

PRODUCT MONOGRAPH

Pr ZOLEDRONIC ACID INJECTION

5 mg/100 mL zoledronic acid (as zoledronic acid monohydrate)
Solution for intravenous infusion

Bone Metabolism Regulator

DIN Owner:
Dr. Reddy's Laboratories Limited
Bachupally 500 090 - INDIA

Date of Preparation:
March 11, 2014

Imported By: **Innomar Strategies Inc.**
3470 Superior Court
Oakville, Ontario L6L 0C4
CANADA

Date of Revision:
October 30, 2014

Submission Control Number: 178083

Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	4
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	8
DRUG INTERACTIONS	14
DOSAGE AND ADMINISTRATION	14
OVERDOSAGE	16
ACTION AND CLINICAL PHARMACOLOGY	16
STORAGE AND STABILITY.....	19
SPECIAL HANDLING INSTRUCTIONS	19
DOSAGE FORMS, COMPOSITION AND PACKAGING	19
PART II: SCIENTIFIC INFORMATION	20
PHARMACEUTICAL INFORMATION.....	20
CLINICAL TRIALS.....	21
DETAILED PHARMACOLOGY	28
TOXICOLOGY	29
REFERENCES	36
PART III: CONSUMER INFORMATION.....	38

Pr
ZOLEDRONIC ACID INJECTION
5 mg/100 mL zoledronic acid (as zoledronic acid monohydrate)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous infusion	5 mg/100 mL ^a	<ul style="list-style-type: none">• mannitol• sodium citrate dihydrate• water for injection

^a One vial with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis.

INDICATIONS AND CLINICAL USE

Zoledronic Acid Injection 5 mg/100 mL is indicated for:

- The prevention of postmenopausal osteoporosis in women with osteopenia as a single intravenous infusion.
- The treatment of Paget's disease of the bone in men and women, as a single-dose intravenous infusion. Treatment is indicated in patients with Paget's disease of the bone with elevations in serum alkaline phosphatase (SAP) of at least two times the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease to induce remission (normalization of serum alkaline phosphatase). The effectiveness of zoledronic acid injection is based on serum alkaline phosphatase (SAP) levels.

Geriatrics (> 65 years of age):

No overall differences in safety and efficacy were observed according to age (see **WARNINGS AND PRECAUTIONS – Special Populations**).

Pediatrics (<18 years of age):

Safety and efficacy in children and growing adolescents have not been established. Zoledronic acid injection should not be given to this patient population.

Important Limitations of Use:

The optimal duration of use has not been determined. Patients should have the need for continued therapy re-evaluated on a periodic basis (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, or to any bisphosphonates or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING SECTION** of the Product Monograph.
- Severe renal impairment with creatinine clearance <35 mL/min and in those with evidence of acute renal impairment. These patients are at an increased risk of renal failure (see **WARNINGS and PRECAUTIONS**).
- Pregnancy and nursing mothers.
- Non-corrected hypocalcemia at the time of infusion.

WARNINGS AND PRECAUTIONS

General

Patients being treated with zoledronic acid injection should not be treated with other drugs containing zoledronic acid concomitantly.

Patients being treated with zoledronic acid injection should not be treated with other bisphosphonates concomitantly.

Patients must be appropriately hydrated prior to administration of zoledronic acid injection, especially for patients who are elderly or on diuretic therapy.

Infusion duration

The 5 mg single dose of zoledronic acid injection 5 mg/100 mL should be infused in **no less than 15 minutes**.

Cardiovascular

Atrial Fibrillation

There have been reports of serious atrial fibrillation in patients treated with zoledronic acid. Atrial fibrillation may occur at any time during treatment.

An increased incidence of atrial fibrillation has been observed in clinical trials conducted on other indications not approved for zoledronic acid injection. This increased incidence of atrial fibrillation was not observed in clinical trials conducted on Paget's disease, in the trial in post-hip fracture patients, or in the trial for the prevention of postmenopausal osteoporosis. The mechanism behind the increased incidence of atrial fibrillation is unknown.

Cerebrovascular Accident

There have been reports of serious cerebrovascular accidents in patients treated with zoledronic acid, some with a fatal outcome.

The signs and symptoms of cerebrovascular accidents can occur at any time during treatment.

Endocrine and Metabolism

Hypocalcemia

It is recommended that all patients should have their serum calcium levels and vitamin D levels assessed before treatment with zoledronic acid injection (e.g., as part of their annual examination). Pre-existing hypocalcemia must be treated by adequate administration of calcium and vitamin D before initiating zoledronic acid injection (see **CONTRAINDICATIONS**). Other disturbances of mineral metabolism (e.g., diminished parathyroid reserve; thyroid surgery, parathyroid surgery, intestinal calcium malabsorption) must also be effectively treated.

It is strongly advised that patients receive adequate calcium and vitamin D supplementation. All patients should be counseled regarding the importance of calcium and vitamin D supplementation in maintaining serum calcium levels and on the symptoms of hypocalcemia. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.

Renal

The use of zoledronic acid injection in patients with severe renal impairment (creatinine clearance <35 mL/min) and in those with evidence of acute renal impairment is contraindicated due to an increased risk of renal failure in this population (see **DOSAGE AND ADMINISTRATION**).

Zoledronic acid has been associated with renal dysfunction manifested as deterioration in renal function, and acute renal failure (see **ADVERSE REACTIONS-Clinical Trial Adverse Drug Reactions and Post-Market Adverse Drug Reactions**). Renal impairment has been observed following the administration of zoledronic acid injection, including after a single administration. Renal failure requiring dialysis or with a fatal outcome has occurred especially in patients with history of renal impairment or other risk factors. Risk factors include advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see **DRUG INTERACTIONS**), or dehydration occurring after zoledronic acid injection administration. It may increase with underlying renal disease and dehydration secondary to fever, sepsis, gastrointestinal losses, diuretic therapy, advanced age, etc. (see **Post-Marketing Experience**). In some post marketing cases, acute renal failure has occurred in patients with no underlying risk factors for renal impairment. Renal impairment may lead to increased exposure of concomitant medications and/or their metabolites that are primarily renally excreted (see **DRUG INTERACTIONS**)

The following precautions should be taken to minimize the risk of renal adverse reactions:

- Creatinine clearance should be calculated based on actual body weight using Cockcroft-Gault formula before each zoledronic acid injection dose. Transient increase in serum creatinine may be greater in patients with underlying impaired renal function. Interim monitoring of creatinine clearance should be performed in at-risk patients.
- Zoledronic acid injection should be used with caution when concomitantly used with other medicinal products that could impact renal function (see **DRUG INTERACTIONS**). Creatinine clearance should be monitored in patients at-risk for acute renal failure who are taking concomitant medications that are primarily excreted by the kidney.
- Patients should be appropriately hydrated, prior to administration of zoledronic acid injection, especially elderly patients and those receiving diuretic therapy. On the day of infusion, it is recommended that patients eat and drink normally, which includes drinking at least 2 glasses of fluids (500 mL or 2 cups), such as water, before and after the administration of zoledronic acid injection (see “**Information to be provided to the Patients**”).
- A single dose of zoledronic acid injection should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see **DOSAGE AND ADMINISTRATION**).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported rarely in the treatment of postmenopausal osteoporosis with zoledronic acid as well as with other oral and intravenous bisphosphonates. The condition currently termed Osteonecrosis of the jaw has unknown etiology and pathogenesis, and may or may not originate in the bone. ONJ has been reported in patients with cancer receiving treatment regimens that include bisphosphonates such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with invasive dental procedures, such as root canal or dental extraction. Many had signs of local infection including osteomyelitis. A causal relationship between bisphosphonate use and ONJ has not been established.

A routine dental examination with appropriate preventive dentistry should be performed prior to treatment with bisphosphonates, such as zoledronic acid injection, in patients with possible risk factors (e.g., cancer, chemotherapy, anti-angiogenic drugs, head and neck radiotherapy, corticosteroids, poor oral hygiene). While receiving treatment, these patients should avoid invasive dental procedures, if possible, but should continue with regular dental cleaning and oral hygiene. For patients requiring oral surgery, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. In patients who develop ONJ while on bisphosphonate therapy, surgery at the affected area may exacerbate the condition. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In post-marketing experience with multiple dose regimen bisphosphonates, including zoledronic acid injection, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients. The time to onset of symptoms varied from one day to several months after starting the drug. A subset of patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Atypical, low-energy, or low trauma fractures of the femoral shaft have been reported in bisphosphonate-treated patients. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to above the supracondylar flare and are transverse or short oblique in orientation without evidence of comminution. Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. Poor healing of these fractures was also reported. Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain should be suspected of having an atypical fracture and should be evaluated to rule out an incomplete femur fracture. Patients presenting with an atypical femur fracture should also be assessed for symptoms and signs of fracture in the contralateral limb. Interruption of bisphosphonate therapy should be considered pending a risk/benefit assessment. Although causality has not been established, the role of bisphosphonates cannot be ruled out.

Respiratory

While not observed in clinical trials with zoledronic acid injection, there have been reports of

bronchoconstriction in ASA (acetylsalicylic acid) sensitive patients receiving bisphosphonates. Zoledronic acid injection must be used with caution in ASA-sensitive patients.

Ophthalmologic

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

Sexual Function/Reproduction

Fertility: Fertility was decreased in female rats dosed subcutaneously with 0.1 mg/kg/day of zoledronic acid. There are no data available in humans.

Special Populations

Pregnant Women: Zoledronic acid injection should not be used during pregnancy as zoledronic acid may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.0 or 4.5 times the human systemic exposure (an i.v. dose of 5 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk have not been established.

There are no studies in pregnant women using zoledronic acid. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Women: It is not known whether zoledronic acid injection is excreted in human milk. Because many drugs are excreted in human milk, it should not be administered to a nursing woman.

Pediatrics (<18 years of age): The safety and effectiveness of zoledronic acid injection in pediatric patients have not been established.

Geriatrics (>65 years of age): No overall differences in safety and efficacy were observed according to age.

Phase 3 studies of zoledronic acid injection in the treatment of Paget's disease of bone included 132 (75.5%) zoledronic acid injection-treated patients who were at least 65 years of age, while 68 (37.4%) zoledronic acid injection-treated patients were at least 75 years old. No overall differences in efficacy or safety were observed between these patients and younger patients.

Information to be Provided to the Patient

Physicians should instruct their patients to read the Patient Information before starting therapy with zoledronic acid injection 5 mg/100 mL.

- Zoledronic acid injection is given as one single infusion into a vein by a nurse or a doctor, and the infusion time must **not be less than 15 minutes**.

- Before being given zoledronic acid injection patients should tell their doctor if they have kidney problems and what medications they are taking (see **ADVERSE REACTIONS-Renal dysfunction**).
- Patients being treated with zoledronic acid injection should not be treated with other drugs containing zoledronic acid concomitantly.
- Zoledronic acid injection should not be given if the patient is pregnant or plans to become pregnant, or if they are breast-feeding (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).
- If the patient had surgery to remove some or all of the parathyroid glands or thyroid gland in their neck, or had sections of their intestine removed, or are unable to take calcium supplements, they should tell the doctor.
- It is strongly advised that patients receive adequate calcium and vitamin D supplementation in order to maintain normal blood calcium levels. Supplementation of both calcium and vitamin D is especially important in the days before and following zoledronic acid injection administration. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.
- On the day of infusion, it is recommended that patients eat and drink normally, which includes drinking at least 2 glasses of fluids (500 mL or 2 cups) such as water, before and after the administration of zoledronic acid injection.
- Patients should also be aware of the most common side effects. Patients may experience one or more side effects that could include: fever and chills; muscle, bone or joint pain; nausea; fatigue; and headache. Most of these side effects are mild to moderate and occur within 3 days after taking zoledronic acid injection. They usually go away within 3 days after they start, but may last for up to 7-14 days. The incidence of post-dose symptoms occurring within the first 3 days after administration of zoledronic acid injection, can be reduced with the administration of acetaminophen or ibuprofen shortly following zoledronic acid injection administration.
- Some patients experienced hypocalcemia. Hypocalcemia is usually asymptomatic, but symptoms may include numbness or tingling sensations, especially in the area around the mouth, muscle cramps or muscle spasms. Patients should consult their physician immediately if they develop these symptoms of hypocalcemia after zoledronic acid injection treatment (see **ADVERSE REACTIONS**).
- Redness, swelling and or pain at the infusion site may occur. Redness, itching, or pain to the eyes may occur.
- There have been some reports of persistent pain and/or a non-healing sore of the mouth or jaw, if you experience these symptoms tell your doctor or dentist.
- There have been some reports of eye inflammation. Patients should consult their physician if this occurs.

Monitoring and Laboratory Tests

Hypocalcemia: Serum calcium levels and vitamin D levels should be assessed for all patients before treatment with zoledronic acid injection (e.g., as part of their annual examination). The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.

Renal: Creatinine clearance should be calculated before each dose of zoledronic acid injection. Interim

monitoring of creatinine clearance should be performed in at-risk patients.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

- *Prevention of postmenopausal osteoporosis*

The safety of zoledronic acid injection in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, double-blind, placebo-controlled trial of postmenopausal women aged 45 years or older. 181 women were exposed to zoledronic acid injection as a single 5 mg dose administered at randomisation and 202 patients were exposed to placebo for two years (see **CLINICAL TRIALS**). All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day.

The incidence of serious adverse events was 9.4% and 11.4% for the zoledronic acid and the placebo groups, respectively. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 0.5% for the zoledronic acid and the placebo groups, respectively.

The incidence of the most frequent treatment-emergent adverse events for the zoledronic acid group was reported as follows: myalgia (22.7%), pyrexia (21%), headache (20.4%), chills (18.2%), pain in extremity (16%), pain (14.9%), nausea (11.6%), fatigue (9.9%), influenza (8.3%), non-cardiac chest pain (7.7%), dizziness (6.1%), hypercholesterolemia (5.5%), sciatica (5%), bone pain (3.3%), asthenia (2.8%), and hypoesthesia (2.2%).

- *Paget's disease of bone*

In general, zoledronic acid injection 5 mg/100 mL was well-tolerated in Paget's disease trials. Consistent with intravenous administration of bisphosphonates, zoledronic acid injection has been most commonly associated with the following signs and symptoms, the majority of which occur within 3 days following the administration: influenza-like illness (transient post-dose symptoms), pyrexia, myalgia, arthralgia, and bone pain. In Paget's disease trials, one or more of these events which were suspected to be related to drug were reported in 25% of patients in the zoledronic acid injection-treated group compared to 8% in the risedronate-treated group within the first 3 days following the zoledronic acid injection administration. After the first 3 days, rates for these symptoms were reduced to 3% for zoledronic acid injection-treated patients and 3% for risedronate-treated patients. The majority of these symptoms resolved within 3 days of their onset.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

- *Prevention of postmenopausal osteoporosis*

Table 1: Adverse Reactions Occurring in at least 2% of women with osteopenia receiving zoledronic acid injection 5 mg IV infusion (administered as a single dose at randomisation) and greater than placebo in the prevention of postmenopausal osteoporosis trial over 2 years

System Organ Class	Zoledronic Acid Injection 5 mg IV % (N=181)	Placebo % (N=202)
Endocrine Disorders		
Hypothyroidism	2.8	1.5
Gastrointestinal disorders		
Nausea	11.6	7.9
Constipation	7.2	6.9
Dyspepsia	6.6	5.0
Vomiting	5.0	4.5
Vascular disorders		
Hypertension	8.3	6.9
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	22.7	6.9
Back pain	16.6	11.9
Pain in extremity	16.0	9.9
Neck pain	6.6	5.0
Musculoskeletal pain	5.5	5.4
Pain in jaw	3.9	2.5
Bone pain	3.3	1.0
Arthritis	2.2	1.5
General Disorders and Administrative Site Conditions		
Pyrexia	21.0	4.5
Chills	18.2	3.0
Pain	14.9	3.5
Fatigue	9.9	4.0
Non-cardiac chest pain	7.7	3.0
Edema peripheral	3.9	3.5
Influenza-like illness	3.3	2.0
Asthenia	2.8	1.0
Malaise	2.2	0.5
Immune system disorders		
Seasonal allergy	2.8	1.5
Infections and infestations		
Influenza	8.3	5.9
Tooth infection	2.8	1.0
Injury, poisoning, and procedural complications		
Joint sprain	2.8	1.5
Post-traumatic pain	2.8	2.5
Metabolism and nutrition disorders		
Hypercholesterolemia	5.5	2.0
Nervous system disorders		

Headache	20.4	11.4
Dizziness	6.1	3.5
Sciatica	5.0	2.0
Hypoesthesia	2.2	2.0
Reproductive system and breast disorders		
Vulvovaginal dryness	2.2	2.0
Respiratory, thoracic and mediastinal disorders		
Cough	6.1	5.0
Pharyngolaryngeal pain	3.9	2.5
Nasal congestion	2.2	2.0

- *Paget's disease of bone*

Adverse reactions suspected (investigator assessment) to be drug related and occurring in at least 2% of the Paget's patients receiving zoledronic acid injection (single, 5 mg, intravenous infusion) or risedronate (30 mg, oral, daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 2.

Table 2: Adverse reactions suspected^a to be drug related occurring in at least 2% of Paget's patients receiving zoledronic acid injection (single 5 mg i.v. infusion) or risedronate (oral 30 mg daily for 2 months) over a 6-month follow-up period

System organ class	single 5 mg i.v. zoledronic acid injection administration	30 mg/day x 2 months risedronate
	% (N = 177)	% (N = 172)
Metabolism and nutrition disorders		
Hypocalcemia	3	1
Nervous system disorders		
Headache	7	4
Lethargy	4	1
Gastrointestinal disorders		
Diarrhea	2	0
Nausea	6	2
Dyspepsia	2	2
Infections and infestations		
Influenza	3	0
Musculoskeletal, connective tissue and bone disorders		
Myalgia	6	4
Bone pain	5	1
Arthralgia	4	2
General disorders and administrative site conditions		
Influenza-like illness	9	5
Pyrexia	7	1
Rigors	7	1
Fatigue	5	2
Pain	3	2
Asthenia	2	1

Respiratory, thoracic and mediastinal disorders		
Dyspnea	2	0

^a Investigator assessment.

Table 3: Most frequent adverse reactions occurring in at least 5% of Paget’s patients in any group receiving zoledronic acid injection (single 5 mg i.v. infusion) or risedronate (oral 30 mg daily for 2 months) by time of occurrence

System organ class	AE occurrence ≤ 3 days after treatment initiation		AE occurrence > 3 days after treatment initiation	
	Single 5 mg i.v. zoledronic acid injection administration % (N = 177)	30 mg/day x 2 months risedronate % (N = 172)	single 5 mg i.v. zoledronic acid injection administration % (N = 177)	30 mg/day x 2 months risedronate % (N = 172)
Nervous system disorders				
Headache	7	4	4	6
Dizziness	3	1	5	3
Gastrointestinal disorders				
Diarrhea	2	1	4	5
Nausea	6	2	3	5
Infections and infestations				
Nasopharyngitis	1	0	5	8
Musculoskeletal, connective tissue and bone disorders				
Myalgia	7	4	1	1
Bone pain	5	1	4	4
Arthralgia	5	0	5	11
Back pain	2	1	2	7
Pain in extremity	0	1	7	7
General disorders and administrative site conditions				
Influenza-like illness	10	4	1	2
Pyrexia	7	1	1	1
Rigors	7	1	1	1
Fatigue	7	2	2	2

Iritis/uveitis/episcleritis/conjunctivitis: In the prevention of postmenopausal osteoporosis trial, conjunctivitis was reported in two patients (1.1%) in the zoledronic acid group. Uveitis/iritis was reported in 3 patients (1.7%) in the zoledronic acid group and in no patients (0%) in the placebo group.

Renal impairment: In the prevention of postmenopausal osteoporosis trial, one zoledronic acid-treated patient (0.6%) reported a creatinine clearance value of <30 mL/min. One zoledronic acid-treated patient (0.6%) reported a creatinine clearance value of <30 mL/min and a ≥30% decline in CrCl during the study from a baseline value of ≤60 mL/min. One zoledronic acid-treated patient (0.6%) had renal failure confirmed by adjudication. No patients in the placebo group had renal failure, acute renal failure, or decreased CrCl.

Bronchoconstriction in ASA (acetylsalicylic acid) Sensitive Asthma Patients: While not observed in clinical trials with zoledronic acid injection there have been previous reports of bronchoconstriction in ASA-sensitive patients receiving bisphosphonates.

Osteonecrosis of the Jaw (ONJ): ONJ has not been observed in the prevention of postmenopausal osteoporosis, or the Paget's disease trials with zoledronic acid injection.

Abnormal Hematologic and Clinical Chemistry Findings

Serum creatinine and creatinine clearance

- *Paget's disease of bone*

No clinically significant changes in serum creatinine have occurred in the Paget's disease trials.

Hypocalcemia

- *Postmenopausal osteoporosis*

In the prevention of postmenopausal osteoporosis trial, one patient (0.5%) treated with zoledronic acid injection (administered at randomization and at Month 12, see **CLINICAL TRIALS**) had a confirmed event of hypocalcemia with a notable decline of calcium level of 1.70 mmol/L from a screening value of 2.17 mmol/L one month following the first infusion of zoledronic acid injection.

- *Paget's disease of bone*

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels, that were usually asymptomatic, have been observed. Approximately 21% of subjects had serum calcium levels <2.1 mmol/L (<8.4 mg/dL) 9-11 days following zoledronic acid injection infusion. In the Paget's disease trials, symptomatic hypocalcemia was observed in approximately 1% of patients, all of which resolved.

Post-Market Adverse Drug Reactions

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 injection exposure.

Cardiovascular: Atrial fibrillation, Cerebrovascular accident, some with a fatal outcome (see **WARNINGS AND PRECAUTIONS**).

Eye disorders: Orbital inflammation, Scleritis, uveitis, conjunctivitis, iritis, episcleritis (see **WARNINGS AND PRECAUTIONS**)

General disorders and administration site conditions: Fever, Flu-like symptoms (pyrexia, asthenia, fatigue, or malaise) persisting for greater than 30 days.

Immune system disorders: Hypersensitivity, bronchoconstriction, urticaria, angioedema, and anaphylactic reactions/shock (rarely)

Metabolism and nutrition disorders: Hypocalcaemia, Dehydration, Osteonecrosis of the jaw

Musculoskeletal and connective tissue disorders: Arthralgia, Myalgia, low-energy femoral shaft fractures (see **WARNINGS AND PRECAUTIONS**)

Nervous system disorders: Headache

Renal and urinary disorders: Renal failure requiring dialysis or with fatal outcome. Increased serum creatinine was reported in patients with 1) underlying renal disease, 2) dehydration secondary to fever, sepsis, gastrointestinal losses, or diuretic therapy, or 3) other risk factors such as advanced age, or concomitant nephrotoxic drugs in the post-infusion period (see **WARNINGS AND PRECAUTIONS**).

Vascular disorders: Hypotension

DRUG INTERACTIONS

Overview

Zoledronic acid injection is not metabolized in humans. Zoledronic acid is eliminated by renal excretion (see **PART II, PHARMACOLOGY, Pharmacokinetics**).

Drug-Drug Interactions

No *in vivo* drug interaction studies have been performed for zoledronic acid injection. *In vitro* and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

Table 4: Established or Potential Drug-Drug Interactions

(Legend: CT = Clinical Trial; T = Theoretical)

Zoledronic acid	Ref	Effect	Clinical comment
Aminoglycosides	T	↓ serum calcium level	Caution is advised when bisphosphonates, including zoledronic acid, are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.
Loop Diuretics	T	↑ risk of hypocalcemia	Caution should also be exercised when zoledronic acid injection is used in combination with loop diuretics due to an increased risk of hypocalcemia.
Nephrotoxic Drugs	T		Caution is indicated when zoledronic acid injection is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.
Drugs primarily excreted by the kidney	T	↑ systemic exposure	In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidneys may increase

Drug-Food Interactions

The interaction of zoledronic acid has not been studied with regards to food.

Drug-Herb Interactions

The interaction of zoledronic acid with herbal medications or supplements has not been studied.

Drug-Laboratory Interactions

No data suggest that zoledronic acid interferes with laboratory tests.

Drug-Lifestyle Interactions

Specific drug-lifestyle interaction studies have not been conducted with zoledronic acid.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

- *Prevention of postmenopausal osteoporosis*

The recommended dose is a single intravenous infusion of zoledronic acid injection.

Re-treatment for prevention of postmenopausal osteoporosis

Specific re-treatment data after 24 months are not available. After one treatment with zoledronic acid injection 5 mg intravenous infusion in the prevention of postmenopausal osteoporosis trial, the effect on lumbar spine BMD was observed for up to 24 months (see **CLINICAL TRIALS-Table 6**). There are no clinical efficacy data available beyond the 24 months' duration of the trial.

- *Treatment of Paget's disease of bone*

The recommended dose is a single intravenous infusion of zoledronic acid injection.

Re-treatment of Paget's disease

After the initial treatment with zoledronic acid injection in Paget's disease, an extended remission period is observed in responding patients. Re-treatment consists of one additional intravenous infusion of 5 mg zoledronic acid injection after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available (see **CLINICAL TRIALS**).

Zoledronic acid injection (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line.

Patients should be advised to be appropriately hydrated before the administration of zoledronic acid injection.

The infusion time **must not be less than 15 minutes** (see **WARNINGS AND PRECAUTIONS**) and the infusion rate should be constant. Zoledronic acid injection should only be given by intravenous infusion. The total volume of the zoledronic acid injection solution should be infused. Zoledronic acid injection must never be given as a bolus injection.

Renal

The use of zoledronic acid injection in patients with severe renal impairment (creatinine clearance < 35mL/min) is contraindicated. Zoledronic acid injection should be used with caution in patients with mild to moderate renal impairment. There are no safety and efficacy data to support the adjustment of the zoledronic acid injection dose based on baseline renal function. Therefore, no dosage adjustment is required in patients with a creatinine clearance of ≥ 35 mL/min (See **WARNINGS AND PRECAUTIONS**). Patients must be appropriately hydrated prior to administration of zoledronic acid injection, and this is especially important for patients receiving diuretic therapy (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**).

Calcium and vitamin D intake

It is strongly advised that patients receive adequate calcium and vitamin D supplementation especially in the days before and following zoledronic acid injection administration (see **WARNINGS AND PRECAUTIONS**). All patients should be counseled regarding the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of

hypocalcemia. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.

Post-Infusion Management

About 25% of patients experienced transient post-dose symptoms within the first 3 days of their zoledronic acid injection infusion (see **ADVERSE REACTIONS**). Symptomatic management can be considered on an individual basis. No anaphylactic reactions have been observed in the clinical trials but good medical practice dictates caution (see **CONTRAINDICATIONS**).

Dosing Considerations

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of zoledronic acid injection on an individual patient basis.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Center.

Clinical experience with acute overdose with zoledronic acid injection is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcemia, reversal may be achieved with supplemental oral calcium and vitamin D and/or an infusion of calcium gluconate.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Zoledronic acid injection belongs to the class of nitrogen containing bisphosphonates and acts primarily on bone in order to protect the bone against excessive and abnormal osteoclastic and osteoblastic activity. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and, as with other bisphosphonates, localizes preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase (FPP) which is critical for the regulation of a variety of cell processes important for osteoclast function, but this does not exclude other inhibitory mechanisms. In vitro assays have demonstrated that zoledronic acid has the highest potency to inhibit FPP synthase amongst available nitrogen containing bisphosphonates. This higher inhibition of FPP synthase correlated with a greater anti-resorptive potency as observed *in vivo* in rats. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Pharmacodynamic effects

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralization or mechanical properties of bone. Histomorphometric data from long-term rat and monkey studies showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclastic activity and in activation frequency of new remodeling sites in both trabecular and haversian bone. Continuing bone remodeling was observed in bone samples from all

animals treated with clinically relevant doses of zoledronic acid. There was no evidence of a mineralizing defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Bone histology and bone markers

- *Paget's disease*

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with zoledronic acid injection. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect. These results were consistent with biochemical marker evidence of normalization of bone turnover.

Pharmacokinetics

Pharmacokinetic data in patients with postmenopausal osteoporosis, osteoporosis and Paget's disease of bone are not available.

Distribution: Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid 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} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post infusion, and an estimated terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36 , respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 43-55% at 50 ng/mL, a concentration of zoledronic acid within the range observed after 15 minute infusion of the 5 mg dose. It was only slightly less (about 43%) at 500 ng/mL a concentration of zoledronic acid greater than the expected C_{max} . Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Metabolism: Zoledronic acid is not metabolized in humans. It was found to have little or no capacity as a direct acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes. Therefore, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolized via the cytochrome P450 enzyme systems. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney.

Excretion: In 64 patients, on average $39 \pm 16\%$ (\pm SD) of the administered zoledronic acid dose was recovered in the urine within 24 hours with only trace amounts of drug found in urine after 48 hours. The cumulative percentage 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, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma

concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h (\pm SD).

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study with patients, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid plasma concentration at the end of the infusion ([mean \pm SD] 403 ± 118 ng/mL vs. 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs. 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations and Conditions

Pediatrics: Pharmacokinetic data of zoledronic acid in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients who ranged in age from 38 years to 84 years.

Gender: The pharmacokinetics of zoledronic acid were not affected by gender.

Race: The pharmacokinetics of zoledronic acid were not affected by race.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows no biotransformation, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid and no required dosage adjustment. Following an intravenous dose of 20 nCi ^{14}C -zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance =50 to 80 mL/min, N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance =30 to 50 mL/min, N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of ≥ 30 mL/min. Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, the risk is doubled at a creatinine clearance of 10 mL/min. Zoledronic acid injection is contraindicated in patients with severe renal impairment (creatinine clearance < 35 mL/min) due to an increased risk of renal failure in this population (see **CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS**). Zoledronic acid injection should be used with caution in patients with mild to moderate renal impairment.

STORAGE AND STABILITY

Store zoledronic acid injection at room temperature between 15°C-30°C. The zoledronic acid injection vial is for single use only. Zoledronic acid injection should be used immediately and the entire volume in the vial should be administered. Any unused solution should be discarded.

SPECIAL HANDLING INSTRUCTIONS

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

- Solution does not need to be diluted before administration.
- Strict adherence to the intravenous route is recommended for the parenteral administration of zoledronic acid injection.
- The entire volume in the vial should be administered.

Compatibility

- Zoledronic acid injection must not be allowed to come in contact with any calcium- or other divalent cations-containing solutions, and it should be administered as a single dose through a separate vented infusion line.
- Zoledronic acid injection is considered to be compatible with the typical vented infusion line materials polyvinylchloride (PVC), polyurethane (PUR) and polyethylene (PE).

DOSAGE FORMS, COMPOSITION AND PACKAGING

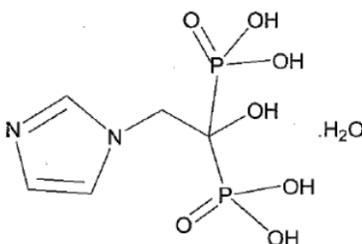
Zoledronic acid injection 5 mg/100 mL is available as a ready-to-use solution for intravenous infusion (sterile solution at a pH between 6.0 to 7.0). Each mL contains 0.05 mg zoledronic acid (zoledronic acid monohydrate), 49.50 mg of mannitol, 0.30 mg of sodium citrate dihydrate, and water for injection. Zoledronic acid injection 5 mg solution for intravenous infusion is filled in 100 ml, Tubular, Type - I, Flint glass vial stoppered with 32 mm chlorobutyl grey colored rubber stopper and sealed with 32 mm flip off seal. The drug product vials comes with a convenient plastic hanger to facilitate the infusion set-up.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Common name:	Zoledronic acid monohydrate
Chemical name:	1-Hydroxy-2-(1-imidazol) ethylene-1, 1-diphosphonic acid monohydrate
Molecular formula:	$C_5H_{10}N_2O_7P_2 \cdot H_2O$
Molecular weight:	290 g/mol
Structural formula:	



Physicochemical properties:

Description:	White to almost white crystalline solid
Solubility:	Sparingly soluble in 0.1N Sodium hydroxide solution
pH:	The pH of a 0.7% aqueous solution of zoledronic acid monohydrate in water is between 1.5 and 2.5

CLINICAL TRIALS

Prevention of postmenopausal osteoporosis

Study demographics and trial design

The efficacy and safety of zoledronic acid injection in the prevention of osteoporosis in postmenopausal women were assessed in a 2-year randomized, multicenter, double-blind, placebo-controlled study of 581 postmenopausal women aged 45 years and older. Women were stratified by years since menopause into two strata; Stratum I women < 5 years from menopause (n=224) and Stratum II women > 5 years from menopause (n=357).

At the baseline visit, women in both Strata I and II were randomized to one of three treatment groups:

- Zoledronic acid injection 5 mg i.v. given as a single dose at randomization and placebo given at Month 12 (n=70 in Stratum I and n=111 in Stratum II)
- Zoledronic acid injection 5 mg i.v. given annually at randomization and at Month 12 (n=77 in Stratum I and n=121 in Stratum II)
placebo given at randomization and at a Month 12 (n=77 in Stratum I and n=125 in Stratum II)

Zoledronic acid injection was administered as a 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline. Women were Caucasian (94% in Stratum I and 92% in Stratum II) and had osteopenia (lumbar spine BMD T-score -1.0 to -2.5 and femoral neck BMD T-score greater than -2.5).

Table 5: Summary of patient demographics in the Prevention of postmenopausal osteoporosis study

Study #	Trial design	Dosage, route of administration and duration	Study subjects		Mean age (Range)		Gender Male/ Female (N= randomized patients)
			Zoledronic acid injection	Placebo	Zoledronic acid injection	Placebo	
N2312	Randomized, double-blind, stratified placebo-controlled parallel group efficacy/safety study	Single dose of 5 mg Zoledronic acid /100 mL over 15 min (or placebo infusion) per 12 months Duration: 24 months	Stratum I: ZOL 2x5 mg N = 77 Stratum II: ZOL 2x5 mg N = 121 ZOL 1x5 mg N = 111	N = 202 Stratum I: N = 77 Stratum II: N = 125	Stratum I: ZOL 2x5 mg 53.6 (46.0 – 63.0) Stratum II: ZOL 1x5 mg 53.7 (46.0 – 65.0) Stratum II: ZOL 2x5 mg 63.9 (46.0 – 78.0) ZOL 1x5 mg 63.4 (47.0 – 83.0)	Stratum I: 54.4 (45.0 – 68.0) Stratum II: 64.2 (46.0-81.0)	581 (0 % male/ 100% female)

Study Results

Effect on Bone Mineral Density (BMD)

Zoledronic acid injection significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Treatment with zoledronic acid injection given as a single dose at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, treatment with a single dose of zoledronic acid injection resulted in 6.3% increase in lumbar spine BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months relative to placebo (both $p < 0.0001$). Similar increases in lumbar spine BMD were observed in both Strata when zoledronic acid was administered annually. There was no significant difference seen in either Stratum for the percent increase from baseline in lumbar spine BMD over 24 months relative to placebo when zoledronic acid was administered either as a single dose or annually.

Table 6: Between-treatment comparison for percentage change in lumbar spine BMD at Month 24 (LOCF) relative to baseline, by stratum (ITT population)

Treatment	n	LSM	Pair-wise treatment comparison	LSM difference	95% CI of difference⁽¹⁾	p-value (2)
Stratum I						
ZOL 1x5 mg	70	4.03	ZOL 1x5 mg - placebo	6.27	5.15, 7.39	<0.0001
Placebo	77	-2.24				
Stratum II						
ZOL 1x5 mg	111	4.76	ZOL 1x5 mg - placebo	5.41	4.46, 6.36	<0.0001
Placebo	125	-0.65				

LSM = least squares mean, CI = confidence interval

Stratum I: women < 5 years from menopause, Stratum II: women \geq 5 years from menopause

(1) 95% confidence interval is calculated based on a t-distribution.

(2) p-value is obtained from ANOVA with treatment and pooled country as explanatory variables.

Treatment with a single dose of zoledronic acid injection significantly increased BMD at 24 months relative to placebo at other bone sites including total hip, femoral neck, trochanter, and distal radius.

Table 7: Effects of zoledronic acid injection on bone mineral density of the total hip, femoral neck, trochanter, and distal radius (ITT population), at 24 months, by stratum, for zoledronic acid 5 mg vs. placebo

Stratum	Location	Zoledronic Acid Injection n LS Mean (SE)	Placebo n LS Mean (SE)	LS Mean difference (95% CI) ¹	p-value
Stratum I					
	Total hip	58 2.55 (0.317)	71 -2.10 (0.293)	4.65 (3.86, 5.43)	<0.0001
	Femoral neck	58 2.01 (0.549)	71 -1.55 (0.508)	3.56 (2.20, 4.92)	<0.0001
	Trochanter	58 4.51 (0.449)	71 -1.93 (0.415)	6.44 (5.32, 7.55)	<0.0001
	Distal radius	57 -0.27 (0.424)	71 -3.23 (0.384)	2.96 (1.92, 4.00)	<0.0001
Stratum II					
	Total hip	97 2.11 (0.282)	115 -1.04 (0.265)	3.16 (2.40, 3.91)	<0.0001
	Femoral neck	97 1.46 (0.366)	115 -1.18 (0.343)	2.65 (1.67, 3.62)	<0.0001
	Trochanter	97 3.97 (0.372)	115 -0.65 (0.348)	4.62 (3.63, 5.61)	<0.0001
	Distal radius	96 -0.13 (0.336)	112 -1.85 (0.317)	1.72 (0.82, 2.61)	0.0002

n: number of patients

LS : Least Squares

SE: Standard Error

¹ 95% CI computed from three-way ANOVA model with treatment, geographical region, and gender as factors

Paget's disease of bone

Study demographics and trial design

Zoledronic acid 5 mg was studied in male (approximately 70%) and female (approximately 30%) patients aged above 30 years with primary mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6-3.0 times the upper limit of the age-specific normal reference range at the time of study entry). Diagnosis of Paget's disease of bone was confirmed by radiographic evidence.

The efficacy of one infusion of zoledronic acid injection versus oral daily doses of 30 mg risedronate for 2 months was demonstrated in two, 6-month, double-blind, active-controlled comparative clinical trials. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of six months. SAP excess was defined as the difference between the measured level and midpoint of normal range. The normal laboratory reference range for SAP is 31-110 U/L for females and males between 20-58 years, and 35-115 U/L for females and males >58 years.

Table 8: Summary of patient demographics for clinical trials in Paget’s disease of bone

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N= population treated)	Mean age (Range)		Gender Male/Female n (%)
				Zoledronic Acid Injection	RIS	
2304	international, randomized, double-blind, safety and efficacy trials	One dose of 5 mg zoledronic acid injection/100 mL over 15 min (or placebo infusion) or 30 mg oral risedronate o.d. for 2 months (or placebo capsules). Duration: 6 months	Zoledronic Acid Injection: N = 89	70.4 (42.0 –94.0)	72.1 (44.0 – 87.0)	Zoledronic Acid Injection: 62 (68.9)/ 28 (31.1) RIS: 61 (74.4)/ 21 (25.6)
RIS: N = 82			≥65 years: 65 (72.2)	≥65 years: 65 (79.3)		
2305			Zoledronic Acid Injection: N = 88	71.3 (45.0 – 92.0)	68.2 (34.0 – 88.0)	Zoledronic Acid Injection: 62 (67.4)/ 30 (32.6) RIS: 57 (61.3)/ 36 (38.7)
			RIS: N = 90	≥65 years: 71 (77.2)	≥65 years: 64 (68.8)	

Study results

In both trials, zoledronic acid injection demonstrated a significantly greater and more rapid therapeutic response compared with the active comparator risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of bone formation (SAP, serum N- terminal propeptide of type I collagen (P1NP)) and bone resorption (serum CTx 1 (cross-linked C-telopeptides of type I collagen) and urine α-CTx). In the Paget’s trials, zoledronic acid injection reduced the bone markers to the normal laboratory reference ranges (see Table 9).

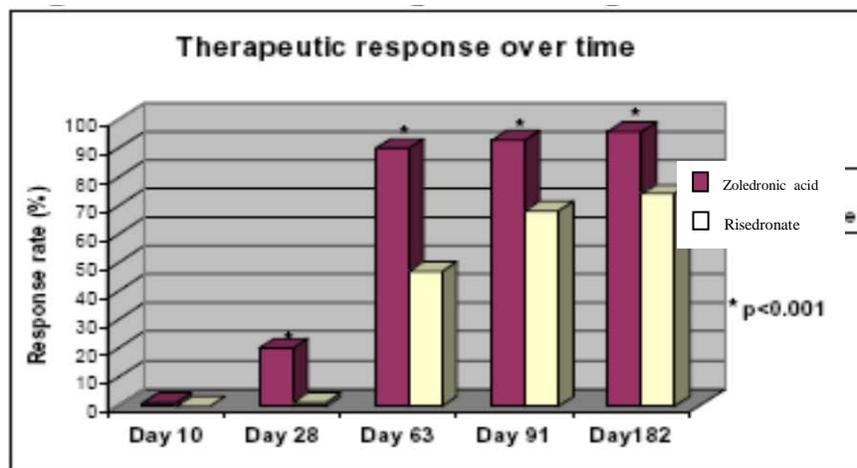
Table 9: Combined study results in the Paget’s disease of bone

Primary Endpoints	Zoledronic Acid Injection 5 mg	Risedronate 30mg	p-value
Primary efficacy variable Proportion of therapeutic responders at 6 months	96% (169/176)	74% (127/171)	< 0.001
SAP Normalization	89% (156 /176)	58% (99/171)	< 0.0001
Secondary efficacy variables			
<i>Bone Turnover Markers</i>			

Comparison for log serum CTx ratio at Day 10	0.09	0.50	< 0.001
Comparison for log urine α -CTx ratio at Day 10	0.05	0.54	< 0.001
Comparison for log SAP ratio at Day 28	0.49	0.71	< 0.001
<i>Responders</i>			
Proportion of subjects who achieved normalization at Day 28	7% (13/176)	1% (1/170)	< 0.001
Time to first therapeutic response (mean/median days)	62.8/64	100.6/89	< 0.001

At 6 months (182 days), combined data from both trials showed that 96.0% (169/176) of zoledronic acid injection-treated patients achieved a therapeutic response as compared with 74.3% (127/171) of patients treated with risedronate ($p < 0.001$) (see Figure 1). In addition, at 6 months, 88.6% (156/176) of zoledronic acid injection-treated patients achieved remission (normalization of SAP levels) compared to 57.9% (99/171) of patients treated with risedronate ($p < 0.0001$) (see Figure 2).

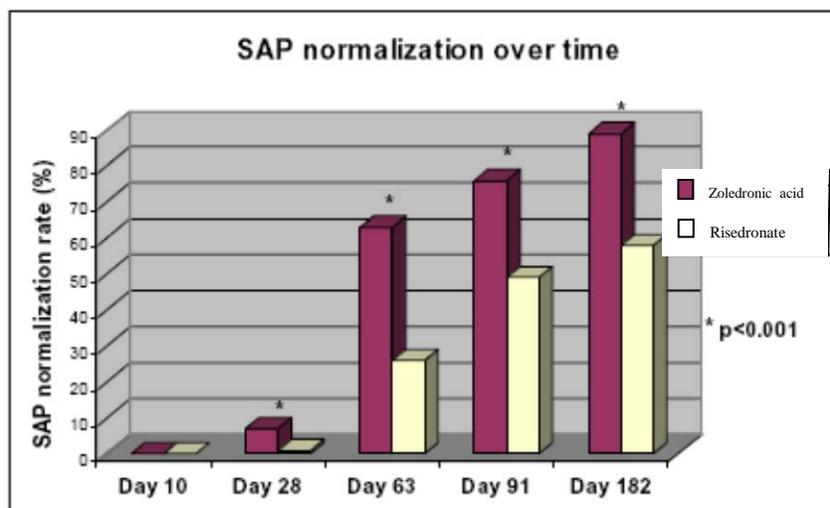
Figure 1 Therapeutic response



Therapeutic response over time:

Visit *n/N (proportion)*: Day 10: Zoledronic acid injection* 2/165 (0.01); RIS 0/165 (0.00); Day 28: Zoledronic acid injection* 35/176 (0.20); RIS 2/170 (0.01); Day 63 zoledronic acid injection* 158/176 (0.90) RIS 81/171 (0.47); Day 91 zoledronic acid injection* 163/176 (0.93) RIS 116/171 (0.68); Day 182 zoledronic acid injection* 169/176 (0.96) RIS 127/171 (0.74).

Figure 2 SAP normalization over time



SAP normalization overtime:

Visit n/N (proportion): Day 10: Zoledronic acid injection* 0/165 (0.00) RIS 0/165 (0.00); Day 28 : Zoledronic acid injection* 13/176 (0.07) RIS 1/170 (0.01); Day 63 Zoledronic acid injection* 111/176 (0.63) RIS 45/171 (0.26); Day 91 Zoledronic acid injection* 134/176 (0.76) RIS 83/171 (0.49); Day 182 Zoledronic acid injection* 156/176 (0.89) 99/171 (0.58).

Onset of action

Zoledronic acid injection treatment results in a more rapid treatment response than treatment with risedronate. The median time to therapeutic response was significantly faster (64 days) for zoledronic acid compared to risedronate-treated patients (89 days) (see Table 10).

Table 10: Time to first therapeutic response (Intent-to-treat patients)

Treatment	Mean (median) days	N	Number of Responders	P-value ⁽¹⁾
Zoledronic Acid Injection	62.8 (64)	182	169	<0.0001
Risedronate	106.6 (89)	175	131	---

A therapeutic response is defined as normalization of SAP or a reduction of $\geq 75\%$ from baseline in SAP excess. N is the number of patients

¹ P-value is calculated from the Wald test of the Cox proportional hazards regression model.

Therapeutic response by disease factor

The therapeutic response to zoledronic acid was similar across all demographic and disease severity groups (gender, age, previous bisphosphonate use, and disease severity). At 6 months, in each of the baseline disease severity subgroups (baseline SAP $< 3 \times \text{ULN}$, $\geq 3 \times \text{ULN}$) the percentage of zoledronic acid injection-treated patients who achieved therapeutic response was 96.7% and 95.3% compared to risedronate-treated patients at 74.7% and 73.6%, respectively both at $p < 0.0001$ (see Table 11).

In patients who had previously received treatment with oral bisphosphonates, a significantly greater therapeutic response was observed with zoledronic acid injection (96.4%) relative to risedronate (55.0%) ($p < 0.0001$). In patients naïve to previous treatment, a greater therapeutic response was also observed with zoledronic acid injection (97.6%) relative to risedronate (85.5%) ($p = 0.0075$) (see Table 11).

Table 11: Proportion of patients who achieved therapeutic response at 6 months by disease factors

Subgroup	Zoledronic Acid Injection n/N (Proportion)	Risedronate n/N (Proportion)	p-value ¹ for treatment difference
Baseline SAP			
< 3xULN	87/90 (0.97)	74/99 (0.75)	<0.0001
≥ 3xULN	82/86 (0.95)	53/72 (0.74)	<0.0001
Last Paget's therapy			
Oral bisphos.	53/55 (0.96)	33/60 (0.55)	<0.0001
IV bisphos.	22/25 (0.88)	21/26 (0.81)	0.4590
Clodronate	6/6 (1.00)	2/2 (1.00)	NA
Others	8/8 (1.00)	6/7 (0.86)	0.2733
No previous therapy	80/82 (0.98)	65/76 (0.86)	0.0075
Symptomatic pain at screening			
No	60/60 (1.00)	54/66 (0.82)	0.0006
Yes	109/116 (0.94)	73/105 (0.70)	<0.0001

SAP = serum alkaline phosphatase. ULN = upper limit of normal.

A therapeutic response is defined as normalization of SAP or a reduction of $\geq 75\%$ from baseline in SAP excess. N=number of patients with baseline and at least one post-baseline SAP measurements.

n = number of patients with therapeutic response at visit.

¹p-value is based on a Mantel-Haenszel test controlling for study for each category.

The relative change in SAP at Day 28 (the third of seven secondary efficacy variables in the closed testing procedure) for the combined pivotal trials demonstrated a statistically significant reduction relative to baseline for zoledronic acid compared to risedronate ($p < 0.001$). The statistically significant reduction in SAP for zoledronic acid injection compared to risedronate was also demonstrated at Days 10, 63, 91, and 182 in the extended observation period.

Extended observation period

Paget's disease of bone: Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended observation period. Since a larger population of zoledronic acid injection-treated patients achieved therapeutic response, a larger number of patients in the zoledronic acid injection group (N=153) entered the extended observation period compared to the risedronate group (N=115).

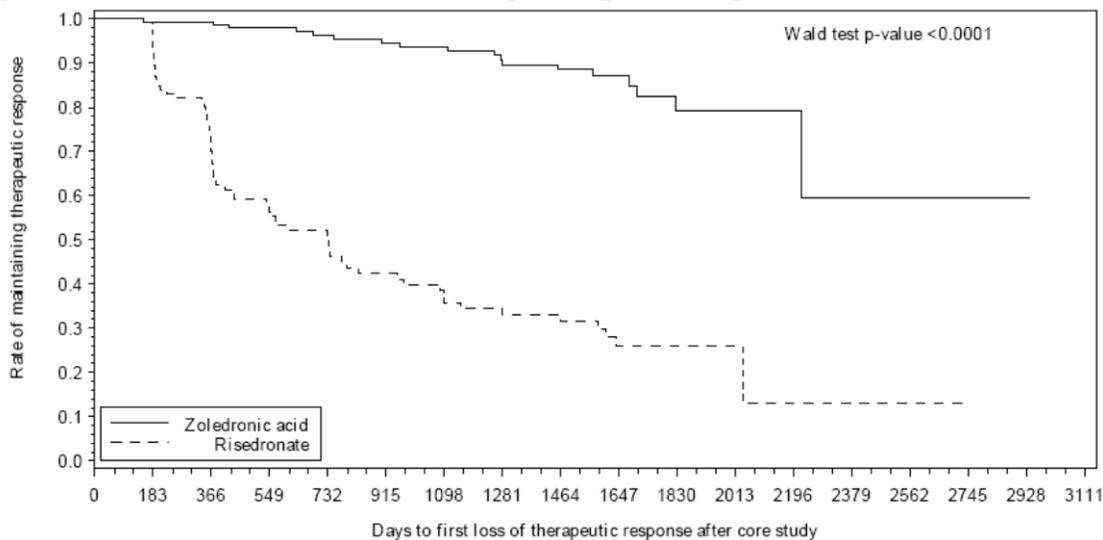
After a mean duration of follow-up of 3.8 years from the initial time of dosing, the proportion of patients ending the Extended Observation Period due to the need for re-treatment (clinical judgment) was higher for risedronate (48 patients, or 41.7%) compared with zoledronic acid (11 patients, or 7.2%). The

Kaplan-Meier model estimated mean time of ending the Extended Observation Period due to the need for Paget's re-treatment from the initial dose was longer for zoledronic acid (7.7 years) than for risedronate (5.1 years).

The cumulative rate of maintaining therapeutic response in the extended follow-up period is displayed in Figure 3.

Six patients who achieved therapeutic response 6 months after treatment with zoledronic acid injection, and later experienced disease relapse during the extended follow-up period, were re-treated with zoledronic acid injection after a mean time of 6.5 years from initial treatment to re-treatment. Five of these six patients had SAP within the normal range at Month 6 (Last Observation Carried Forward, LOCF) (83.3%, 95% CI: 35.9%, 99.6%).

Figure 3 Cumulative rate of maintaining therapeutic response over time



Time to first loss of therapeutic response: the occurrence of an SAP level that no longer meets the criteria of a therapeutic response (less than 75% reduction in SAP excess and/or SAP above the upper limit of the normal range).

DETAILED PHARMACOLOGY

Bone safety studies

Dose-response and duration of action of a single intravenous injection of zoledronic acid (0.8–500 µg/kg) were investigated in ovariectomized (OVX) adult rats for 8 months after dosing, which corresponds to approximately 8 remodeling cycles over 2.7 years in humans. A single dose of zoledronic acid protected against ovariectomy-induced bone loss; both the magnitude and duration of the effect were dose-dependent. The two highest doses of 100 and 500 µg/kg significantly increased total bone mineral density, trabecular bone volume, trabecular number and connectivity density to levels above those of the sham-operated controls. Lower doses produced a weaker and less-prolonged effect. Mechanical testing at study termination showed a dose-dependent increase in bone strength to values above those of the sham-operated controls at the higher dose. Histomorphometric analysis and measurement of plasma osteocalcin levels confirmed that bone formation was present at

32 weeks post-injection even at the highest dose of 500 µg/kg. This dose in rats is approximately 3.4 fold higher than the 5 mg dose administered to a 50 kg patient.

In addition, two studies were performed in OVX rats (12-months treatment with 0.3, 1.5 and 7.5 µg/kg) and OVX rhesus monkeys (16-months treatment with 0.5, 2.5 and 12.5 µg/kg) using once-a-week subcutaneous injections. Zoledronic acid treatment dose-dependently prevented all the OVX-induced changes in bone mineral density, bone mechanics and biochemical markers of bone metabolism in serum and urine. Often full efficacy was achieved with the intermediate dose, whereas the low dose had either no or only a slight effect. Drug treatment was well tolerated, there were no clinically meaningful adverse events in either species. Static and dynamic histomorphometric analysis of bones from both of these experiments indicated that zoledronic acid dose-dependently prevented the changes induced by OVX in both trabecular and haversian bone. Moreover, there was no indication of any abnormality in bone or marrow tissue, no evidence of a mineralizing defect, no accumulation of osteoid, and no woven bone. Except for its high anti-resorptive potency, the effect of zoledronic acid on bone was qualitatively similar to that published for other bisphosphonates. These results demonstrate bone safety in a laboratory rodent and a non-human primate species with a more frequent dosing regimen, and a 5-to-8 fold higher total yearly dose (based on 5 mg human dose), than the planned once a year dosing in humans. Overall, the results provide preclinical evidence for the efficacy and bone safety of zoledronic acid.

TOXICOLOGY

Acute Toxicity

Table 12: Acute Toxicology

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: compound-related renal tubular lesions LD ₅₀ = 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: clinical signs, mortality after 6 days, intestinal hemorrhage
Mouse	s.c.	10,50	10 mg/kg: no clinical signs 50 mg/kg: mortality, clinical signs LD ₅₀ = 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, where the kidney was identified as a target organ.

Subacute and Chronic Toxicity

Table 13: 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 day (every third for 18 days)	≥ 0.06 mg/kg: local irritation, pharmacol bone changes ≥ 0.6 mg/kg: gastric lesions 3.2 mg/kg: mortality, clin signs; ↓ BW/FC, clin lab alterations, ↑ adrenal, kidney, liver wghts, 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, 0.1→0.2	≥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; pharmacol. bone changes ≥ 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. Pharmacologic bone changes. 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, pharmacological bones changes. 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	Mou se	p.o.	0, 0.3, 3, 10, 30→20	0.3 – 30→20 mg/kg: mortality; respiratory signs; ↓ FC; pharmacologic bone changes 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 recov.	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 recov.	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.	1→30, 10 (for 9d); 30 (for 10d) ^a	1→30 mg/kg: clin. signs; micro findings in kidneys, esophagus, liver; pharmacol bone changes. 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. Recov	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

Table 14: Reproductive Toxicity Studies

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: ↓ maternal BW. 9/10 dams with total resorption (embryo/fetal death) of progeny; remaining dam w/ only 2 fetuses (one with cleft palate).
Segment II	Rat	s.c.	0.1, 0.2, 0.4	≥ 0.2 mg/kg: ↓ maternal BW; ↓ fetal 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 fetuses; some fetuses with edema, cleft palate, short lower jaw, abnormal ossification
Segment II range- finding (non- pregnant)	Rabbit	s.c.	0.2,0.6,2	0.6 or 0.2 mg/kg suitable doses for main study.
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: ↓ fetal wgt; no signs of abnormal fetal development.
Segment II	Rabbit	s.c.	0,01, 0.03, 0.1	Maternal toxicity at 0.01 mg/kg due to ↓ blood calcium. No embryo/fetotoxicity or teratogenicity.

Adverse maternal effects were associated with drug-induced hypocalcemia.

Carcinogenesis

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥ 0.002 times the anticipated human intravenous dose, based on a comparison of relative body surface areas). These increases were not considered to be related to zoledronic acid administration as their occurrence lacked a dose response and the incidences were within the historical control range for animals of this age and strain in the testing facility. Moreover these neoplasms are not biologically relevant as the Harderian gland is a unique, highly specialized organ which is not present or known to have any correlate in the human. Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed.

Table 15: Carcinogenesis

Species	Route	Doses	Findings
Mouse	p.o.	0.1,0.3,1.0	≥ 0.1 mg/kg: nonproliferative hyperostosis ≥ 0.3 mg/kg: \downarrow BW
Rat	p.o.	0.1,0.5,2.0	≥ 0.1 mg/kg: nonproliferative hyperostosis ≥ 0.5 mg/kg: \downarrow BW,FC 2.0 mg/kg: \uparrow extramedullary hematopoiesis

In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential.

Mutagenesis

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Table 16: Mutagenesis

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

^a Bacterial test systems (*S. typhimurium*), with/without metabolic activation.

^bBatch control

^cBacterial 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.

Impairment of Fertility:

Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

REFERENCES

1. 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.
2. 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.
3. 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 bisphosphonate zoledronate in Paget's disease. *Arthritis Rheum* 1998; 41: 354-360.
4. 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.
5. 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.
6. 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.
7. Body JJ, Diel I, Bell R. Profiling the safety and tolerability of bisphosphonates. *Semin Oncol*. 2004 Oct;31(5 Suppl 10):73-8.
8. Reid IR, et al. Intravenous zoledronic acid in post menopausal women with low bone mineral density. *N Engl J Med* 2002; 346:653-661.
9. Hornby SB, Evans GP, Hornby SL, Pataki A, Glatt M, Green JR. Long-Term Zoledronic Acid Treatment Increases Bone Structure and Mechanical Strength of Long Bones of Ovariectomized Adult Rats. *Calcif Tissue Int* 2003; 72:519-527.
10. Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, Mesenbrink P, Su G, Pak J, Zelenakas K, Luchi M, Richardson P, Hosking D. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med*. 2005 Sep 1;353(9):898-908.
11. Rogers MJ. New insights into the molecular mechanism of action of bisphosphonates. *Curr Pharmaceut Design* 2003; 9 (32):2643-2658
12. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, Rojers MJ. Structure-Activity Relationships for inhibition of Farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing

bisphosphonates. *J Pharmacol Exper Ther* 2001; 296(2):235-242.

13. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis (HORIZON Pivotal Fracture Trial). *N Engl J Med.* 2007; 356(18):1809-22.
14. Lyles KW, Colòn-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture. *N Engl J Med.* 2007;Sept 17, [Epub ahead of print].
15. Reid DM, Devogelaer J-P, Saag K, Roux C, Lau C-S, Reginster J-Y, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomized controlled trial. *Lancet* 2009; 373: 1253–63.
16. PRODUCT MONOGRAPH ACLASTA (zoledronic acid) 5 mg/100 mL injection can be found at www.novartis.ca Last revised: September 11, 2014.

PART III: CONSUMER INFORMATION

**Pr
ZOLEDRONIC ACID INJECTION**

5 mg/100 mL zoledronic acid
(as zoledronic acid monohydrate)

This leaflet is part III of a three-part "Product Monograph" published when zoledronic acid 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 injection. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

Zoledronic acid injection is only approved to be used once for prevention of postmenopausal osteoporosis.

What is Zoledronic Acid Injection used for?

Zoledronic acid injection is used:

- In the prevention of osteoporosis in postmenopausal women with low bone mass, given as a single treatment.
- In the treatment of Paget's disease, given as a single treatment.

What it does

Zoledronic acid injection contains zoledronic acid which is a member of a class of substances called Bisphosphonates.

Zoledronic acid injection binds specifically to bone and it does not stay in your blood. Zoledronic acid injection slows down bone resorption (caused by osteoclasts) which allows the bone-forming cells (osteoblasts) time to rebuild normal bone.

What is osteoporosis?

Osteoporosis is a disease that involves the thinning and weakening of the bones, which is common in women after the menopause and may also occur in men.

What is Paget's disease of bone?

In Paget's disease, bone breaks down too much and the new bone made is not normal. If Paget's disease is not treated, bones like the skull, spine, and legs become deformed and weaker than normal. This can cause problems like bone pain and arthritis. The bones can also break easily. Paget's disease of bone sometimes runs in families. Paget's disease may be discovered by X-ray examination or blood tests.

When should zoledronic acid injection not be used? You should not be treated with zoledronic acid injection if you:

- Have low calcium levels in your blood (*Hypocalcemia*) or vitamin D deficiency
- If you have severe kidney problems
- Are pregnant or plan to become pregnant.
- Are breast-feeding.
- Are allergic (*hypersensitive*) to zoledronic acid or any of the other ingredients of zoledronic acid injection or any other bisphosphonate

What is the medicinal ingredient?

zoledronic acid.

What are the important nonmedicinal ingredients?

Mannitol, sodium citrate dihydrate, water for injection.

What dosage form does it come in?

Zoledronic acid injection 5 mg/100 mL is a solution for intravenous infusion and it comes in a 100 mL glass vial. Each 100 mL solution contains 5 mg of zoledronic acid.

WARNINGS AND PRECAUTIONS

Be sure that you have discussed zoledronic acid injection treatment with your doctor.

If you are being treated with another intravenous form of zoledronic acid, you should not be treated with zoledronic acid injection.

If you are being treated with zoledronic acid injection, you should not be treated with other bisphosphonates (such as alendronate, risedronate, clodronate, etidronate, ibandronate and pamidronate) at the same time.

BEFORE you take zoledronic acid injection talk to your doctor or pharmacist if you:

- Are unable to take daily calcium and/or vitamin D supplements
- Are pregnant or plan to become pregnant.
- Are breast-feeding.
- Have kidney problems. Worsening of kidney function, including kidney failure may happen when you take zoledronic acid injection.
- Had some or all of your parathyroid glands or thyroid gland surgically removed
- Had sections of your intestine removed
- Need any dental procedures such as a root canal or tooth extraction (this does not include regular dental cleaning). Your doctor may possibly request a dental examination with any necessary preventive dentistry carried out prior to treatment with zoledronic acid injection. You should continue regular dental cleanings and practice good oral hygiene.
- Have rapid and irregular heart beat
- Have a sudden headache, numbness in your face or limbs, particularly down one side of your body; experience confusion and have trouble talking or understanding what is being said to you; have vision problems, and trouble walking or keeping your balance.
- Have asthma from taking ASA (acetylsalicylic acid such as Aspirin®)
- Have any pain in your hip, groin, or thigh. Zoledronic acid injection can cause unusual fractures in the thigh bone.

Zoledronic acid injection is not recommended for patients under 18 years of age.

IMPORTANT PLEASE READ

Zoledronic acid injection is to be given by intravenous infusion in no less than 15 minutes.

INTERACTIONS WITH THIS MEDICATION

Tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including any you have bought without a prescription. It is especially important for your doctor to know if you are taking :

- any medicines known to be harmful to your kidneys (such as nonsteroidal anti-inflammatory drugs (NSAIDs)).
- water pill (diuretics)
- aminoglycoside antibiotics (a type of medicine used to treat severe infections).

Can I continue my daily activities? After your zoledronic acid injection infusion, there is no restriction on your normal activities such as standing, sitting, taking a walk or exercising.

PROPER USE OF THIS MEDICATION

How is Zoledronic Acid Injection given?

Zoledronic acid injection is given as an infusion into a vein for 15 minutes by your doctor or nurse.

Your doctor will ask you to drink at least two glasses of water (500 mL or 2 cups) before and after the treatment.

Usual dose:

For prevention of Osteoporosis: 5 mg given as single dose.

For Paget's disease: 5 mg given as single dose.

Zoledronic acid injection may work for longer than one year, and your doctor will let you know if you need to be treated again

The infusion nurse or doctor may ask you to stay for a short period of time after the infusion.

It is very important to take calcium and vitamin D supplements as directed by your doctor to reduce the possibility of having low blood calcium levels, to prevent loss of bone and to help rebuild bone.

Overdose

If you think you have taken too much Zoledronic acid injection, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, zoledronic acid injection may have some unwanted side effects in addition to its beneficial effects.

The most common side effects
Post-dose symptoms include:

- Fever
- Fatigue
- Chills
- Malaise (unwell feeling)
- Bone, joint and/or muscle pain or stiffness
- Headache
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea
- Back pain
- Pain in extremity
- Influenza-like illness
- Weakness
- Pain
- Shortness of breath
- Dizziness
- Excessive sweating
- Tiredness
- Disturbed digestion
- Decreased appetite
- Non-cardiac chest pain

Other side effects:

- Low blood calcium (hypocalcemia) the symptoms include) numbness or tingling sensations (especially in the area around the mouth) or muscle spasms. Contact your doctor immediately if you notice any of these symptoms after your zoledronic acid injection treatment.
- Allergic reactions such as itchy rash and swelling mainly of the face and throat.
- Increased or irregular heartbeat
- Rheumatoid arthritis/arthritis (inflammation of the joints)
- Urinary tract infection
- Constipation
- High blood cholesterol levels
- Pain in jaw
- Pain in neck
- Joint sprain
- Post-traumatic pain
- Cough
- Congestion of the nose
- Pharyngolaryngeal pain (pain at the back of the mouth and in the voice box)

IMPORTANT PLEASE READ

- Seasonal allergy
- Vaginal dryness
- Sciatica (pain in the leg caused by injury to or compression of sciatic nerve)
- Hypoesthesia (reduced sense of touch)
- Rare cases of dehydration
- Persistent post-dose symptoms
- Jaw bone problems: rarely, patients have jaw problems associated with delayed healing and infection, often following tooth extraction
- Very rare cases of low blood pressure
- Very rare cases of unusual fractures in a specific part of the thigh bone. If you develop new or unusual pain in the thigh or groin, contact your doctor.

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

Symptom / effect		Talk with your healthcare professional or pharmacist	
		Only if severe	In all cases
Common	<i>Post-dose symptoms:</i> fever, chills, fatigue, pain, malaise	√	
	Bone, joint, and/or muscle pain or stiffness		√
	Headache	√	
	Nausea, vomiting, diarrhea, abdominal pain	√	
	Shortness of breath	√	
	Dizziness	√	
	Excessive sweating	√	
	Rash	√	
Uncommon	Tiredness, weakness, lethargy	√	
	<i>Low blood calcium (hypocalcemia):</i> numbness, tingling sensation (especially in the area around the mouth), muscle spasms		√
	Rapid and irregular heartbeat, palpitations	√	

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

Symptom / effect		Talk with your healthcare professional or pharmacist	
		Only if severe	In all cases
	A sudden headache, numbness in your face or limbs, particularly down one side of your body; experience confusion and have trouble talking or understanding what is being said to you; have vision problems, and trouble walking or keeping your balance		
	Kidney failure (weakness, tiredness, loss of appetite, puffy eyes, hands and feet, changes in urine color or absence of urine production, changes in kidney function laboratory tests)		√
	Eye disorder (Eye pain, light sensitivity, eye redness, decreased vision, eye inflammation)		√
	Skin reactions (redness, swelling and/or pain) at the infusion site	√	
Rare	<i>Osteonecrosis of the jaw:</i> (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		√

IMPORTANT PLEASE READ

If you have questions about these side effects, talk to your doctor.

This is not a complete list of side effects. For any unexpected effects while taking zoledronic acid injection, contact your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM			
Symptom / effect		Talk with your healthcare professional or pharmacist	
		Only if severe	In all cases
	the mouth, teeth or jaw, swelling or gum infections, bad breath)		
Very rare	Difficulty breathing with wheezing or coughing in asthma patients who are allergic to ASA	√	
	<i>Avascular necrosis (osteonecrosis) of the hip or knee</i> : poor blood supply to an area of bone leading to bone death: bone pain, joint pain, muscle spasms, joint stiffness	√	
	Failure of broken bone to heal (<i>non-union</i>) or broken bone taking longer than usual to heal (<i>delayed union</i>): persistent pain at the fracture site, no or slow progress in bone healing on imaging tests.	√	
	Severe allergic reactions (rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing, loss of conscious due to shock (dangerously low blood pressure)		√
	Thigh or groin pain		√

HOW TO STORE IT

Store zoledronic acid injection at room-temperature between 15°C-30°C.

Keep the original packaging unchanged and sealed until the doctor or the nurse administers zoledronic acid injection.

Remember to keep zoledronic acid injection and all medications safely away from children.

REPORTING SUSPECTED SIDE-EFFECTS

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at Med Effect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program
Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at MedEffect (<http://hc-sc.gc.ca/dhp-mps/medeff/index-eng.php>).

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.

IMPORTANT PLEASE READ

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting the sponsor,

DIN Owner:

Dr. Reddy's Laboratories Limited

Bachupally 500 090 - INDIA

1-855-845-1739

druginfo@drreddys.com

Imported By: **Innomar Strategies Inc.**

3470 Superior Court

Oakville, Ontario L6L 0C4

CANADA

Last Revised: October 30, 2014

