safety evaluable patients)

Renal involvement †	zoledronic acid for injection 4 mg	AREDIA 90 mg	Placebo
Renally excreted			
Number of patients	221	163	76
Total with chemotoxicity	161 (72.9%)	100 (61.3%)	54 (71.1%)
Nausea	113 (51.1%)	68 (41.7%)	37 (48.7%)
Vomiting NOS[1]	75 (33.9%)	48 (29.4%)	23 (30.3%)
Anorexia	55 (24.9%)	23 (14.1%)	28 (36.8%)
Appetite decreased NOS	39 (17.6%)	16 (9.8%)	7 (9.2%)
Stomatitis	25 (11.3%)	21 (12.9%)	6 (7.9%)
Alopecia	24 (10.9%)	18 (11.0%)	9 (11.8%)
Malaise	6 (2.7%)	3 (1.8%)	5 (6.6%)
Cachexia	4 (1.8%)	1 (0.6%)	3 (3.9%)
Gingivitis	3 (1.4%)	3 (1.8%)	0 (0.0%)
Mouth ulceration	3 (1.4%)	2 (1.2%)	0 (0.0%)
Gingival disorder NOS	0 (0.0%)	0 (0.0%)	1 (1.3%)
Malnutrition NOS	0 (0.0%)	2 (1.2%)	0 (0.0%)
Pallor	0 (0.0%)	0 (0.0%)	1 (1.3%)
Nephrotoxic			
Number of patients	471	248	164
Total with chemotoxicity	345 (73.2%)	191 (77.0%)	116 (70.7%)
Nausea	249 (52.9%)	136 (54.8%)	73 (44.5%)
Vomiting NOS	194 (41.2%)	99 (39.9)%	58 (35.4%)
Anorexia	117 (24.8%)	46 (18.5%)	48 (29.3%)
Alopecia	93 (19.7%)	54 (21.8%)	24 (14.6%)
Appetite decreased NOS	63 (13.4%)	23 (9.3%)	17 (10.4%)
Stomatitis	59 (12.5%)	36 (14.5%)	7 (4.3%)
Malaise	18 (3.8%)	10 (4.0%)	8 (4.9%)
Mouth ulceration	13 (2.8%)	5 (2.0%)	1 (0.6%)
Malnutrition NOS	6 (1.3%)	2 (0.8%)	1 (0.6%)
Pallor	6 (1.3%)	2 (0.8%)	2 (1.2%)
Gingivitis	5 (1.1%)	2 (0.8%)	0 (0.0%)
Cachexia	3 (0.6%)	0 (0.0%)	4 (2.4%)
No renal involvement			
Number of patients	0	1	0
Total with chemotoxicity	0 (0%)	1 (100%)	0 (0%)
Nausea	0 (0%)	1 (100%)	0 (0%)

1 NOS: Not otherwise specified.

† Each chemotherapeutic agent is classified in one of the three categories: renally excreted, nephrotoxic, or no renal involvement (See Tables 4-1 and 4-2)

Table 4-1 Listing of chemotherapy agents by renal involvement †

Renal toxic

Preferred term	Preferred term
Adriamycin + Cyclophosphamide	Methotrexate
Adriamycin + Vincristine + MTX	Methotrexate sodium
Aldesleukin	Mitomycin
BCG Vaccine	Oxaliplatin
Carboplatin	Paclitaxel
Cisplatin	Raltitrexed
Cyclophosphamide	Streptozocin
Cyclophosphamide + 5-FU + Methotrexate	Strontium-89
Cyclophosphamide + 5-FU + Prednisolone	Taxol + Carboplatin
Cyclophosphamide + Doxorubicin + 5-FU	Tegafur
Cyclophosphamide + Epirubicin	Tegafur Uracil
Dacarbazine	Teniposide
Etanercept	Thalidomide
Gallium Nitrate	Thiotepa
Gemcitabine	Topotecan Hydrochloride
Gemcitabine Hydrochloride	Trastuzumab
Hydroxycarbamide	Carboplatin + Etoposide
Ifosfamide	CMF + Dexamethasone
Interferon	CMF + Tamoxifen
Interferon Alfa	FAC + Tamoxifen Citrate
Interferon Beta	Topotecan
Interferon Gamma	EVCMF
Interferon NOS[1]	(Epirubicine+Vincri.+Cycloph.+MTX+5FU)
Interleukin-2	
M – VAC	

[1] NOS: Not otherwise specified.

† David S. Fischer, M.Tish Knobf, Henry J. Durivage. The Cancer Chemotherapy Handbook, 5th edition. 1997.

Table 4-2 Listing of chemotherapy agents by renal involvement†

Renally excreted

Preferred term	Preferred term
5-FU + Calcium folinate	Floxuridine
Adriamycin + 5-FU	Flurouracil
Betamethasone	Formestane
Betamethasone Sodium Phosphate	Irinotecan
Bleomycin	Irinitecan Hydrochloride
Bleomycin Sulfate	Lomustine
Busulfan	Melphalan
Capecitabine	Melphalan + Prednisolone
Carmustine	Mitoxantrone
Cytarabine	Mitoxantrone Hydrochloride
Daunorubicin	Tropisetron Hydrochloride
Dexrazoxane Hydrochloride	Vinblastine
Docetaxel	Vinblastine Sulfate
Doxorubicin	Vincristine
Doxorubicin Hydrochloride	Vincristine Sulfate
Epirubicin	Vindesine
Epirubicin Hydrochloride	Vinorelbine

Table 4-2 Listing of chemotherapy agents by renal involvement[†]

Renally excreted	
Preferred term	**Preferred term**
Etoposide	Vinorelbine Bitartrate
Exemestane	Vinorelbine Ditartrate
	Pirarubicin

[†] David S. Fischer, M.Tish Knobf, Henry J. Durivage. The Cancer Chemotherapy Handbook, 5th edition. 1997.

Bone metastases from breast cancer: Placebo-controlled trial in Japanese Patients

In a placebo-controlled clinical study in breast cancer patients with bone metastases, 227 patients were evaluated for safety (114 zoledronic acid for injection and 113 placebo) (see **CLINICAL TRIALS**). Table 5 below illustrates AEs that occurred more frequently in the zoledronic acid for injection arm compared to placebo. The adverse events occurring during the study were generally of a type and frequency expected in patients with cancer and bone metastases, many of whom were undergoing concurrent antineoplastic therapy.

Table 5 Most Commonly Reported AEs (incidence >10 %) occurring more frequently in the zoledronic acid for injection arm compared to Placebo

	Zoledronic acid for injection 4 mg	Placebo (n=113)
	n (%)	n (%)
Pyrexia	63 (55.3)	37 (32.7)
Malaise	51 (44.7)	36 (31.9)
Headache NOS	34 (29.8)	32 (28.3)
Hypoaesthesia	28 (24.6)	22 (19.5)
Arthralgia	24 (21.1)	18 (15.9)
Dyspnoea NOS	21 (18.4)	15 (13.3)
Epigastric pain	19 (16.7)	8 (7.1)
Leukopenia NOS	17 (14.9)	16 (14.2)
Myalgia	15 (13.2)	13 (11.5)
Pruritus NOS	13 (11.4)	12 (10.6)
Oedema lower limb	13 (11.4)	4 (3.5)
Anaemia NOS	12 (10.5)	7 (6.2)
Pain NOS	12 (10.5)	11 (9.7)

Shows no. of subjects experiencing at least 1 AE in category in question

Post-Market Adverse Drug Reactions

Cases of ONJ have been reported in patients treated with zoledronic acid for injection. A large retrospective study of the frequency and risk factors for ONJ in cancer patients receiving intravenous bisphosphonates (Hoff, A. et al., 2008) indicated a higher proportion of reported cases in certain cancers, such as advanced breast cancer (1.2%) and multiple myeloma (2.4%), compared to the overall study population (0.72%). The majority of the reported cases of ONJ were associated with invasive dental procedures (such as tooth extraction, dental surgery, or local trauma including poorly fitting dentures), or periodontal disease. Many patients reporting ONJ also had signs of local infection, including osteomyelitis (see **WARNINGS AND PRECAUTIONS, Musculoskeletal, Osteonecrosis, Osteonecrosis of the Jaw**).

Cases of osteonecrosis of other anatomical sites including the femur, hip, humerus, external auditory canal, tibia, ribs, spine, knee, and metatarsal bones have also been reported in patients treated with zoledronic acid for injection (see **WARNINGS AND PRECAUTIONS, Musculoskeletal, Osteonecrosis, Osteonecrosis of Other Anatomical Sites**).

Cases of anaphylactic reactions/shock, atrial fibrillation, hypotension leading to syncope or circulatory collapse (primarily in patients with underlying risk factors), somnolence, uveitis, episcleritis, scleritis, orbital inflammation, hypersensitivity reactions including cases of severe allergic reactions, bronchospasm, interstitial lung disease (ILD), urticaria, severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures have also been reported. There were reports that had ocular events, bone, joint, and/or muscle pain, and ILD with a bisphosphonate, including zoledronic acid for injection, and had a re-occurrence when re-challenged.

Post marketing events of arthritis and joint swelling, likely occurring as part of an acute phase reaction, have been reported with zoledronic acid for injection administration.

In clinical trials and from post-market surveillance, hypocalcaemia has been reported in patients treated with zoledronic acid for injection. QTc prolongation and neurologic adverse events (including seizures, numbness, and tetany) have been reported secondary to cases of severe hypocalcaemia. In addition, cardiac arrhythmias have been reported with cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia was life-threatening. Time from the first injection of zoledronic acid to the initial hypocalcaemia-related neurologic or cardiac adverse events ranged from 1 day to several months.

Evidence supports a causal relationship between hypocalcaemia and zoledronic acid therapy based on temporal relationship and the secondary QTc prolongation and neurological events as sequelae of the hypocalcaemia.

In clinical trials and from post-market surveillance, serious cases of acquired Fanconi syndrome have been reported in patients treated with zoledronic acid for injection (see **WARNINGS AND PRECAUTIONS, Renal**).

Spontaneously reported adverse drug reactions are presented above. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to zoledronic acid for injection exposure.

DRUG INTERACTIONS

Zoledronic acid is not systemically metabolized and does not affect human cytochrome P450 enzymes *in vitro*. Zoledronic acid is not highly bound to plasma proteins (approximately 55%) and therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Drug-Drug Interactions

Co-administration of thalidomide (100 mg once daily for 14 days and then 200 mg thereafter) with zoledronic acid for injection (4 mg given as a 15-minute infusion) in a phase III study did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance in patients with multiple myeloma.

Caution is indicated when Zoledronic Acid for Injection is used with other potentially nephrotoxic drugs (see also **WARNINGS AND PRECAUTIONS, General, Drug Interactions**).

Caution is advised when Zoledronic Acid for Injection is administered with aminoglycosides, calcitonin, or loop diuretics; since these agents may have an additive effect on the risk of developing hypocalcaemia (see also **WARNINGS AND PRECAUTIONS, General, Drug Interactions**).

A drug interaction with zoledronic acid for injection therapy and the concomitant use of anti-angiogenic drugs has been established in cases of ONJ. Retrospective analyses indicate that the incidence of ONJ is increased in patients treated with bisphosphonates and anti-angiogenic drugs concomitantly.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Renal function should be assessed in all patients prior to the administration of each dose of Zoledronic Acid for Injection. Patients with mild to moderate renal impairment require a reduction in dose (see **DOSAGE AND ADMINISTRATION**, **Recommended Dose and Dosage Adjustment).** Zoledronic Acid for Injection is not recommended in patients with severe renal impairment (see **WARNINGS AND PRECAUTIONS, Serious Warnings and Precautions box, and Special populations, Renal Impairment**).

Serum calcium should be measured prior to each dose of Zoledronic Acid for Injection. Zoledronic acid for injection is contraindicated in patients who have non-corrected hypocalcaemia at the time of infusion (see **CONTRAINDICATIONS**).

Patients must be maintained in a well hydrated state prior to and following administration of Zoledronic Acid for Injection.

Renal Impairment: Zoledronic acid for injection is excreted exclusively via the kidney and the risk of adverse reactions may be greater in patients with impaired renal function.

Zoledronic acid for injection has not been tested in patients with severe renal impairment (defined in clinical trials as serum creatinine > 400 μmol/L or > 4.5 mg/dL in patients with tumour-induced hypercalcaemia and serum creatinine > 265 μmol/L or > 3.0 mg/dL in patients with bone metastases of solid tumours and osteolytic lesions of multiple myeloma (defined in pharmacokinetic studies as baseline creatinine clearance <30 mL/min). Therefore, its use is not recommended in this patient population (see ACTION **AND CLINICAL PHARMACOLOGY, Special Populations and Conditions**).

Hepatic Impairment: As only limited clinical data are available for patients with hepatic impairment, dosage recommendations cannot be given for this group.

Recommended Dose and Dosage Adjustment

Tumour-Induced Hypercalcaemia
The recommended dose of Zoledronic Acid for Injection in hypercalcaemia (albumin-corrected serum calcium ≥ 3.0 mmol/L (12 mg/dL)) is 4 mg given as a single dose intravenous infusion

over no less than 15 minutes following standard rehydration procedures.

Albumin-corrected serum calcium (CSC, mmol/L) = tCa + 0.02 (mid-range albumin-measured albumin).

Prior to treatment with Zoledronic Acid for Injection, renal excretion of excess calcium should be promoted by restoring and maintaining adequate fluid balance and urine output.

Patients who initially show complete or partial response may be retreated with Zoledronic Acid for Injection 4 mg if serum calcium does not return to normal or does not remain normal after initial treatment, although retreatment with zoledronic acid for injection 4 mg in TIH patients has not been assessed for efficacy and safety in prospective studies. It is recommended that at least one week must elapse before retreatment to allow for a full response to the initial dose. In addition, retreatment should be given to **only** those patients who can tolerate the standard rehydration procedures (i.e., 3 to 5 litres of fluids per day and more than 400 meq of sodium chloride per day). In any patient requiring repeated administration, serum BUN and creatinine must be evaluated and possible deterioration in renal function must be assessed prior to each re-administration (see **WARNINGS AND PRECAUTIONS**).

Dosage Adjustment: Mild to Moderate Renal Impairment

Dose reduction in patients with tumour-induced hypercalcaemia with mild to moderate renal impairment is not recommended.

Bone Metastases of Solid Tumours and Osteolytic Lesions of Multiple Myeloma

The recommended dose of Zoledronic Acid for Injection in patients with documented metastatic bone lesions from solid tumours and patients with osteolytic lesions of multiple myeloma for patients with CrCl > 60 mL/min is 4 mg, given as a single dose intravenous infusion over no less than 15 minutes every 3 to 4 weeks. In patients requiring antineoplastic therapy, Zoledronic Acid for Injection should be administered either prior to or after this treatment. Patients will be required to take an oral calcium supplement of 500 mg and a multivitamin containing at least 400 IU of Vitamin D daily. If a patient has a prior history of hypercalcaemia or develops hypercalcaemia during treatment with calcium and Vitamin D supplementation, the patient is advised to discontinue taking calcium and Vitamin D.

Zoledronic acid for injection has been used with cyclophosphamide, doxorubicin, paclitaxel, anastrozole, melphalan and tamoxifen. It has been given less frequently with docetaxel, dexamethasone, prednisone, carboplatin, letrozole, vinorelbine, cisplatin and gemcitabine.

Dosage Adjustment: Mild to Moderate Renal Impairment

Zoledronic acid for injection has been used in patients with bone metastases of solid tumours and osteolytic lesions of multiple myeloma with mild to moderate renal impairment in clinical trials; their risk of renal deterioration was increased compared to that of patients with normal renal function. Therefore, if Zoledronic Acid for Injection is to be administered to patients with mild to moderate renal impairment (defined as baseline CrCl 30 mL/min to 60 mL/min), doses should be reduced. The following dosing recommendations are based on data from pharmacokinetic studies; however, the efficacy and safety of adjusted dosing has not been prospectively assessed in clinical trials.

Upon treatment initiation, the recommended Zoledronic Acid for Injection doses for patients with reduced renal function (mild and moderate renal impairment) are listed in the following table. These doses are calculated based on pharmacokinetic data in order to achieve the same AUC as that achieved in patients with CrCl of 75 mL/min (see **ACTION AND CLINICAL PHARMACOLOGY, Special Populations and Conditions and Renal Impairment**). Creatinine clearance is calculated using the Cockcroft-Gault formula‡:

$$^{‡}\text{CrCl (mL/min)} = \frac{1.2\,[140\text{-age (years)}] \times [\text{total body weight (kg)}]\ \{\text{multiply by 0.85 for females}\}}{\text{serum creatinine (μmol/L)}}$$

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

‡ Doses calculated assuming target AUC of 0.66 (mg·hr/L) (CrCl = 75 mL/min)

During treatment, serum creatinine should be measured before each Zoledronic Acid for Injection dose and treatment should be withheld if renal function has deteriorated. In the clinical studies, renal deterioration was defined as follows:

- For patients with normal baseline creatinine (< 123 μmol/L or < 1.4 mg/dL), an increase of 44 μmol/L or 0.5 mg/dL
- For patients with abnormal baseline creatinine (> 123 μmol/L or >1.4 mg/dL), an increase of 88 μmol/L or 1.0 mg/dL

In the clinical studies, zoledronic acid for injection treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic Acid for Injection should be re-initiated at the same dose as that prior to treatment interruption.

Renal function should be monitored appropriately during therapy with Zoledronic Acid for Injection. Patients with evidence of renal function deterioration should be appropriately evaluated and consideration should be given as to whether the potential benefit outweighs the possible risk.

Administration

Reconstitution

Method of Preparation

Zoledronic acid for injection Concentrate

Vials of Zoledronic Acid for Injection concentrate contain overfill allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid for injection). The content of the vials is withdrawn using a sterile syringe. This concentrate should immediately be diluted in 100 mL of sterile 0.9% w/v Sodium Chloride Injection, USP, or 5% w/v Dextrose Injection, USP. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection. Any unused portion of Zoledronic Acid for Injection concentrate should be discarded.

Reduced Doses for Patients with Baseline CrCl ≤ 60 mL/min: Withdraw an appropriate volume of the 5 mL - Zoledronic Acid for Injection concentrate as needed:

- 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 concentrate must be diluted in 100 mL of sterile 0.9% w/v Sodium Chloride Injection, USP, or 5% w/v Dextrose Injection, USP. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Incompatibilities

Zoledronic Acid for Injection must not be mixed or come into contact 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 over no less than 15 minutes.**

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene, and polypropylene (pre-filled with 0.9 % w/v sodium chloride solution or 5 % w/v glucose solution), showed no incompatibility with zoledronic acid for injection.

Stability of Diluted Zoledronic Acid for Injection Solutions

After aseptic reconstitution and dilution, it is preferable to use the product immediately. If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be stored at 2°C - 8°C. If refrigerated, the solution should be equilibrated to room temperature prior to administration. The total time between dilution, storage at 2°C - 8°C, and end of administration must not exceed 24 hours.

Strict adherence to the intravenous route is recommended for the parenteral administration of Zoledronic Acid for Injection.

***Note*: Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

Store zoledronic acid for injection concentrate at room temperature (15°C - 30°C).

OVERDOSAGE

Clinical experience of acute overdose with zoledronic acid for injection is limited. There have been two patients who received maladministration of 32 mg of zoledronic acid for injection given over 5 minutes. Neither patient experienced any clinical nor laboratory toxicity. Clinically relevant hypocalcaemia should be corrected by intravenous administration of calcium gluconate.

In an open label study of zoledronic acid for injection 4 mg in breast cancer patients, a female patient received a single 48 mg dose of zoledronic acid in error. Two days after the overdose the patient experienced a single episode of hyperthermia (38°C), which resolved after treatment. All other evaluations were normal and the patient was discharged seven days after the overdose.

A patient with Non-Hodgkin's Lymphoma received zoledronic acid for injection 4 mg daily on four successive days for a total dose of 16 mg. The patient developed paraesthesia and abnormal liver function tests with increased GGT (nearly 100 U/L, exact value unknown). The outcome of this case is not known.

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.

For management of a suspected drug overdose, contact your regional poison centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

The principal pharmacologic action of zoledronic acid for injection is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. Zoledronic acid accumulates in bone, where it blocks the resorption of mineralized bone and cartilage. *In vitro*, zoledronic acid has a very large ratio between the desired inhibition of bone resorption and the adverse effects on bone mineralization. *In vitro*, zoledronic acid inhibits osteoclastic activity and induces apoptosis in osteoclasts, as well as reducing the formation and recruitment of osteoclasts into bone. Zoledronic acid inhibits the osteoclastic hyperactivity and accelerated bone resorption induced by various stimulatory factors released by tumours. In long-term animal studies, doses of zoledronic acid similar to those recommended for the treatment of hypercalcaemia inhibit bone resorption without adversely affecting the formation, mineralization, or mechanical properties of bone.

In addition to inhibiting osteoclastic bone resorption, zoledronic acid exerts direct anti-tumour effects on cultured human myeloma and breast cancer cells, inhibiting their proliferation and inducing apoptosis. Zoledronic acid also inhibits the proliferation of human endothelial cells *in vitro* and is anti-angiogenic in animal tumour models. *In vitro*, zoledronic acid reduces the invasion of human breast cancer cells into the extracellular matrix.

Preclinical data suggest that low micromolar concentrations of zoledronic acid are cytostatic and pro-apoptotic *in vitro* to a range of human cancer cell lines (breast, prostate, lung, bladder, myeloma). This anti-tumour efficacy may be enhanced when used in combination with other anti-cancer drugs. Preclinical data suggest that zoledronic acid is also anti-proliferative for human foetal osteoblasts and promotes their differentiation, a property that may be potentially relevant for the treatment of bone metastases in prostate cancer. Zoledronic acid has been shown to inhibit the proliferation of human endothelial cells *in vitro* and is anti-angiogenic *in vivo*. Zoledronic acid at picomolar concentrations has been shown to inhibit tumour cell invasion through extracellular matrix in preclinical cancer models.

Pharmacodynamics

Clinical studies in TIH demonstrated that the effect of zoledronic acid for injection is characterized by decreases in serum calcium and urinary calcium excretion. Normalization of serum calcium by day 4 was greater for the zoledronic acid for injection 4 mg and 8 mg doses (45% and 56%, respectively) compared with AREDIA (pamidronate) 90 mg (33%).

Tumour-Induced Hypercalcaemia

Osteoclastic hyperactivity resulting in excessive bone resorption is the underlying pathophysiologic derangement in tumour-induced hypercalcaemia (TIH, hypercalcaemia of malignancy) and metastatic bone disease. Excessive release of calcium into the blood as bone is resorbed results in polyuria and gastrointestinal disturbances, with progressive dehydration and decreasing glomerular filtration rate. This results in increased renal resorption of calcium, setting up a cycle of worsening systemic hypercalcaemia. Correction of excessive bone resorption and adequate fluid administration to correct volume deficits are, therefore, essential to the management of hypercalcaemia.

Most cases of hypercalcaemia associated with malignancy occur in patients who have breast cancer, squamous-cell tumours of the lung or head and neck, renal cell carcinoma, and certain haematologic malignancies, such as multiple myeloma and some types of lymphomas. A few less common malignancies, including vasoactive intestinal-peptide-producing tumours and cholangiocarcinoma, have a high incidence of hypercalcaemia as a metabolic complication. Patients who have tumour-induced hypercalcaemia can generally be divided into two groups according to the pathophysiologic mechanism involved.

In humoral hypercalcaemia, osteoclasts are activated and bone resorption is stimulated by factors such as parathyroid-hormone-related protein, which are elaborated by the tumour and circulate systemically. Humoral hypercalcaemia usually occurs in squamous-cell malignancies of the lung or head and neck or in genitourinary tumours such as renal cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

Extensive invasion of bone by tumour cells can also result in hypercalcaemia due to local tumour products that stimulate bone resorption by osteoclasts. Tumours commonly associated with locally mediated hypercalcaemia include breast cancer and multiple myeloma.

Total serum calcium levels in patients who have tumour-induced hypercalcaemia may not reflect the severity of hypercalcaemia, since concomitant hypoalbuminaemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcaemic conditions; however, these are not commonly or rapidly available in many clinical situations. Therefore, adjustment of the total serum calcium value for differences in albumin levels is often used in place of measurement of ionized calcium; several nomograms are in use for this type of calculation (see **DOSAGE AND ADMINISTRATION**).

Bone Metastases of Solid Tumours and Osteolytic Lesions of Multiple Myeloma

Osteolytic bone lesions and metastases commonly occur in patients with multiple myeloma, breast cancer, non-small cell lung cancer, renal cell carcinoma and a variety of other solid tumours. Bone lesions associated with bone metastases from prostate carcinoma classically are osteoblastic in contrast to those from other carcinomas, which are usually osteolytic or mixed osteolytic/osteoblastic. Adenocarcinoma of the prostate spreads most commonly to the well vascularized areas of the skeleton such as the vertebral column, ribs, skull, and the proximal ends of the long bones. Prostate carcinoma cells have long been believed to gain access to the vertebral column and ribs via the Batson venous plexus, which is a low pressure, high volume plexus of vertebral veins that join the intercostal veins.

These bone changes in patients with evidence of osteolytic and osteoblastic skeletal destruction may cause severe bone pain that requires either radiation therapy or narcotic analgesics (or both) for symptomatic relief. These changes also cause pathologic fractures of bone in both the axial and appendicular skeleton. Axial skeletal fractures of the vertebral bodies may lead to spinal cord compression or vertebral body collapse with significant neurologic complications. Patients may also experience episode(s) of hypercalcaemia.

Pharmacokinetics

Summary: Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid for injection were given to 64 cancer patients with bone metastases. The post infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} after 24 hours post infusion with population half-lives of $t_{½\alpha}$ 0.24 hours and $t_{½\beta}$ 1.87 hours for the early disposition phases of the drug, followed by a prolonged period of very low concentrations in plasma between days 2 and 28 post infusion, with a terminal elimination half-life $t_{½\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was linearly related to dose. The accumulation of zoledronic acid following a 28-day dosing schedule over 3 cycles was low, with mean AUC_{0-24h} ratios cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

Distribution: *In vitro* and *ex vivo* studies showed low affinity of zoledronic acid 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 was low (with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of zoledronic acid).

Biotransformation/Metabolism: Zoledronic acid does not inhibit human P-450 enzymes *in vitro.* Zoledronic acid does not experience biotransformation.

Excretion: In animal studies <3% of the administered intravenous dose was found in the faeces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a cancer patient with bone metastases, the radioactivity excreted in the urine consisted solely of intact drug.

In 64 cancer patients with bone metastases on average (± s.d.) 39 ± 16% of the administered dose was recovered in the urine within 24 hours, with only trace amounts of drug found in urine post day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone tissue, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations days 2 to 28 post dose. The 0–24 h renal clearance of zoledronic acid was on average (±s.d.) 3.7 ± 2.0 L/h.

Linearity/Non-linearity: Zoledronic acid clearance was reasonably independent of dose and demographic variables, with effects of body weight, gender and race on clearance being within the bounds of the inter-patient variability of clearance, which was 36%.

Increasing the infusion time from 5 minutes to 15 minutes caused a 30% decrease in the zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

Special Populations and Conditions

There are no pharmacokinetic data in patients with hypercalcaemia.

Paediatrics: There are no pharmacokinetic data in paediatric patients (see **WARNINGS AND PRECAUTIONS**).

Geriatrics: The pharmacokinetics of zoledronic acid for injection were not affected by age in cancer patients with bone metastases aged 38 years to 84 years.

Race: The pharmacokinetics of 2 mg, 4 mg and 8 mg zoledronic acid have been evaluated in a Phase I study of Japanese patients with cancer and bone metastasis.

Japanese female subjects had substantially higher systemic exposure, i.e., 47% higher AUC_{0-24h} and 39% higher C_{max} than the North American population (see the Table below) following a single dose intravenous of zoledronic acid for injection (4 mg over 15 minutes). The exposure of Japanese males were comparable to that of the North American population based on the limited data (n=4 and 1 for AUC and C_{max}, respectively).

Comparative PK between Japanese and North American Population (mean ± SD)

	Japan		North America	
	Female (n=14)	Male (n=4 or 1)	Female (n=16)	Male (n=29)
AUC_{0-24h}, ng-h/mL	154 ± 38	118 ± 40	114 ± 22	100 ± 32
C_{max}, ng-h/mL	111 ± 22	64	87 ± 20	77 ± 28

Hepatic Impairment: There are no pharmacokinetic data in patients with impaired liver function. Zoledronic acid for injection is not cleared by the liver; therefore impaired liver function may not affect the pharmacokinetics of zoledronic acid for injection.

Renal Impairment: Limited pharmacokinetic data are available for zoledronic acid for injection in patients with severe renal impairment (CrCl <30 mL/min). The pharmacokinetic studies were conducted in cancer patients (n=64) typical of the target clinical population, showing renal function mainly in the range of normal to moderately impaired [mean (± s.d.) CrCl 84 ± 29 mL/min, range 22 - 143 mL/min]. In these 64 patients the renal clearance of zoledronic acid was found to closely correlate with CrCl, representing in the mean (± s.d.) 75 ± 33% of the CrCl. Creatinine clearance is calculated by the Cockcroft-Gault formula† (see **DOSAGE AND ADMINISTRATION**):

$$^{\dagger}\text{CrCl (mL/min)} = \frac{1.2\ [140\text{-age (years)}] \times [\text{total body weight (kg)}]\ \{\text{multiply by } 0.85 \text{ for females}\}}{\text{serum creatinine } (\mu\text{mol/L})}$$

Patients with mild renal impairment (CrCL 50 - 80 mL/min) showed increases in plasma AUC of 26% to 36%, whereas patients with moderate renal impairment (CrCl 30 - 50 mL/min) showed increases in plasma AUC of 27 - 41%, compared to patients with normal renal function (CrCl > 80 mL/min). However, there were no further increases in the systemic exposure after multiple doses in patients with impaired renal function (see **WARNINGS AND PRECAUTIONS**).

The population-derived relationship of zoledronic acid for injection clearance with CrCl offers an algorithm for dose reduction in renal impairment. zoledronic acid for injection systemic clearance (CL) in individual patients can be calculated from the population clearance of zoledronic acid for injection and that individual's CrCl, as CL (L/h) = 6.5 x $(CrCl/90)^{0.4}$. This formula can be used to predict zoledronic acid for injection AUC in patients, where $CL=Dose/AUC_{0-4}$. The average AUC_{0-24} in patients with normal renal function was 0.42 mg•h/L and the calculated $AUC_{0-\infty}$ for a patient with CrCl of 75 mL/min was 0.66 mg•h/L following a 4 mg dose of zoledronic acid for injection.

STORAGE AND STABILITY

Store Zoledronic Acid for Injection concentrate at room temperature (15°C - 30°C).

After aseptic reconstitution and dilution, it is preferable to use the product immediately. If not used immediately after dilution with infusion media, the solution should be stored at 2°C - 8°C. If refrigerated, the solution should be equilibrated to room temperature prior to administration. The total time between dilution, storage at 2°C - 8°C and end of administration must not exceed 24 hours. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used (see **DOSAGE AND ADMINISTRATION, Administration**).

Zoledronic Acid for Injection must be kept out of the reach and sight of children and pets.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Zoledronic Acid for Injection is available as a concentrate in vials. Each vial of Zoledronic Acid for Injection concentrate delivers 4 mg of zoledronic acid corresponding to 4.264 mg zoledronic acid monohydrate. Available in cartons containing 1 vial.

Primary Packaging Material:
Transparent glass vial with dark grey bromobutyl rubber stopper and green aluminium flip-off seal.

Composition

Zoledronic acid for injection Concentrate

Each 5 mL of Zoledronic Acid for Injection concentrate contains 4 mg Zoledronic acid sterile liquid concentrate plus overfill. This corresponds to 4.264 mg of zoledronic acid monohydrate. *Inactive Ingredients*: 220 mg mannitol per vial, USP, as bulking agent, sodium citrate, USP as buffering agent and water for injection.

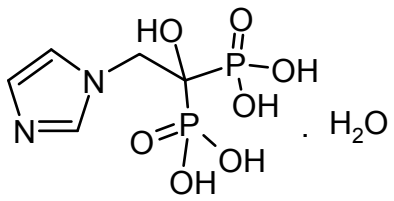
PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Zoledronic acid
Chemical name:	[1-Hydroxy-2-(1H-imidazol-1-yl)-ethylidene]-bisphosphonic acid monohydrate
Molecular formula:	$C_5H_{10}N_2O_7P_2 \cdot H_2O$
Molecular mass:	290.09 g/mol

Structural formula:



Physicochemical properties:

Description:	White to off white powder
Solubility:	Slightly soluble in water; practically insoluble in Ethanol (96%), methanol, dimethyl formamide, ethyl acetate, dimethyl sulphoxide, chloroform and acetone
pH:	About 2.0

CLINICAL TRIALS

Tumor-Induced Hypercalcaemia

Two identical multicenter, randomized, double-blind, double-dummy studies of zoledronic acid for injection 4 mg given as a 5-minute infusion or AREDIA (pamidronate) 90 mg given as a 2-hour infusion were conducted in patients with tumour-induced hypercalcaemia (TIH). **Note: Administration of Zoledronic Acid for Injection 4 mg given as a 5-minute intravenous infusion has been shown to result in an increased risk of renal toxicity, as measured by increases in serum creatinine, which can progress to renal failure. The incidence of renal toxicity and renal failure has been shown to be reduced when zoledronic acid for injection 4 mg is given as a 15-minute intravenous infusion over no less than 15 minutes** (see **WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION**). TIH was defined as corrected serum calcium (CSC) concentration of ≥ 12.0 mg/dL (3.00 mmol/L). The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to ≤ 10.8 mg/dL (2.70 mmol/L) within ten days after drug infusion. Each treatment group was considered efficacious if the lower bound of the 95% confidence interval for the proportion of complete responders was >70%. This was achieved for the zoledronic acid for injection 4 mg group in each study, but not for the AREDIA 90 mg group. To assess the effects of zoledronic acid for injection versus those of AREDIA, the two multicenter TIH studies were combined in a pre-planned analysis. The results showed that zoledronic acid for injection 4 mg was statistically superior to AREDIA 90 mg for the proportion of complete responders at day 7 and day 10. The results also demonstrated a faster normalization of CSC by day 7 for zoledronic acid for injection 4 mg.

The following response rates were observed (Table 6):

Table 6 Proportion of Complete Responders by Day in pooled TIH studies

	Day 4	**Day 7**	**Day 10**
zoledronic acid for injection 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)	88.4% (p=0.002)
AREDIA 90 mg (N=99)	33.3%	63.6%	69.7%

P-values vs. AREDIA 90mg based on Cochran-Mantel Haenszel adjusting for baseline CSC

Secondary efficacy variables, time to relapse and duration of complete response, were also assessed. Time to relapse was defined as the duration (in days) from study infusion until the last CSC value ≤ 11.6 mg/dL (2.90 mmol/L). Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC ≤ 10.8 mg/dL (2.70 mmol/L). The results showed that zoledronic acid for injection 4 mg had a statistically longer time to relapse than AREDIA.

Table 7 Results for Secondary Efficacy Variables in pooled TIH studies

	Zoledronic Acid For Injection 4 mg			**AREDIA 90 mg**	
	N	Median (days)	P-value	N	Median (days)
Time to relapse	86	30	0	99	17
Duration of complete response	76	32	NA	69	18

P-values vs. AREDIA 90 mg based on Cox regression adjusted for baseline CSC

NA: Duration of complete response was not analyzed in the subset of complete responders

Bone Metastases of Solid Tumours and Osteolytic Lesions of Multiple Myeloma

Three randomized, controlled trials in patients with bone metastases of solid tumours and osteolytic lesions of multiple myeloma were conducted with zoledronic acid for injection. The planned duration of therapy in the core studies were 15 months in the trial in patients with prostate cancer, 13 months in the trial in patients with breast cancer and multiple myeloma, and 9 months in the trial in patients with lung cancer and other solid tumours. In addition, an extension phase was included in each trial in order to primarily determine the safety of long-term exposure to zoledronic acid for injection. Patients who successfully completed the primary core phase of treatment were given the option to extend treatment for a total of 24 months (prostate cancer), 25 months (breast cancer and multiple myeloma), and 21 months (lung and other solid tumours). In the trials with patients with breast cancer and multiple myeloma, and in patients with lung cancer and other solid tumours, only the core phase was reported for efficacy as a high percentage of patients did not choose to participate in the extension phase.

The studies were amended twice because of renal toxicity. The zoledronic acid for injection infusion duration was increased from 5 minutes to 15 minutes. After all patients had been accrued, but while dosing and follow-up continued, patients in the 8-mg zoledronic acid for injection treatment arm were switched to 4 mg. Patients who were randomized to the zoledronic acid for injection 8 mg group are not included in these analyses.

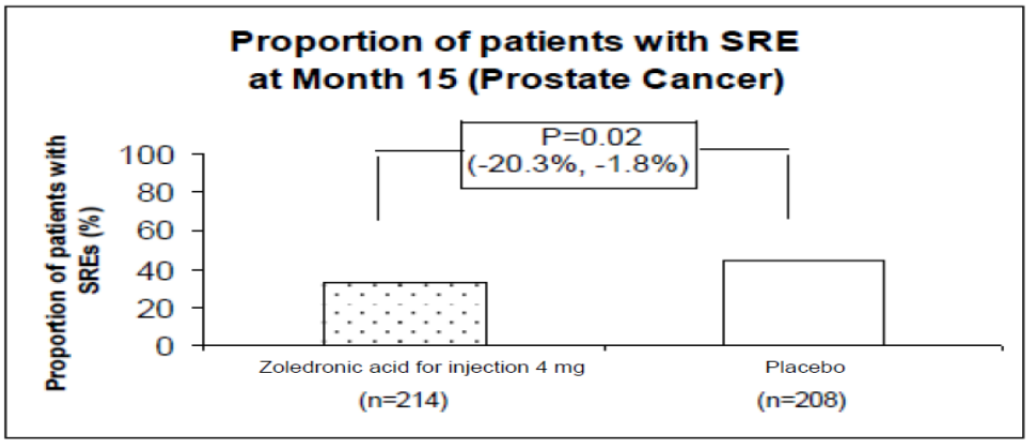
Each study evaluated skeletal-related events (SREs), defined as any of the following: pathologic fracture (vertebral or non-vertebral), radiation therapy to bone (including the use of radioisotopes), surgery to bone or spinal cord compression. A change in antineoplastic therapy due to increased pain was considered as an SRE in the prostate cancer study only. Planned analyses included the proportion of patients with an SRE during the core phase of the study (the primary efficacy endpoint) and main secondary efficacy endpoints including time to the first SRE (i.e. the hazard ratio for the first occurrence of an SRE not taking death into consideration (censoring deaths), and multiple event analysis. Multiple event analysis using the Andersen-Gill approach was performed to evaluate the overall effect of zoledronic acid for injection on the occurrence of skeletal complications. This analysis takes into account all clinically meaningful events experienced by the study patients, and considers the total number of events experienced as well as the time from randomization to each event. However, the assumptions required for this analysis are strong and it is difficult to assess whether the data meet the assumptions. For the multiple event analysis, events that occurred in close proximity were counted as one event.

Radiation therapy to bone and pathological fractures were the most common type of skeletal related events.

Bone Metastases due to Prostate Cancer

In a phase III randomized, double-blind trial, zoledronic acid for injection was compared to placebo for the prevention of Skeletal Related Events (SREs) in prostate cancer patients with bone metastases. A total of 422 patients (214 zoledronic acid for injection 4 mg, 208 placebo) with metastatic bone disease from prostate cancer with a rising serum PSA despite hormonal treatment were randomized to receive either zoledronic acid for injection 4 mg administered over 15 minutes or placebo every 3 weeks. The primary efficacy variable was the proportion of patients having an SRE at 15 months. The proportion of patients experiencing at least one SRE (33% for zoledronic acid for injection 4 mg vs. 44% for placebo, $p = 0.02$) demonstrated statistically significant superiority for zoledronic acid for injection vs. placebo (see Figure 1).

Figure 1



Zoledronic acid for injection was superior to placebo for time to first SRE at 15 months (hazard ratio of 0.67, 95% CI: 0.49, 0.91), median of 321 days for placebo vs. median not reached for zoledronic acid for injection 4 mg. Zoledronic acid for injection demonstrated a statistically significant superiority over placebo for time to fracture (p= 0.01).

In addition, of the 146 (81 zoledronic acid for injection, 65 placebo) patients who completed the core phase of the trial, 132 (74 zoledronic acid for injection, 58 placebo) consented to enter the extension phase and 85 (49 zoledronic acid for injection and 36 placebo) completed it. At 24 months, the zoledronic acid for injection 4 mg group had a significantly lower proportion of patients experiencing at least one SRE (of all patients initially randomized) when compared with placebo (38% for zoledronic acid for injection 4 mg, 49% for placebo, p=0.03). No adjustments to the p-values for the two analysis time points were made. The multiple event analysis indicated that prostate cancer patients receiving zoledronic acid for injection 4 mg had a 36% overall reduction in risk (hazard ratio of 0.64, 95% CI: 0.485, 0.84; p=0.002) for skeletal complications compared to placebo over the course of the trial. See Table 8 for the results of the main secondary efficacy analyses.

Table 8 Results of main secondary efficacy variables (Core + Extension Phase)

	Prostate Cancer Patients All SRE			
	Core Phase		Core + Extension Phase	
	Zoledronic acid for injection 4 mg	Placebo	Zoledronic acid for injection 4 mg	Placebo
N	214	208	214	208
Time to First SRE				
Hazard Ratio (95% CI) vs. placebo	0.67 (0.49, 0.91)		0.68 (0.50, 0.91)	
Median Time to SRE[§] (days)	n.r.[§§]	321	488	321
P-Value[†]	0.01		0.01	
Multiple Event Analysis				
Hazard Ratio (95% CI) vs. placebo	0.64 (0.47, 0.87)		0.64 (0.48, 0.84)	
P-Value[†]	0.004		0.002	

[§] Median Time to first SRE not taking death into consideration (i.e. deaths were censored).

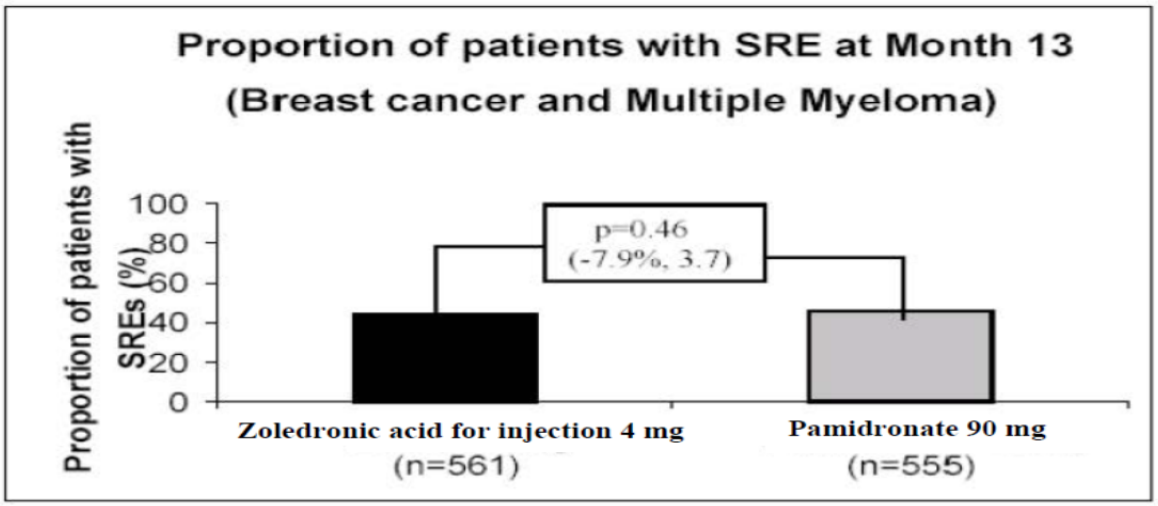
[§§] Not reached.

[†]p-values vs. placebo based on Cox-regression stratified by presence of distant metastases at initial diagnosis or not.

Bone Metastases from Breast Cancer and Osteolytic Lesions of Multiple Myeloma

The second phase III randomized, double-blind trial was designed to demonstrate comparable efficacy of zoledronic acid for injection 4 mg to AREDIA 90 mg. A total of 1116 patients (561 zoledronic acid for injection 4 mg, 555 AREDIA 90 mg) with either Durie-Salmon Stage III multiple myeloma or Stage IV breast cancer with at least one bone lesion were treated with zoledronic acid for injection 4 mg via 15-minute intravenous (IV) infusion or AREDIA 90 mg via 2-hour IV infusion every 3 to 4 weeks. The primary efficacy endpoint was the proportion of patients experiencing at least one skeletal-related event (SRE) at 13 months. The proportion of patients with an SRE was 44% and 46% for zoledronic acid for injection 4 mg and AREDIA 90 mg, respectively (p=0.46) (see Figure 2).

Figure 2



Zoledronic acid for injection was demonstrated to be comparable to AREDIA in efficacy for the endpoint of the proportion of patients with an SRE in a non-inferiority analysis. There were no significant differences between zoledronic acid for injection and AREDIA in time to first SRE.

The multiple event analysis indicated that patients with breast cancer and multiple myeloma receiving zoledronic acid for injection 4 mg in this trial had an 11.5% overall reduction in risk (hazard ratio of 0.88, 95% CI: 0.75, 1.05; p =0.15) for skeletal complications, compared to patients receiving AREDIA 90 mg over the core phase of the trial. See Table 9 for the results of the main secondary efficacy analyses.

Table 9 - Results of main secondary efficacy variables (Core Phase)
Breast Cancer and Multiple Myeloma Patients
All SRE

	Zoledronic acid for injection 4 mg	**AREDIA 90 mg**
N	561	555
Time to First SRE		
Hazard Ratio (95% CI) vs. AREDIA 90 mg	0.91 (0.77, 1.09)	
Median Time to SRE[§] (days)	373	363
P-Value†	0.32	
Multiple Event Analysis		
Hazard Ratio (95% CI) vs. AREDIA 90 mg	0.88 (0.75, 1.05)	
P-Value†	0.15	

[§]Median Time to first SRE not taking death into consideration (i.e. deaths were censored).
†p-value vs. AREDIA 90 mg based on Cox-regression stratified by cancer type.

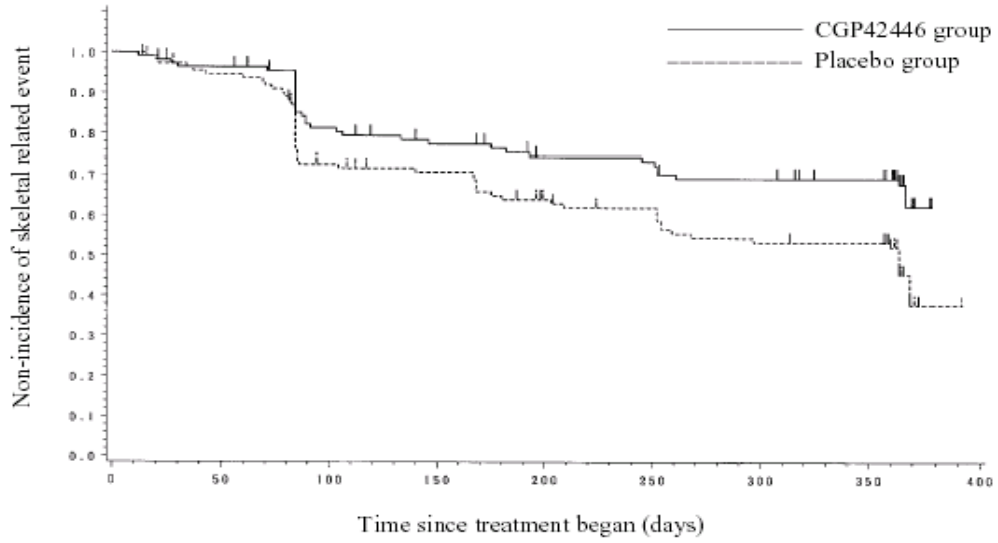
In addition, of the 690 (353 zoledronic acid for injection, 337 AREDIA) patients who completed the core phase of the trial, 417 (212 zoledronic acid for injection, 205 AREDIA) consented to enter the extension phase. Another 111 patients continued with open-label AREDIA which at the time was the standard of care. A total of 246 (123 zoledronic acid for injection, 123 AREDIA) patients completed the extension phase. In the extension phase, only the safety data are reported (see **ADVERSE REACTIONS**).

Bone metastases from breast cancer: Placebo-controlled trial in Japanese Patients

Zoledronic acid for injection was also studied in a double-blind, randomized, placebo-controlled, Phase III trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of zoledronic acid for injection on the skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcaemia and adjusted for prior fracture), divided by the total risk period. Patients received either 4 mg zoledronic acid for injection or placebo every four weeks for one year. Patients were evenly distributed between zoledronic acid for injection -treated and placebo groups.

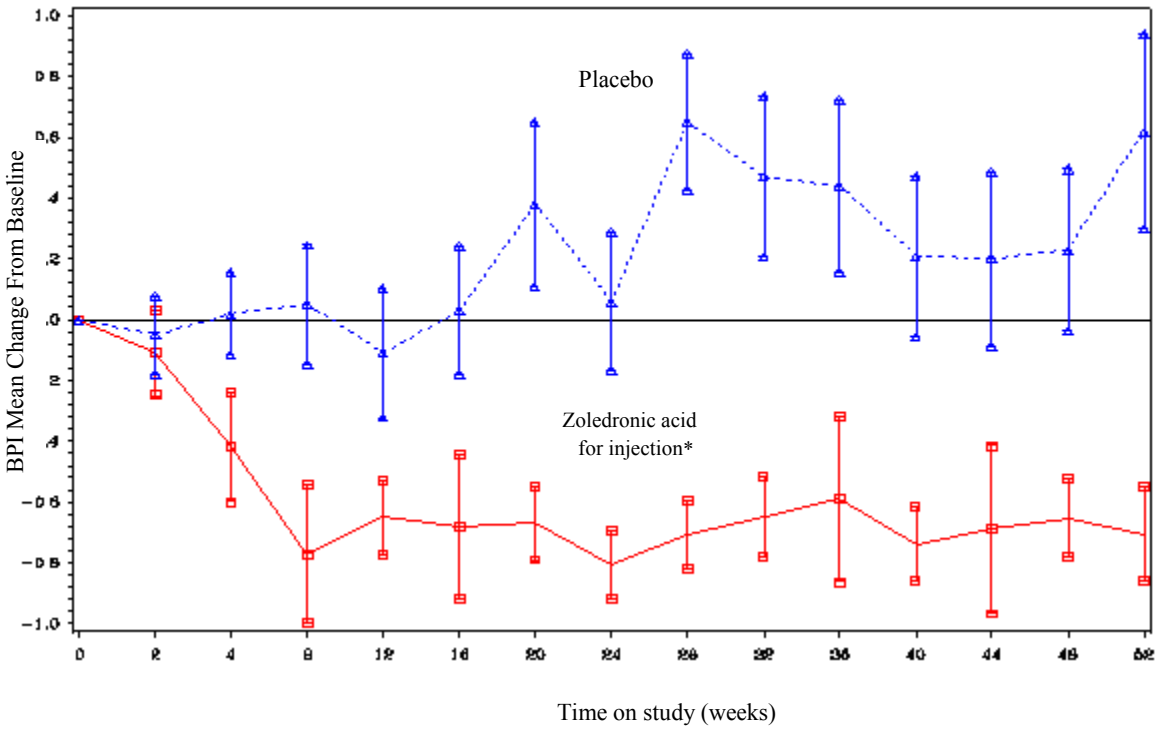
The SRE rate ratio at one year was 0.61, indicating that treatment with zoledronic acid for injection reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the zoledronic acid for injection -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 for injection -treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid for injection reduced the risk of SREs by 41 % in a multiple event analysis (risk ratio= 0.59, p=0.019) compared with placebo.

Figure 3 - Time to onset of the first SRE (–TIH)



In the zoledronic acid for injection -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 4). Zoledronic acid for injection inhibited the worsening of the analgesic score more than placebo. In addition, 71.8% of zoledronic acid for injection-treated patients versus 63.1% of placebo patients showed improvement or no change in the Eastern Cooperative Oncology Group (ECOG) performance score at the final observation.

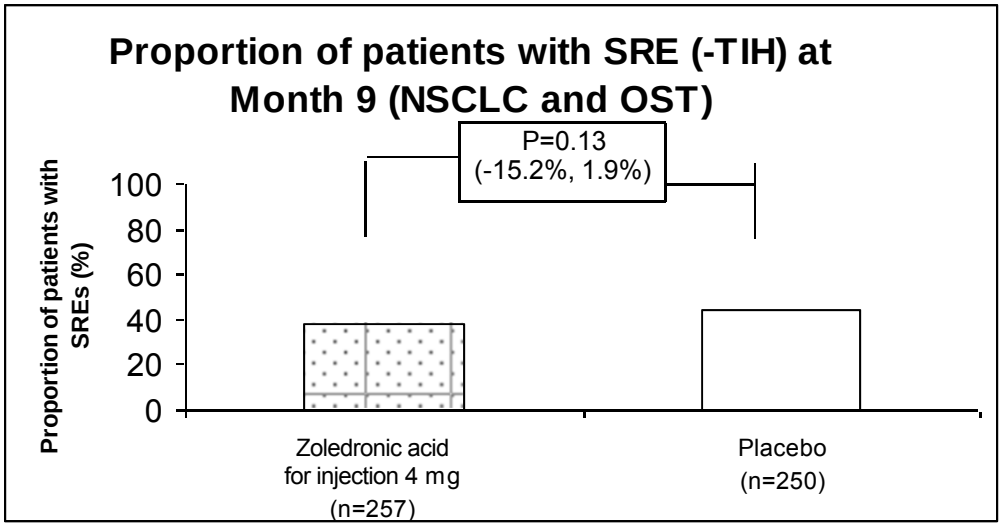
Figure 4 - Mean change from baseline in Brief Pain Inventory (BPI) pain scores by treatment group and time on study.



Bone metastases from solid tumours other than breast cancer or prostate cancer

A third phase III randomized, double-blind, placebo-controlled trial compared zoledronic acid for injection to placebo for the prevention of SREs in patients who had solid tumours other than breast cancer or prostate cancer, with osteolytic or mixed bone metastases. Patients had to have at least 1 lytic metastasis for study entry. A total of 257 patients were randomized to zoledronic acid for injection 4 mg; 134 patients with non-small cell lung cancer (NSCLC) and 123 with other solid tumours (OST). A total of 250 patients were randomized to placebo (130 patients with NSCLC, 120 with OST). Patients received either an intravenous infusion of zoledronic acid for injection 4 mg or placebo every 3 weeks. The primary efficacy variable was the proportion of patients having an SRE at nine months. At nine months, the zoledronic acid for injection 4 mg group had a lower proportion of patients experiencing an SRE when compared with placebo (38% for zoledronic acid for injection 4 mg, 44% for placebo, p=0.13), see Figure 5. The difference for the primary efficacy variable was not statistically significant. However, when tumour-induced hypercalcaemia (TIH) was also included as an SRE, the proportion of patients having an SRE reached statistical significance favouring zoledronic acid for injection 4 mg over placebo (38% for zoledronic acid for injection 4 mg and 47% for placebo, p=0.04).

Figure 5



Study patients had a median overall survival of 6 months. Zoledronic acid for injection extended the median time to an SRE by greater than two months (67 days) [median of 230 days vs. 163 days, p = 0.02; see Table 10].

The multiple event analysis indicated that patients with lung cancer and other solid tumours (other than breast cancer or prostate cancer) receiving zoledronic acid for injection 4 mg had a 27% overall reduction in risk (hazard ratio of 0.73, 95% CI: 0.57, 0.95; p=0.02) for skeletal complications compared to placebo over the core phase of the trial. See Table 9 for the results of the main secondary efficacy analyses.

Table 10 Results of main secondary efficacy variables (Core Phase)

NSCLC and OST Patients
All SRE (-TIH)

	Zoledronic acid for injection 4 mg	**Placebo**
N	257	250
Time to First SRE		
Hazard Ratio (95% CI) vs. placebo	0.73 (0.55, 0.96)	
Median Time to SRE[§] (days)	230	163
P-Value†	0.02	
Multiple Event Analysis		
Hazard ratio (95% CI) vs. placebo	0.73 (0.57, 0.95)	
P-Value†	0.02	

[§]Median Time to first SRE not taking death into consideration (i.e. deaths were censored).
†p-value vs. placebo based on Cox-regression stratified by cancer type.

In addition, of the 131 (68 zoledronic acid for injection, 63 placebo) patients who completed the core phase of the trial, 69 (34 zoledronic acid for injection, 35 placebo) consented to enter the extension phase and 16 (8 zoledronic acid for injection,8 placebo) completed it. In the extension phase, only the safety data are reported (see **ADVERSE REACTIONS**).

DETAILED PHARMACOLOGY

Zoledronic acid for injection belongs to a highly potent class of bisphosphonates which act specifically on bone. It is an inhibitor of osteoclastic bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In a variety of preclinical assays of bone metabolism, zoledronic acid inhibits bone resorption in vitro at concentrations of 0.3-30 nM, and in vivo at doses of 0.3-30 µg/kg without exerting any untoward effects on either bone formation or mineralization.

In addition to inhibiting osteoclastic bone resorption, zoledronic acid for injection exerts direct anti-tumour effects on cultured human myeloma and breast cancer cells, inhibiting proliferation and inducing apoptosis. It also inhibits human endothelial cell proliferation *in vitro* and is anti-angiogenic in animals. Moreover, the observation that zoledronic acid for injection reduces the invasion of human breast cancer cells through extracellular matrix *in vitro* indicates that it may possibly have anti-metastatic properties.

In broad safety screening, no adverse effects were detected on the cardiovascular or central nervous systems at pharmacologically relevant doses for the inhibition of bone resorption.

TOXICOLOGY

Acute Toxicity

Species	Route	Doses (mg/kg)	Findings
Rat	i.v.	0.6, 6, 30, 60, 80	> 6 mg/kg: mortality and clinical signs 6 mg/kg: renal findings LD50 = approximately 13 mg/kg
Rat	i.v.	1.6, 8, 16, 32	> 8 mg/kg: mortality, clinical signs, necropsy findings in kidney, liver, GI tract > 1.6 mg/kg: ↓ BW, FC, injection site irritation max. non lethal dose: 1.6 mg/kg min. lethal dose: 8 mg/kg
Dog	i.v.	2,10	2 mg/kg: no clinical signs 10 mg/kg: mortality
Mouse	s.c.	10,50	10 mg/kg: no clinical signs 50 mg/kg: mortality, clinical signs LD50 = 10-50 mg/kg in males and > 10 mg/kg in females
Rat	p.o.	200, 2000	> 200 mg/kg:↓ FC,BW, clinical signs, necropsy findings in stomach: enlarged, red lesions 2000 mg/kg: 100% mortality

The acute parenteral toxicity of zoledronic acid was moderate to marked in the mouse, rat and dog. The estimated LD_{50} in the mouse (s.c.) and rat (i.v.) was 10-50 mg/kg (males)/>10 mg/kg (females) and 13 mg/kg (males), respectively. Compound-related renal tubular lesions were observed in the rat after one dose at 6 mg/kg. A single intravenous injection in the dog produced clinical signs, intestinal haemorrhage and mortality after 6 days in one male at 10 mg/kg. The other male received 2 mg/kg and survived the 14-day post-dose observation period without clinical signs.

Subacute and Chronic Toxicity

Study Type	Species	Route	Doses (mg/kg)	Findings
Intravenous				
10-Day range-Finding	Rat	i.v.	0.06, 0.6, 6	0.06 mg/kg: well tolerated 0.6 mg/kg: clin. signs; micro in kidneys, liver 6 mg/kg: sacrifice due to severe clin. signs; micro in bone, kidneys, stomach, liver, thymus, spleen, lymph nodes NOAEL: 0.06 mg/kg
2-Week	Rat	i.v.	0.06, 0.6, 3.2 (every third day for 18 days)	≥ 0.06 mg/kg: local irritation, non-proliferative hyperostosis ≥ 0.6 mg/kg: gastric lesions 3.2 mg/kg: mortality, clin signs; ↓BW/FC, clin lab alterations, ↑adrenal, kidney, liver wgts, nephropathy, hepatocellular hypertrophy NOAEL: not established
10-Day range-finding	Dog	i.v.	0.1, 1	≥ 0.1 mg/kg: micro in bone rib, injection sites 1 mg/kg: clin. signs; micro findings in stomach, intestine, liver, lung, thymus NOAEL: 0.1 mg/kg
4-Week + 1 mo. Recovery	Dog	i.v.	0.02, 0.06, 0.2	≥ 0.06 mg/kg: clinical signs 0.2 mg/kg: clin. signs; micro in GI tract NOAEL: 0.02 mg/kg
3-Month + 1 mo. Recovery	Dog	i.v.	0.01,0.03, 0.160.2	≥0.01 mg/kg: genital tract atrophy (F); ↑primary spongiosa in bone; splenic histiocytosis; lung inflammation, thymic atrophy ≥ 0.03 mg/kg: moribund sacrifice at 0.1 → 0.2 mg/kg due to inj. site irritation, ↓ BW/FC,↑ ALAT/ASAT, ↓ bone AP, PO4, creatinine and ↓ RBC indices; inj. site ulceration, kidney lesions, genital tract (M) & pancreatic atrophy, inflammation of urinary bladder, esophagus, stomach and liver. NOAEL: not established
26/52-wk+ 6 mo. Recovery	Dog	i.v.	0.005,0.03, 0.1	All doses: inj site irritation; ↓ phosphate; non-proliferative hyperostosis ≥0.03 mg/kg : micro in kidneys, GI tract; ↑ BUN,↑ total protein. 0.1 mg/kg: ↓ creatinine, ↑ ASAT, ↓Ca. NOAEL: 0.005 mg/kg
Bone analyses (26/52-wk + 6 mo. Recovery)	Dog	i.v.	0.005,0.03, 0.1	All biomechanical parameters assessing bone quality showed either no deleterious effect or an increase in quality at pharmacologically efficacious doses.

Subcutaneous				
10-Day range-finding	Rat	s.c.	0.2,0.6,2	2 mg/kg: clin. signs; microscopic changes in kidneys, liver; spleen, thymus, lymph nodes, lung and adrenals. ≥ 0.6 mg/kg: clin. signs ≥ 0.2 mg/kg: Local irritation at the injection sites
1-Month + 1 mo recovery	Rat	s.c.	0.02,0.06,0.2	0.2 mg/kg: swelling at injection site; clin. signs; micro findings in liver, lymph nodes ≥ 0.06 mg/kg: clin. signs; micro findings of spleen, injection sites, skeletal muscle; NOAEL: 0.02 mg/kg
3-Month + 1 mo recovery	Rat	s.c.	0.01,0.03,0.1	Tolerated without mortality at doses up to and including 0.1 mg/kg. Non-proliferative hyperostosis. NOAEL 0.01 mg/kg in females. No NOAEL in males due to reduced BW/FC at all doses.
6/12-Month + 6 mo recovery	Rat	s.c.	0.001,0.003, 0.01	≥0.001 mg/kg: ↓ bone AP, ↑ reticulocyte count, splenic hemosiderosis and congestion, ↑ splenic hematopoiesis, ↑ cellularity of femoral/tibial marrow, non-proliferative hyperostosis. Following bone morphometry, no deleterious effects after administration for 12 months. ≥0.003 mg/kg: ↓ RBC parameters, ↑ fibrinogen, renal tubular changes, progressive nephropathy. 0.01 mg/kg: testicular tubular atrophy Bone morphometry on bone (tibia) did not reveal deleterious effects NOAEL: 0.001 mg/kg

Oral				
13-week	Mouse	p.o.	0, 0.3, 3, 10, 30→20	0.3 - 30→20 mg/kg: mortality; respiratory signs; ↓FC; non-proliferative hyperostosis 3 - 30→20 mg/kg: ↓BW; laryngeal, tracheal & bronchial inflammation
10-Day range-finding	Rat	p.o.	1,10,100	1 and 10 mg/kg: well-tolerated 100 mg/kg: mortality & moribund sacrifice after 1 wk; clin. signs; gastritis, GI tract necrosis, acute renal tubular lesions, liver changes; lymphoid depletion spleen, thymus.
1-Month + 1 mo recovery	Rat	p.o.	62060	6 mg/kg: well-tolerated ≥20 mg/kg: clin signs; liver, spleen, lymph nodes 60 mg/kg: mortality; GI tract, kidneys, salivary glands, thymus, adrenal, lung, trachea NOAEL: 6 mg/kg
6-Month + 1 mo recovery	Rat	p.o.	0.1,1, 10	≥0.1 mg/kg: bone ≥1 mg/kg: clin signs 10 mg/kg: mortality NOAEL: 0.1 mg/kg
10-Day	Dog	p.o.	1630, 10 (for 9d); 30 (for 10d) [a]	1 → 30 mg/kg: clin. signs; micro findings in kidneys, esophagus, liver; non-proliferative hyperostosis. 10 mg/kg: no significant findings
1-Month	Dog	p.o.	3,10, 30	≥ 3 mg/kg: clin signs ≥ 10 mg/kg: mortality; liver, lung, thymus 30 mg/kg: gingiva, pancreas, adrenals
6-Month + 1 mo. recovery	Dog	p.o.	0.01, 0.1, 1	Well-tolerated at doses of up to 1 mg/kg. Histological bone changes were considered pharmacologic NOAEL: 1 mg/kg

[a] From day 9 of dosing: 30 mg/kg for an additional 10 days

Reproductive Toxicity Studies

Zoledronic acid was evaluated for potential adverse effects on fertility, labour, delivery and lactation of the parental generation rats as well as development, behaviour and fertility of the F1 generation at doses of 0.01, 0.03 and 0.1 mg/kg; however, many females in the treated groups either died or were sacrificed while moribund at parturition due to difficulty in delivery (dystocia) such that the study was terminated on lactation day 7.

Teratology 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 as manifested by external, visceral and skeletal malformations. There were also dose-related increases in the incidence of poor skeletal ossification at ≥ 0.2 mg/kg and evidence of maternal toxicity at ≥ 0.2 mg/kg as well as foetal toxicity at 0.4 mg/kg.

In the rabbit, reduced number of litters with viable foetuses, increased post-implantation loss and total resorption were observed at 0.1 mg/kg. Fatality was shown in dams with decreased serum calcium level at all doses.

Study Type	**Species**	**Route**	**Doses (mg/kg)**	**Findings**
Segment I	Rat	s.c.	0.01, 0.03, 0.1	≥ 0.01: maternal toxicity and severe effects on parturition such that the study was terminated on lactation day 7.
Segment II range-finding	Rat	s.c.	0.2, 0.6, 2	≥ 0.2 mg/kg: irritation at injection site ≥ 0.6 mg/kg: 9 maternal BW. 9/10 dams with total resorption (embryo/foetal death) of progeny; remaining dam w/ only 2 foetuses (one with cleft palate).
Segment II	Rat	s.c.	0.1, 0.2, 0.4	≥ 0.2 mg/kg: ↓ maternal BW; ↓ foetal wgt; anomalies of viscera and/or skeleton w/ wavy ribs & delay in skeletal maturation. 0.4 mg/kg: 9/24 dams with total resorption of foetuses; some foetuses with oedema, cleft palate, short lower jaw, abnormal ossification
Segment II range-finding (pregnant)	Rabbit	s.c.	0.1,0.2,0.4	0.2, 0.4 mg/kg: early termination due to severe clinical signs/toxicity. 0.1 mg/kg: Reduced foetal weight; foetal visceral and skeletal development were not examined.
Segment II	Rabbit	s.c.	0,01, 0.03, 0.1	Maternal toxicity at ≥ 0.01 mg/kg due to ↓ blood calcium. Reduced number of litters with viable foetuses, increased post-implantation loss and total resorption at 0.1 mg/kg. Foetal/embryo development abnormalities cannot be assessed due to an insufficient exposure in the surviving dams.

Carcinogenicity

Zoledronic acid was administered orally (gavage) to rats and mice for at least 104 weeks without evidence of carcinogenic potential. Chronic parenteral administration was not feasible given the potential of the compound to cause severe local irritation, often after only one or several doses. As zoledronic acid, and bisphosphonates in general, manifest poor oral bioavailability, fasting procedures were instituted to facilitate absorption. Nevertheless, the pharmacological bone changes typically observed following long term bisphosphonate administration (non-proliferative hyperostosis) to young animals with growing skeletons gave clear evidence of systemic exposure to zoledronic acid in both species at all doses. An increased incidence of Harderian gland adenomas/adenocarcinomas was observed in males at 0.1 and 1.0 mg/kg and females at doses ≥ 0.3 mg/kg. These increases were not considered to be related to zoledronic acid administration or biologically meaningful as the Harderian gland is a unique, highly specialized organ which is not present or known to have any correlate in humans; thus, it has no relevance.

Species	Route	Doses (mg/kg)	Findings
Mouse	p.o.	0.1,0.3,1.0	≥ 0.1 mg/kg: non-proliferative hyperostosis ≥ 0.3 mg/kg: ↓BW
Rat	p.o.	0.1,0.5,2.0	≥ 0.1 mg/kg: non-proliferative hyperostosis ≥ 0.5 mg/kg: ↓ BW,FC 2.0 mg/kg: ↑ extramedullary hematopoiesis

Mutagenicity

Study Type	Findings
in vitro: Ames [a], Ames [b], Ames [c] Range: [a]5000 µg/plate (-S9/+S9), [b]390 - 25000 µg/plate, [c]1250 µg/plate (-S9/+S9)	Negative
in vitro: Cytogenetics test on Chinese hamster cells Range: 9.7 - 1250 µg/mL	Negative
in vitro: Gene mutation test using V79 Chinese hamster cells Range: 2 - 15 µg/mL	Negative
in vivo: Micronucleus in rats Range: 2.6 • 10.4 mg/kg	Negative

[a] Bacterial test systems (S. typhimurium), with/without metabolic activation.
[b] Batch control
[c] Bacterial test system (S. typhimurium/ E. coli), with/without metabolic activation.

There was no evidence of mutagenicity for zoledronic acid in a battery of tests covering various endpoints of genotoxicity.

REFERENCES

1. Anderson PK, and Gill RD, Cox's regression model for counting processes: a large sample study. *Ann Statist* 1982; 10: 1100-20.

2. Arden-Cordone M, Siris E, Lyles K, et al., Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; 60: 415-418.

3. Body J, Jortholary A, Romieu G, et al., A dose-finding study of zoledronate in hypercalcemic cancer patients. *J Bone Miner Res* 1999; 9: 1557-1561.

4. Buckler H, Fraser W, Hosking D, et al., Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; 24 (S5): 81S-85S.

5. Fraunfelder FW, Fraunfelder FT. Bisphosphonates and ocular inflammation. *N Engl J Med* 2003; 348(12):1187-8.

6. Fraunfelder FW, Rosenbaum JT. Drug-induced uveitis. Incidence, prevention and treatment. *Drug Safety* 1997; 17(3):197-207.

7. Garnero P, Gineyts E, Schaffer A, et al., Measurement of urinary excretion of nonisomerized and beta-isomerized forms of type I collagen breakdown products to monitor the effects of the biphosphonate zoledronate in Paget's disease. *Arthritis Rheum* 1998; 41: 354-360.

8. Green JR, Müller K, Jaeggi KA. Preclinical Pharmacology of CGP 42-446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res* 1994; 9: 745-751.

9. Green J, Seltenmeyer Y, Jaeggi K, Widler L, Renal tolerability profile of novel, potent bisphosphonates in two short-term rat models, *Pharmacol Toxicol* 1997; 80: 225-230.

10. Ishizuna K, Ota D, Fukuuchi A, et al., A case of femoral diaphyseal fracture after long-term treatment with zoledronic acid. *Breast Cancer* 2011; 18:DOI 10.1007/s12282-011-0304-3

11. Moore MM, Beith JM. Acute unilateral anterior uveitis and scleritis following a single infusion of zoledronate for metastatic breast cancer. *Med J Aust* 2008; 188(6): 370-371

12. Puhaindran ME, Farooki A, Steensma M, et al., Atypical Subtrochanteric Femoral Fractures in Patients with Skeletal Malignant Involvement Treated with Intravenous Bisphosphonates. *J Bone Joint Surg Am.* 2011; 93:1235-42

13. Risser F, Pfister C, Degen P, An enzyme inhibition assay for the quantitative determination of the new bisphosphonate zoledronate in plasma. *J Pharm Biomed Anal* 1997; 15: 1877-1880.

14. Rosen Lee S, Gordon D, Kaminski M, et al., Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions of multiple myeloma: A phase III, double-blind, comparative trial. *The Cancer Journal.* September/October 2001; 7 (5), 377-387.

15. Rosen LS, Gordon DH, Dugan W, et al., Zoledronic acid is superior to pamidronate for treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer*. 2004; 100:36-43.

16. Rosen LS, Gordon DH, Kaminski M, et al., Long-term efficacy and safety of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma and breast cancer. *Cancer*. 2003; 98:1735-1744.

17. Saad F, Gleason Donald M, Murray R, et. al., A randomized, placebo-controlled trial of zoledronic acid in patients with hormone-refractory metastatic prostate carcinoma. *Journal of the National Cancer Institute* October 2, 2002; 94 (19), 1458-1468.

18. Saad F, Gleason Donald M, et al., Long-term efficacy of zoledronic acid for the prevention of skeletal complications in patients with metastatic hormone-refractory prostate cancer. *Journal of the National Cancer Institute* June 2, 2004; 96 (11):879-882.

19. Therneau M, Hamilton SA. rhDNase as an example of recurrent event analysis. *Statist Med* 1997; 16:2029-47.

20. McArthur H, Estilo C, Huryn J, et al (2008). Osteonecrosis of the jaw (ONJ) among intravenous (IV) bisphosphonate- and/or bevacizumab-treated patients at Memorial Sloan-Kettering Cancer Center (MSKCC). J Clin Oncol 26S: Updated Abstract 9588 (with poster, presented at ASCO 2008)

21. Zometa® Concentrate product monograph, control# 200447, date of revision: April 13, 2017.

PART III: CONSUMER INFORMATION

Zoledronic Acid for Injection
Concentrate
For Intravenous Infusion

This leaflet is part III of a three-part "Product Monograph" published when Zoledronic Acid for Injection was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Zoledronic Acid for Injection. Contact your doctor or pharmacist if you have any questions about the drug.

Please read this information carefully before starting treatment with Zoledronic Acid for Injection.

ABOUT THIS MEDICATION

What the medication is used for:

Zoledronic Acid for Injection is used to:
1) reduce the abnormal amount of calcium in the blood for example, in the presence of a tumour. This is because tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia.

2) prevent or delay skeletal complications for example, fractures of the bone and bone pain requiring surgery or radiotherapy, as a result of bone metastases (cancer that has spread from the tumour to the bone) due to different types of tumours.

What it does:

Zoledronic Acid for Injection is a member of a group of substances called bisphosphonates. These strongly bind to the bone and slow down the rate of bone change. In addition, Zoledronic Acid for Injection may prevent bone destruction and uncontrolled bone growth associated with the tumour spreading to the bone.

When it should not be used:

You should not be given Zoledronic Acid for Injection if you are:

- pregnant
- breastfeeding
- allergic to zoledronic acid, other bisphosphonates (the group of substances to which Zoledronic Acid for Injection belongs) or to any other non medicinal ingredients in Zoledronic Acid for Injection
- hypocalcaemic (have low calcium levels in your blood)

What the medicinal ingredient is:

Zoledronic acid.

What the important nonmedicinal ingredients are:
Mannitol and sodium citrate.

What dosage forms it comes in:
Zoledronic Acid for Injection is available as a concentrate in vials. Each vial of Zoledronic Acid for Injection concentrate delivers 4 mg of zoledronic acid. It is available in cartons containing 1 vial.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
Serious side effects which have been reported with the use of Zoledronic Acid for Injection include:

- **osteonecrosis of the jaw** (a severe bone disease that affects the jaw)
- **deterioration in renal function.** Zoledronic Acid for Injection is not recommended in patients with severe kidney impairment.
- **hypocalcaemia** (low calcium levels in your blood))

If you are being treated with Zoledronic Acid for Injection, you should not be treated with another intravenous form of zoledronic acid (i.e. ACLASTA®) or other bisphosphonates (e.g. alendronate, risedronate, clodronate, etidronate and pamidronate) at the same time.

Your doctor may request an oral examination (an examination of your mouth and teeth) before you start treatment and while you are on treatment with Zoledronic Acid for Injection. This may be required since some patients have experienced serious side effects following dental procedures (such as tooth extraction) while on Zoledronic Acid for Injection; as well, since patients with unhealed open wounds in the mouth, dental infections or periodontal disease (disease affecting the surrounding tissues of a tooth) may be at increased risk of problems with their jaw bones following dental procedures (such as tooth extraction) while on treatment with Zoledronic Acid for Injection.

You should avoid invasive dental procedures during your treatment with Zoledronic Acid for Injection. It is important that you practice good dental hygiene, routine dental care, and have regular dental check- ups while being treated with Zoledronic Acid for Injection. Immediately report any oral symptoms (any symptoms in your mouth), such as loosening of a tooth, pain, swelling, or non-healing of sores or discharge (pus or oozing) during your treatment with Zoledronic Acid for Injection.

BEFORE you use Zoledronic Acid for Injection talk to your doctor or pharmacist if you:

- Have a kidney problem. Worsening of kidney function, including kidney failure (very rarely with fatal outcome), has been reported with the use of Zoledronic Acid for Injection.
- Have asthma and are also allergic to acetylsalicylic acid (ASA).
- Had or have a heart problem. Cases of irregular heart beat (atrial fibrillation) have been observed with the use of Zoledronic Acid for Injection.
- Have any dental problems or any dental procedures planned in the future.
- Have pain, swelling or numbness of the jaw, a "heavy jaw feeling", loosening of a tooth, or any other symptoms in your mouth.

- Have sores in your mouth. This can lead to osteonecrosis of the jaw. Your doctor may check if you:
  - smoke
  - have or have had tooth and/or gum disease
  - have dentures that do not fit well
  - have other medical conditions at the same time, such as: low red blood cell count (anaemia) or if your blood cannot form clots in the normal way.

Your doctor may tell you to stop taking Zoledronic Acid for Injection until all sores in your mouth are healed.

After starting treatment with Zoledronic Acid for Injection

It is important that your doctor checks your progress at regular intervals. He or she may want to take repeated blood tests, especially after starting your treatment with Zoledronic Acid for Injection.

If possible, you should not undergo tooth extraction or any other dental procedures (excluding regular dental cleaning) while you are receiving treatment with Zoledronic Acid for Injection. Please consult your doctor if a dental procedure (excluding regular dental cleaning) is required while you are receiving treatment with Zoledronic Acid for Injection. It is important to maintain good dental hygiene; regularly scheduled dental examinations are recommended.

Tell your doctor if you had or have joint stiffness, aches and pains and difficulty in movement of your thighs, hips, upper arms (in the bones between your shoulders and elbows), lower legs (in the long large bones between your knees and your feet), ribs, backbone, knees, or feet bones (in the five long bones between your ankles and your toes), or pain around your ears. Tell your doctor, as this may be a sign of bone damage due to loss of blood supply to the bone (osteonecrosis).

Driving and using machines

Zoledronic Acid for Injection may affect your ability to drive a car or to operate machinery. Do not drive a car or operate machinery until you know how Zoledronic Acid for Injection affects you.

Use in Children

Zoledronic Acid for Injection should not be used in children.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor about any other medicines you are taking or have recently been taking, including any you have bought without a prescription. It is particularly important that your doctor knows if you are also taking aminoglycosides (a type of medicine used to treat severe infections), calcitonin (a type of medicine used to treat high calcium levels in the blood and Paget's disease), loop diuretics (a type of medicine used to treat high blood pressure or oedema) or other calcium-lowering medicines, since the combination of these with bisphosphonates may cause the calcium level in the blood to become too low. Examples of aminoglycosides include gentamycin sulfate, tobramycin sulfate and streptomycin sulphate; examples of loop diuretics include furosemide, torsemide and ethacrinic acid.

It is also important to inform your doctor if you are taking any drugs that can have an effect on the kidney, since combining these drugs with Zoledronic Acid for Injection may cause kidney function to deteriorate. Some examples of these drugs include aminoglycosides, acetylsalicylic acid (ASA), nonsteroidal anti-inflammatories (e.g. ibuprofen, diclofenac, celecoxib), diuretics (e.g. hydrochlorothiazide, amiloride, spironolactone and indapamide) and Angiotensin-Converting Enzyme (ACE) inhibitors (e.g. enalapril, ramipril, fosinopril).

Tell your doctor if you are taking anti-angiogenic medicines (type of medicines used to treat cancer, e.g. thalidomide, bortezomid, lenalidomide, bevacizumab) as part of your cancer treatment because the combination of these medicines with bisphosphonates may increase the risk of bone damage in the jaw (osteonecrosis).

PROPER USE OF THIS MEDICATION

Usual dose:

Zoledronic Acid for Injection is given by an infusion into a vein which should last no less than 15 minutes. The dose is usually 4 mg. If you have a kidney problem, your doctor may give you a lower dose depending on the severity of your kidney problem.

If you are being treated for multiple myeloma or bone metastases of solid tumours, you will be given one infusion of Zoledronic Acid for Injection every three to four weeks. If you require antineoplastic therapy (therapy that blocks the growth of cancer cells), Zoledronic Acid for Injection should be administered either prior to, or after this treatment. You will also be asked to take an oral calcium supplement of 500 mg and a multivitamin containing at least 400 IU of Vitamin D daily. If you have a prior history of high levels of calcium in the blood or develop high levels of calcium in the blood during treatment with calcium and Vitamin D, you may be advised to discontinue taking calcium and Vitamin D supplements by your doctor.

Your doctor will decide how many infusions you need and how often you should receive them.

If you are being treated for Tumour-Induced Hypercalcaemia (TIH), you will normally only be given one infusion of Zoledronic Acid for Injection. Prior to treatment with Zoledronic Acid for Injection, restoring and maintaining adequate fluid regulation in your body and urine output may help to eliminate excess calcium from your kidneys.

Overdose:
If you think you have taken too much Zoledronic Acid for Injection, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms. You may develop serum electrolyte abnormalities and changes in kidney function, including severe kidney impairment.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Zoledronic Acid for Injection may have, in addition to its beneficial effects, some unwanted effects. These are usually mild and will probably disappear after a short time. The most common side effect is short-lasting fever. Patients may experience a flu- like condition including fever, fatigue, weakness, drowsiness and chills. In some patients, these symptoms may also be accompanied by bone, joint and/or muscle ache, arthritis and joint swelling. In most cases, no specific treatment is required and the symptoms subside after a couple of hours or days. Other common side effects include gastrointestinal problems such as nausea, vomiting and thirst as well as swelling of sores inside the mouth and loss of appetite.

Occasionally, skin reactions (redness and swelling) at the infusion site may occur. Cases of low blood pressure have also occasionally been reported; in very rare cases, this resulted in fainting.

Rare cases of rash, itching, chest pain, swelling mainly of the face and throat, high level of potassium and sodium in the blood, slow heart beat, confusion and a disorder of the kidney function called Fanconi syndrome have been observed.

Very rare cases of severe bone, joint, and/or muscle pain, occasionally incapacitating, as well as sleepiness, irregular heart beat (atrial fibrillation), difficulty breathing with wheezing or coughing, lung disease, severe allergic reaction and itchy rash have also been reported.

Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin or burning sensation, have been reported in patients treated with Zoledronic Acid for Injection. Irregular heart beat has also been reported. There have been reports of abnormal electrical signals of the heart called "prolongation of the QT interval", seizures, numbness, spasm and twitching caused by severely reduced levels of calcium in the blood. In some instances, the reduced calcium level may be life-threatening and require hospitalization. If any of these apply to you, **tell your doctor right away**.

Blood tests indicating worsening of kidney function (higher levels of creatinine) including severe kidney failure have been reported with Zoledronic Acid for Injection; such changes are also known to occur with other drugs of the bisphosphonate class. Your doctor will carry out blood tests to monitor your kidney function prior to each dose of Zoledronic Acid for Injection. If these tests indicate worsening of kidney function, your doctor will withhold further treatment with Zoledronic Acid for Injection until these tests have returned to normal.

The level of calcium, phosphate and/or magnesium in the blood may become too low, but your doctor will monitor this and take necessary measures.

Other bisphosphonates can cause breathing difficulties in patients with asthma who are allergic to acetylsalicylic acid (ASA). This has not been reported with Zoledronic Acid for Injection, in studies done to date.

Eye pain, redness, photophobia (sensitivity to light), excessive tearing or decreased vision should be reported to your physician as they may indicate more serious eye complications which have been associated with Zoledronic Acid for Injection.

Some patients have reported problems with their jaw bones while receiving cancer treatments that include Zoledronic Acid for Injection. Dental hygiene is an important element of your overall cancer care and is important in possibly decreasing the chances of this type of problem occurring. Removable dentures should fit properly and should be removed at night. Please consult with your doctor if you experience pain in your mouth, teeth or jaw, or if your gums or mouth heals poorly. Any non-healing of a dental extraction site or chronic dental infection should be reported and assessed. In addition, if possible you should not undergo tooth extraction or other dental procedures (excluding regular dental cleaning) while on therapy with Zoledronic Acid for Injection.

Please consult your doctor if a dental procedure (excluding regular dental cleaning) is required while you are receiving treatment with Zoledronic Acid for Injection.

Some patients have reported problems with other bones, other than their jaw bones, while on treatment with Zoledronic Acid for Injection. Consult your doctor if you had or have aches and pains and difficulty in movement of your thighs, hips, upper arms, lower legs, ribs, backbone, knees, or feet bones, or if you experience pain around your ears.

Unusual fracture of the thigh bone may occur while receiving treatment with Zoledronic Acid for Injection. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early sign of a possible fracture of the thigh bone.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Common	• Worsening of kidney function (higher levels of creatinine)	√		√
	• Bone, joint and/or muscle pain, joint stiffness			
	• Conjunctivitis		√	

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
Uncommon	• Kidney failure (changes in urine colour or absence of urine production, changes in kidney function laboratory tests, lower back pain, fatigue, nausea, loss of appetite)			√
	• Eye disorders (painful red and/or swollen eye, excessive tearing, light sensitivity, or decreased vision)		√	
	• Allergic reaction to Zoledronic Acid for Injection (swelling of the face, eyes or tongue, difficulty breathing, hives, rash, sudden onset of low blood pressure)			√
	• Dizziness			√
	• Osteonecrosis of the jaw (numbness or feeling of heaviness in the jaw, poor healing of the gums especially after dental work, loose teeth, exposed bone in mouth, pain in the mouth, teeth or jaw, sores or non-healing sores in the mouth or discharge (pus or oozing), swelling, dry mouth, swelling, gum infections, or bad breath)			√
	• Osteonecrosis of other bones (joint stiffness, aches and pains, and difficulty in movement of the thighs, hips, upper arms, lower legs, ribs, backbone, knees, or feet bones, or pain around the ears)			√

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		**Talk with your doctor or pharmacist**		**Stop taking drug and get immediate medical help**
		Only if severe	**In all cases**	
Unknown[1]	• Difficulty breathing with wheezing or coughing			√
	• Irregular heart beat (atrial fibrillation)			√
	• Sleepiness	√		
	• Severe allergic reaction			√
	• Itchy rash			√
	• Thigh pain, weakness or discomfort/Unusual fracture of the thigh bone			√
	• Muscle cramps or twitching, dry skin, burning sensation, or irregular heart beat		√	
	• Disorder in kidney function with release of amino acids, phosphate and glucose in urine (acquired Fanconi syndrome)			√

[1]The frequency with which these side effects may occur cannot be reliably estimated.

This is not a complete list of side effects. If you have any unexpected effects after receiving Zoledronic Acid for Injection, contact your doctor or pharmacist.

HOW TO STORE ZOLEDRONIC ACID FOR INJECTION

Vials (concentrate)

- Store Zoledronic Acid for Injection vials at room temperature (between 15 °C - 30 °C).

Zoledronic Acid for Injection must be kept out of reach and sight of children and pets.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

For more information, please contact your healthcare professionals or pharmacist first, or Marcan Pharmaceuticals Inc. at: 1-855-627-2261 or visit the website at www.marcanpharma.com

The information in this document is current as of the last revision date shown below. For the most current information please visit our website or contact us directly.

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