

Package Insert

1. Name of the medicinal product

Zolidin (Zoledronic Acid Injection 4 mg/5 ml)

2. Qualitative and quantitative composition

Each 5 ml contains:

Zoledronic acid monohydrate eq. to Zoledronic acid anhydrous 4 mg

For the full list of excipients, *see section 6.1.*

3. Pharmaceutical form

Concentrate for solution for infusion

Clear and colourless solution.

4. Clinical particulars

4.1 Therapeutic indications

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

4.2 Posology and method of administration

The Zolidin 4 mg/5 mL concentrate for solution for infusion should be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution before infusion (*see section 6.6 Special precautions for disposal and other handling*). The final Zolidin solution for infusion, should be given as an intravenous infusion of no less than 15 minutes.

Dosage regimen

Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy

In adults and elderly patients, the recommended Zoledronic acid dose is a 4 mg infusion given every 3 to 4 weeks.

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

Treatment of hypercalcemia of malignancy (HCM)

In adult and elderly patients, the recommended Zoledronic acid dose in hypercalcemia (albumin- corrected serum calcium ≥ 12.0 mg/dL or 3.0 mmol/L) is a single 4 mg infusion. Patients must be maintained well hydrated prior to and following administration of Zoledronic acid.

Treatment of patients with renal impairment

Patients with hypercalcemia with malignancy (HCM)

Zoledronic acid treatment in adult patients with hypercalcemia of malignancy (HCM) who also have severe renal impairment should be considered only after evaluating the risks and benefit of treatment. In the clinical studies, patients with serum creatinine >400 micromol/L or >4.5 mg/dL were excluded. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL (*see section 4.4 Special warnings and precautions for use*).

Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy.

When initiating treatment with Zoledronic acid, serum creatinine levels and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine levels using the Cockcroft-Gault formula. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr <30 mL/min. In clinical trials with Zoledronic acid, patients with serum creatinine > 265 micromol/L or > 3.0 mg/dL were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CrCl 30 to 60 mL/min, the following Zoledronic acid dose is recommended (*see section 4.4 Special warnings and precautions for use*).

Table 1

Baseline creatinine clearance (ml/min)	Zoledronic acid recommended dose*
> 60	4.0 mg
50-60	3.5 mg*
40-49	3.3 mg*
30-39	3.0 mg*

*Doses have been calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=75mL/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 mL/min.

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

- For patients with normal baseline serum creatinine (< 1.4 mg/dL), an increase of ≥ 0.5 mg/dL;
- For patients with an abnormal baseline creatinine (> 1.4 mg/dL), an increase of ≥ 1.0 mg/dL.

In the clinical studies, Zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (*see section 4.4 Special warnings and precautions for use*). Zoledronic acid should be resumed at the same dose as that prior to treatment interruption.

Method of administration

Intravenous use.

Zolidin 4 mg concentrate for solution for infusion, further diluted in 100 ml (*see section 6.6*), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced zoledronic acid doses are recommended (*see section "Posology" above and section 4.4*).

Instructions for preparing reduced doses of Zolidin

Withdraw an appropriate volume of the concentrate needed, as follows:

- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

For instructions on the dilution of zoledronic acid before administration, see section 6.6. The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

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

Patients must be maintained well hydrated prior to and following administration of zoledronic acid.

4.3 Contraindications

- Hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients listed in section 6.1
- Pregnancy and breast-feeding women (*see section 4.6*)

4.4 Special warnings and precautions for use

General

All patients, including patients with mild to moderate renal impairment, must be assessed prior to administration of Zoledronic acid to assure that they are adequately hydrated.

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

Standard hypercalcemia-related metabolic parameters, such as albumin-corrected serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating Zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary. Untreated hypercalcemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Zolidin contains the same active ingredient as in Aclasta[®] (zoledronic acid). Patients being treated with Zolidin should not be treated with Aclasta concomitantly. Zolidin should also not be given together with other bisphosphonates since the combined effects of these agents are unknown.

While not observed in clinical trials with Zoledronic acid, there have been reports of bronchoconstriction in acetylsalicylic acid sensitive asthmatic patients receiving bisphosphonates.

Renal insufficiency

Adult patients with HCM and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of continued treatment with Zoledronic acid outweighs the possible risk (*see section 4.2 Posology and method of administration*).

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

Bisphosphonates have been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid or other bisphosphonates as well as use of nephrotoxic drugs or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of Zoledronic acid 4 mg administered over no less than 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of Zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.

Serum creatinine levels should be measured before each Zoledronic acid dose. In patients with mild to moderate renal impairment at the initiation of Zoledronic acid treatment, lower doses are recommended in all adult patients except patients with HCM. In patients who show evidence of renal deterioration during treatment, Zoledronic acid should only be resumed

when creatinine level returns to within 10% of baseline value (*see section 4.2 Posology and method of administration*).

The use of Zoledronic acid is not recommended in patients with severe renal impairment because there are limited clinical safety and pharmacokinetic data in this population, and there is a risk of renal function deterioration in patients treated with bisphosphonates, including Zolidin. In clinical trials, patients with severe renal impairment were defined as those with baseline serum creatinine ≥ 400 micromol/L or ≥ 4.5 mg/dL for patients with HCM and ≥ 265 micromol/L or ≥ 3.0 mg/dL for all other patients, respectively.) In pharmacokinetic studies, patients with severe renal impairment were defined as those with baseline creatinine clearance <30 mL/min (*see section 5. Pharmacological properties, subsection 5.2 Pharmacokinetic properties, see section 4.2 Posology and method of administration*).

Hepatic insufficiency

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

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in adult cancer patients treated with bisphosphonates, including Zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).

Patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.

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

Osteonecrosis of other anatomical sites

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

Atypical fractures of the femur

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

pending evaluation of the patient, based on an individual benefit/risk assessment. Reports of atypical femoral fracture have been received in patients treated with Zoledronic acid; however causality with Zoledronic acid therapy has not been established.

During Zoledronic acid 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 (*see section 4.8 Undesirable effects*). The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when re-challenged with the same drug or another bisphosphonate.

Hypocalcemia

Hypocalcaemia has been reported in patients treated with Zoledronic acid. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcaemia. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when Zoledronic acid is administered with other hypocalcaemia causing drugs, as they may have a synergistic effect, resulting in severe hypocalcaemia (*see section 4.5*). Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

4.5 Interaction with other medicinal products and other forms of interaction

Anticipated interactions to be considered

Caution is advised when bisphosphonates like Zoledronic acid are administered with aminoglycosides or calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (*see section 4.4 Special warnings and precautions for use*).

Caution is indicated when Zoledronic acid is used with other potentially nephrotoxic drugs (*see section 4.8 Undesirable effects*).

Observed interactions to be considered

Caution is advised when Zoledronic acid is administered with anti-angiogenic drugs as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these drugs.

Absence of interactions

In clinical studies, Zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics (except for loop diuretics, see Anticipated interactions to be considered), antibiotics and analgesics without clinically apparent interactions occurring.

No dose adjustment for Zoledronic acid 4 mg is needed when coadministered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zoledronic acid 4 mg given as a 15- minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28).

Coadministration of thalidomide with Zoledronic acid did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro (*see section 5.2 Pharmacokinetic properties*), but no formal clinical interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

Risk Summary

Zoledronic acid should not be used during pregnancy (*see section 4.3 Contraindications*).

There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (*see section 4.3 Contraindications*) while receiving bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk has not been established.

Studies in rats have shown reproductive toxicological effects (*see section Non-clinical safety data*). The potential risk in humans is unknown.

Data

Human Data

There are no adequate and well-controlled studies of Zoledronic acid in pregnant women.

Animal Data

Teratogenicity studies were performed in two species, both via subcutaneous administration of zoledronic acid. In rats teratogenicity was observed at doses ≥ 0.2 mg/kg/day (2.4 fold the anticipated human exposure, based on AUC comparison) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats.

In rabbits no teratogenic or embryo/fetal effects were observed, although maternal toxicity was marked at 0.1 mg/kg/day. Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

Lactation

Risk summary

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid should not be used by breast-feeding women (*see section 4.3 Contraindications*).

Females and males of reproductive potential

Women of child-bearing potential should be informed of the potential hazard to the fetus and be advised to avoid becoming pregnant while receiving Zoledronic acid.

Infertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most serious adverse drug reactions reported in patients receiving Zoledronic acid in the approved indications are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute-phase

reaction, and hypocalcemia. The frequencies of these adverse reactions are shown in Table 2 or shown as adverse reactions from ‘Spontaneous reports and literature cases’ with ‘not known’ frequency.

Frequencies of adverse reactions for Zoledronic acid 4 mg are mainly based on data collected from chronic treatment. Adverse reactions to Zoledronic acid are usually mild and transient and similar to those reported for other bisphosphonates. Those reactions can be expected to occur in approximately one third of patients treated with Zoledronic acid.

Within three days after Zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including pyrexia, fatigue, bone pain, chills, influenza-like illness, arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection Description of selected adverse reaction). Cases of arthralgia and myalgia have been reported.

Very commonly, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels, which is asymptomatic not requiring treatment. Commonly, the serum calcium may fall to asymptomatic hypocalcemic levels.

Gastrointestinal reactions, such as nausea and vomiting have been commonly reported following intravenous infusion of Zoledronic acid. Uncommonly, local reactions at the infusion site, such as redness or swelling and/or pain were also observed.

Anorexia was commonly reported in patients treated with Zoledronic acid 4 mg. Rash or pruritus has been uncommonly observed.

As with other bisphosphonates, cases of conjunctivitis have been commonly reported.

Based on pooled analysis of placebo-controlled studies, severe anemia (Hb < 8.0 g/dL) was commonly reported in patients receiving Zoledronic acid.

Adverse reactions (Table 2) are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$).

Table 2 Adverse drug reactions from clinical trials

<i>Blood and lymphatic system disorders</i>	
Common:	Anaemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
<i>Immune system disorders</i>	
Uncommon:	Hypersensitivity reaction
Rare:	Angioedema
<i>Nervous system disorders</i>	
Common:	Headache
Uncommon:	Dizziness, dysgeusia, hypoaesthesia, hyperaesthesia, tremor
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
<i>Psychiatric disorders</i>	
Common:	Sleep disorder
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusional state

<i>Eye disorders</i>	
Common:	Conjunctivitis
Uncommon:	Blurred vision
Rare:	Uveitis, episcleritis
<i>Gastrointestinal disorders</i>	
Common:	Nausea, vomiting, decreased appetite, constipation
Uncommon:	Diarrhoea, abdominal pain, dyspepsia, stomatitis, dry mouth
<i>Respiratory, thoracic and mediastinal disorders</i>	
Uncommon:	Dyspnoea, cough
Rare:	Interstitial lung disease
<i>Skin and subcutaneous tissue disorders</i>	
Common:	Hyperhidrosis
Uncommon:	Pruritus, rash (including erythematous and macular rash)
<i>Musculoskeletal and connective tissue disorders</i>	
Common:	Bone pain, myalgia, arthralgia, generalised body pain, joint stiffness
Uncommon:	Muscle spasms, osteonecrosis of the jaw
<i>Cardiac disorders</i>	
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
<i>Vascular disorders</i>	
Common:	Hypertension
Uncommon:	Hypotension
<i>Renal and urinary disorders</i>	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
<i>General disorders and administration site conditions</i>	
Common:	Acute phase reaction, pyrexia, influenza-like illness (including: fatigue, chills, malaise and flushing), peripheral oedema, asthenia
Uncommon:	Injection site reactions (including: pain, irritation, swelling, induration, redness), chest pain, weight increased
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
<i>Investigations</i>	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse reactions have been reported during post-marketing experience with Zoledronic acid via spontaneous case reports and literature cases. Since these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency (which is therefore categorized as not known). Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 3 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders
Anaphylactic reaction/shock
Nervous system disorders
Somnolence
Eye disorders
Episcleritis, scleritis and orbital inflammation
Cardiac disorders
Atrial fibrillation
Vascular disorders
Hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors
Respiratory, thoracic and mediastinal disorders
Bronchospasm
Skin and subcutaneous tissue disorders
Urticaria
Musculoskeletal and connective tissue disorders
Severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including Zoledronic acid).

Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been associated with reports of renal function impairment. In a pooled analysis of safety data from Zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancy involving bone, the frequency of renal function impairment adverse events suspected to be related to Zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumors (3.2%). Factors that may increase the potential for deterioration in renal function include: dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zoledronic acid (*see section 4.4 and 4.5*).

Osteonecrosis

Cases of osteonecrosis (primarily of the jaw) but also of other anatomical sites including hip, femur and external auditory canal, have been reported predominantly in cancer patients treated with bisphosphonates, including Zoledronic acid. Many patients with osteonecrosis of the jaw had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic drugs, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-

existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (*see section 4.4*). Data suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

Acute-phase reaction

This adverse drug reaction consists of a constellation of symptoms that includes pyrexia, fatigue, bone pain, chills, influenza-like illness, arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-Zoledronic acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms; these symptoms usually resolve within a few days.

Atrial fibrillation

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

4.9 Overdose

Clinical experience with acute overdosage of Zoledronic acid is limited. Patients who have received doses higher than those recommended should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcemia, calcium gluconate infusions should be administered as clinically indicated.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Mechanisms of action

Zoledronic acid is a highly potent drug that belongs to the bisphosphonates class of drugs, which act primarily on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date.

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear.

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralization or mechanical properties of bone.

In addition to being a very potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:

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

- *In vitro*: inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

5.2 Pharmacokinetic properties

Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients with bone metastases yielded the following pharmacokinetic data.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcemia.

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

Distribution

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

Biotransformation/Metabolism

Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Zoledronic acid does not inhibit human P450 enzymes *in vitro*.

Elimination

Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug given every 28 days. Over the first 24 hours, $39 \pm 16\%$ of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 L/h, independent of dose, and unaffected by gender, age, race, and body weight.

Linearity/non-linearity

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

Special populations

Hepatic impairment

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

Renal impairment

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing $75 \pm 33\%$ of the creatinine clearance, which showed a mean of 84 ± 29 mL/min (range 22 to 143 mL/min) in the 64 cancer patients studied. Population analysis

showed that for a patient with creatinine clearance of 50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 72% of that of a patient showing creatinine clearance of 84 mL/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance <30 mL/min). The use of Zoledronic acid is not recommended in patients with severe renal impairment (*see section 4.4*).

Effect of gender, age and race

The three pharmacokinetic studies conducted in cancer patients with bone metastases reveal no effect by gender, race, age (range 38 to 84 years), and body weight on zoledronic acid total clearance.

CLINICAL STUDIES

Clinical trial results in the treatment of osteolytic, osteoblastic and mixed bone metastases and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy

Zoledronic acid was compared to placebo for the prevention of skeletal-related events (SREs) in adult prostate cancer patients with 214 men receiving Zoledronic acid 4 mg versus 208 receiving placebo. After the initial 15 months of treatment, 186 patients continued for up to an additional 9 months, giving a total duration of double-blind therapy up to 24 months. Zoledronic acid 4 mg demonstrated a significant advantage over placebo for the proportion of patients experiencing at least one skeletal-related event (SRE) (38% for Zoledronic acid 4 mg versus 49% for placebo, p=0.028), delayed the median time to first SRE (488 days for Zoledronic acid 4 mg versus 321 days for placebo, p=0.009), and reduced the annual incidence of event per patient - skeletal morbidity rate (0.77 for Zoledronic acid 4 mg versus 1.47 for placebo, p=0.005). Multiple event analysis showed 36% risk reduction in developing skeletal related events in the Zoledronic acid group compared with placebo (p=0.002). Pain was measured at baseline and periodically throughout the trial. Patients receiving Zoledronic acid reported less increase in pain than those receiving placebo, and the differences reached significance at months 3, 9, 21 and 24. Fewer Zoledronic acid patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 4.

In a second study, Zoledronic acid reduced the number of SREs and extended the median time to an SRE by over two months in the population of adult patients who had other solid tumors involving bone, which had a median survival of only six months (134 patients with non- small-cell lung cancer [NSCLC], 123 with other solid tumors treated with Zoledronic acid vs 130 patients with NSCLC, 120 with other solid tumors treated with placebo). After initial 9 months of treatment, 101 patients entered the 12 month extension study, and 26 completed the full 21 months. Zoledronic acid 4 mg reduced the proportion of patients with SREs (39% for Zoledronic acid 4 mg versus 48% for placebo, p=0.039), delayed the median time to first SRE (236 days for Zoledronic acid 4 mg versus 155 days for placebo, p=0.009), and reduced the annual incidence of events per patient-skeletal morbidity rate (1.74 for Zoledronic acid 4 mg versus 2.71 for placebo, p=0.012). Multiple event analysis showed 30.7% risk reduction in developing skeletal-related events in the Zoledronic acid group compared with placebo (p=0.003). The treatment effect in non- small cell lung cancer patients appeared to be smaller than in patients with other solid tumors. Efficacy results are provided in Table 5.

Table 4: Efficacy results (prostate cancer patients receiving hormonal therapy)						
	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	zoledronic	Placebo	zoledronic	Placebo	zoledronic acid	Placebo

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

* Includes vertebral and non-vertebral fractures

** Accounts for all skeletal events, the total number as well as time to each event during the trial

NR-Not Reached

NA-Not Applicable

Table 5: Efficacy results (solid tumours other than breast or prostate cancer)						
	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	zoledronic acid 4 mg	Placebo	zoledronic acid 4 mg	Placebo	zoledronic acid 4 mg	Placebo
N	257	250	257	250	257	250
Proportion of patients with SREs (%)	39	48	16	22	29	34
p-value	0.039		0.064		0.173	
Median time to SRE (days)	236	155	NR	NR	424	307
p-value	0.009		0.020		0.079	
Skeletal morbidity rate	1.74	2.71	0.39	0.63	1.24	1.89
p-value	0.012		0.066		0.099	
Risk reduction of suffering from multiple events** (%)	30.7	-	NA	NA	NA	NA
p-value	0.003		NA		NA	

* Includes vertebral and non-vertebral fractures

** Accounts for all skeletal events, the total number as well as time to each event during the trial

NR-Not Reached

NA-Not Applicable

In a third phase III randomized, double-blind trial comparing Zoledronic acid 4 mg to pamidronate 90 mg, 1,122 adult patients (564 Zoledronic acid 4 mg, 558 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg Zoledronic acid or 90 mg pamidronate every 3 to 4 weeks. Eight patients were excluded from the efficacy analysis because of good clinical practice non-compliance. 606 patients entered the 12-month, double-blind extension phase. Total therapy lasted up to 24 months. The results demonstrated that Zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of skeletal-related events. The multiple event analyses revealed a significant risk reduction of 16% (p=0.030) in patients treated with Zoledronic acid 4 mg. Efficacy results are provided in Table 6.

Table 6: Efficacy results (breast cancer and multiple myeloma patients)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	zoledronic acid 4 mg	Pam 90 mg	zoledronic acid 4 mg	Pam 90 mg	zoledronic acid 4 mg	Pam 90 mg
N	561	555	561	555	561	555
Proportion of patients with SREs (%)	48	52	37	39	19	24
p-value	0.198		0.653		0.037	
Median time to SRE (days)	376	356	NR	714	NR	NR
p-value	0.151		0.672		0.026	
Skeletal morbidity rate	1.04	1.39	0.53	0.60	0.47	0.71
p-value	0.084		0.614		0.015	
Risk reduction of suffering from multiple events** (%)	16	-	NA	NA	NA	NA
p-value	0.030		NA		NA	

* Includes vertebral and non-vertebral fractures

** Accounts for all skeletal events, the total number as well as time to each event during the trial

NR-Not Reached

NA-Not Applicable

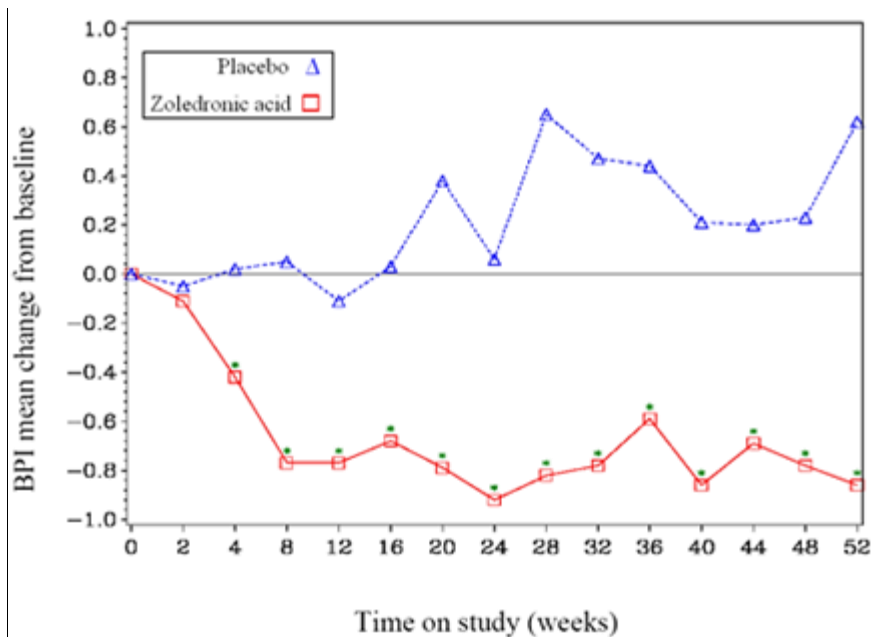
In clinical trials performed in adult patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity.

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

The SRE rate ratio at one year was 0.61, indicating that treatment with Zoledronic acid reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcemia) was 29.8% in the Zoledronic acid-treated group versus 49.6% in the placebo group (p=0.003). Median time to onset of the first SRE was not reached in the Zoledronic acid-treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo.

In the Zoledronic acid-treated group, decreases in pain scores from baseline (using the Brief Pain Inventory, BPI) occurred from 4 weeks onwards and at every subsequent time point during the study, while the pain score in the placebo group remained unchanged or increased from baseline (Figure 1). Zoledronic acid inhibited the worsening of the analgesic score more than placebo. In addition, 71.8% of Zoledronic acid-treated patients versus 63.1% of placebo patients showed improvement or no change in the ECOG performance score at the final observation.

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



Clinical trial results in the treatment of HCM

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

Table 7: Proportion of complete responders by day in the combined HCM studies

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

*p-values denote statistical superiority over pamidronate.

Median time to normo-calcaemia was 4 days. By day 10, the response rate was 87 to 88 % for the Zoledronic acid treatment groups versus 70 % for pamidronate 90 mg. Median time to relapse (re- increase of albumin-corrected serum calcium ≥ 2.9 mmol/L) was 30 to 40 days for patients treated with Zoledronic acid versus 17 days for those treated with pamidronate 90 mg. The results showed that both Zoledronic acid doses were statistically superior to pamidronate 90 mg for time to relapse. There were no statistically significant differences between the two Zoledronic acid doses.

In clinical trials performed in adult patients with hypercalcemia of malignancy (HCM), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

NON-CLINICAL SAFETY DATA

Toxicity studies

In the bolus parenteral studies, zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2 to 3 days in dogs for up to 52 weeks was also well tolerated.

The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphysis of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

The kidney was identified as a major target organ for toxicity in parenteral studies with zoledronic acid. In the intravenous infusion studies, renal tolerability was observed in rats given six infusions at doses of up to 0.6 mg/kg at 3-day intervals, while five infusions of 0.25 mg/kg administered at 3-week intervals were well tolerated in dogs.

Reproduction toxicity

For reproductive toxicity *see section 4.6 Fertility, pregnancy and lactation*.

Mutagenicity

Zoledronic acid was not mutagenic *in vitro* and *in vivo* in the mutagenicity tests performed.

Carcinogenicity

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

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol

Sodium citrate

Water for injections

6.2 Incompatibilities

Studies with containers made from polyethylene and polypropylene, showed no incompatibility with Zolidin.

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

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

6.3 Shelf life

36 months.

Chemical and physical in-use stability has been demonstrated for 36 hours at 2 – 8 °C.

After dilution: From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions of the reconstituted solution for infusion, see section 6.3.

6.5 Presentation

1 x 1 vial pack.

6.6 Special precautions for disposal and other handling

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

Additional information on handling of Zolidin, including guidance on preparation of reduced doses, is provided in section 4.2.

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

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

Healthcare professionals are advised not to dispose of unused Zolidin via the domestic sewage system.

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

7. Marketing authorisation holder

ACCORD HEALTHCARE PRIVATE LIMITED

6 Shenton Way, #38-01 OUE Downtown 1, Singapore 068809

8. Date of revision of the text

29/01/2019