

# **AUSTRALIAN PRODUCT INFORMATION – DBL™ ZOLEDRONIC ACID (ZOLEDRONIC ACID)**

## **1. NAME OF THE MEDICINE**

Zoledronic acid.

## **2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each vial of DBL Zoledronic Acid Concentrated Injection contains 4 mg anhydrous zoledronic acid/5 mL, equivalent to 4.264 mg zoledronic acid monohydrate. Each vial contains an overfill to permit withdrawal of the labelled amount of zoledronic acid from the vial.

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

## **3. PHARMACEUTICAL FORM**

### **Concentrated injection**

DBL Zoledronic Acid Concentrated Injection is a sterile, colourless solution.

## **4. CLINICAL PARTICULARS**

### **4.1 Therapeutic indications**

DBL Zoledronic Acid is indicated for the:

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

## 4.2 Dose and method of administration

### Dosage

#### ***Prevention of skeletal-related events in patients with advanced malignancies involving bone***

*Dosage regimen for adults (including elderly patients)*

The recommended dose is 4 mg given as an intravenous infusion lasting no less than 15 minutes, every 3 to 4 weeks.

DBL Zoledronic Acid Concentrated Injection must be reconstituted and further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution prior to administration. See Method of administration, Instructions for use and handling.

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

#### ***Treatment of tumour-induced hypercalcaemia (TIH) (albumin-corrected serum calcium $\geq 3.0$ mmol/L)***

*Dosage regimen for adults (including elderly patients)*

The recommended dose is 4 mg given as a single intravenous infusion of no less than 15 minutes.

DBL Zoledronic Acid Concentrated Injection must be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution prior to administration. See Method of administration, Instructions for use and handling.

The hydration status of patients must be assessed prior to administration of DBL Zoledronic acid to assure that patients are adequately hydrated prior to and following administration of DBL Zoledronic Acid.

Following an initial dose of 4 mg, the median time to relapse is 30 days.

### Method of administration

DBL Zoledronic Acid is administered intravenously via an infusion line given at a constant infusion rate. The infusion time must not be less than 15 minutes.

It must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line.

### ***Instructions for use and handling***

Aseptic techniques must be followed during the preparation of the infusion.

### ***DBL Zoledronic Acid Concentrated Injection***

Prior to administration, the required amount of concentrate from one vial must be diluted with 100 mL of calcium-free infusion solution (0.9 % w/v sodium chloride solution or 5 % w/v glucose solution).

## Instructions on preparing reduced doses of DBL Zoledronic acid Concentrated Injection

Withdraw an appropriate volume of DBL Zoledronic Acid Concentrated Injection (4 mg/5 mL) solution as needed.

4.4 mL	for 3.5 mg dose
4.1 mL	for 3.3 mg dose
3.8 mL	for 3.0 mg dose

### Storage of diluted solution

DBL Zoledronic Acid contains no antimicrobial agent and is for single use in one patient only. Discard any remaining residue.

After addition of the solution to the infusion media, the infusion solution should be used as soon as practicable to reduce the risk of microbiological hazard. If storage is necessary, hold at 2° - 8°C for not more than 24 hours. If refrigerated, the diluted solution must be allowed to reach room temperature before administration.

### Dosage adjustment

#### *Renal impairment*

The use of DBL Zoledronic Acid is not recommended in patients with severe renal impairment (calculated creatinine clearance by Cockcroft-Gault formula of  $\leq 30$  mL/min) (see sections 4.4 Special warnings and precautions for use and 5.2 Pharmacokinetic properties).

Dose adjustments are not recommended in patients with TIH presenting with mild to moderate renal impairment prior to initiation of therapy (serum creatinine  $< 400$  micromol/L or calculated creatinine clearance by Cockcroft-Gault formula of  $\geq 30$  mL/min) as there are insufficient data to support the efficacy of doses less than 4 mg.

When initiating treatment with DBL Zoledronic Acid in patients with advanced malignancies involving bone, serum creatinine levels and creatinine clearance (CrCl) should be determined. CrCl is calculated from serum creatinine levels using the Cockcroft-Gault formula.

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 - 60 mL/min, the following DBL Zoledronic Acid dose is recommended (see section 4.4 Special warnings and precautions for use):

**Table 1: Dosage recommendation for patients with renal impairment**

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, patients who receive DBL Zoledronic Acid should have serum creatinine assessed prior to each dose (see section 4.4 Special warnings and precautions for use). Patients being treated for TIH who have evidence of deterioration in renal function should be appropriately evaluated, with consideration given as to whether the potential benefit of continued treatment with DBL Zoledronic Acid outweighs the possible risk. Patients being treated for bone metastases should have the dose of zoledronic acid withheld if renal function has deteriorated. In the clinical studies, deterioration in renal function was defined as follows:

- For patients with normal baseline creatinine (<125 micromol/L), increase of > 44 micromol/L
- For patients with abnormal baseline creatinine (>125 micromol/L), increase of > 88 micromol/L.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine returned to within 10% of the baseline value. DBL Zoledronic Acid should be resumed at the same dose administered prior to treatment interruption.

### **Monitoring advice**

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium and potassium, as well as serum creatinine, should be carefully monitored after initiating DBL Zoledronic Acid therapy.

## **4.3 Contraindications**

Clinically significant hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients listed in Section 6.1 List of excipients.

Not recommended in patients with severe renal impairment (calculated creatinine clearance by Cockcroft-Gault formula of,  $\leq 30$  mL/min) (see section 4.4 Special warnings and precautions for use).

Pregnancy and lactation.

## **4.4 Special warnings and precautions for use**

### **Administration of DBL Zoledronic Acid**

DBL Zoledronic Acid should be administered as a single intravenous solution in a line separate from all other drugs and should be administered over a period of no less than 15 minutes.

### **Rehydration**

Patients must be maintained in a well hydrated state prior to and following administration of DBL Zoledronic Acid. Patients must be assessed prior to administration of DBL Zoledronic Acid to ensure that they are adequately hydrated. It is essential in the initial treatment of tumour-induced hypercalcaemia that intravenous rehydration be instituted to restore urine output. Patients should be hydrated adequately throughout treatment but overhydration must be avoided. In patients with cardiac disease, especially in the elderly, additional saline overload may precipitate cardiac failure (left ventricular failure or congestive heart failure). Fever (influenza-like symptoms) may also contribute to this deterioration.

## Monitoring of metabolic parameters

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

Medicines containing the different amounts of the same active ingredient, e.g., 5 mg/100 mL zoledronic acid, may be used for indications related to decreased bone mineral density (e.g., osteoporosis in post-menopausal women, osteoporosis in men, treatment and prevention of osteoporosis caused by long-term glucocorticoid use) and for Paget's disease. **Patients treated with DBL Zoledronic should also not be treated concomitantly with other strengths of zoledronic acid or other bisphosphonate.**

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

Occasional cases of mild, transient hypocalcaemia, usually asymptomatic, have been reported. Symptomatic hypocalcaemia occurs rarely and can be reversed with calcium gluconate. Patients who have undergone thyroid surgery may be particularly susceptible to develop hypocalcaemia due to relative hypoparathyroidism.

## Hypocalcaemia

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

## Monitoring of renal function

Zoledronic acid, in common with other bisphosphonates, has been associated with the development of renal impairment in some subjects, sometimes progressing to renal failure. 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 the use of nephrotoxic drugs, or using a shorter infusion time than 15 minutes. Impairment of renal function may occur in patients with bone metastases receiving zoledronic acid for the prevention of skeletal related events, as well as those with T1H. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of zoledronic acid.

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

Patients who receive DBL Zoledronic Acid should have serum creatinine assessed prior to each dose. Patients being treated for TIH who have a deterioration in renal function should be appropriately evaluated, with consideration given as to whether the potential benefit of continued treatment outweighs the possible risk. Patients being treated for bone metastases who have a deterioration in renal function should have the dose withheld, and have treatment resumed only when the creatinine level returns to within 10% of baseline.

Also see Use in renal impairment later in this section.

### **Osteonecrosis of the jaw**

Osteonecrosis of the jaw (ONJ) has been reported predominantly in patients treated with bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis. Presentation may include jaw pain, toothache, exposed bone, altered sensation and local infection, including osteomyelitis. The condition may result in chronic pain, may be resistant to treatment, and in serious cases may result in disfigurement.

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

Cancer patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates. Patients and their dentists should be advised of the reports of osteonecrosis of the jaw so that dental symptoms developing during treatment can be fully assessed before commencing dental procedures.

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

### **Osteonecrosis of other anatomical sites**

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

### **Atypical fractures of the femur**

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

patient, based on an individual risk 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.

### **Severe musculoskeletal pain**

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients taking bisphosphonates. However, such reports have been infrequent. This category of drugs includes zoledronic acid (see Section 4.8 Adverse effects (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.

### **Use in hepatic impairment**

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

### **Use in renal impairment**

Upon initiation of treatment of bone metastases in patients with mild to moderate renal impairment at baseline, dosage reductions are recommended (see section 4.2 Dose and method of administration, Dosage adjustment, Renal impairment. The use of DBL Zoledronic Acid is not recommended in patients with severe renal impairment (creatinine clearance < 30mL/min).

Dose adjustments are not recommended in patients with TIH presenting with mild to moderate renal impairment. Patients being treated for TIH who have a deterioration in renal function should be appropriately evaluated, with consideration given as to whether the potential benefit of continued treatment outweighs the possible risk.

Limited clinical data are available in patients with pre-existing renal impairment. Zoledronic acid is excreted exclusively via the kidney and the risk of adverse reactions may be greater in patients with pre-existing impairment of renal function. Patients with severe renal impairment (creatinine levels >400 micromol/L for patients with TIH and >265 micromol/L for patients with bone metastases) were excluded from the pivotal clinical studies. In view of the potential impact of bisphosphonates including zoledronic acid, on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (serum creatinine >400 micromol/L) and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance <30 mL/min), the use of DBL Zoledronic Acid is not recommended in patients with severe renal impairment (creatinine clearance <30mL/min)

Also see Sections 4.2 Dose and method of administration, Dosage adjustments, Renal impairment, 4.3 Contraindications and 5.2 Pharmacokinetic properties, Special population, Renal impairment.

### **Use in the elderly**

No dose adjustment is necessary (see section 4.4 Special warnings and precautions for use). However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

### **Paediatric use**

The safety and efficacy of DBL Zoledronic Acid in paediatric patients have not been established.

### **Effects on laboratory tests**

No data available.

## **4.5 Interactions with other medicines and other forms of interactions**

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows moderate binding to plasma proteins and human P450 enzymes *in vitro* (see section 5.2 Pharmacokinetic properties), but no formal clinical interaction studies have been performed.

Caution is indicated when zoledronic acid is used in combination with other potentially nephrotoxic drugs.

In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates are used in combination with thalidomide.

Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

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

## **4.6 Fertility, pregnancy and lactation**

### **Effects on fertility**

The fertility was decreased in rats dosed SC with 0.1 mg/kg/day zoledronic acid (0.1 times the maximum human exposure of 8 mg, based on body surface area (BSA), and pre-implantation loss was increased at 0.01 mg/kg/day. Reversible testicular atrophy occurred in rats at 0.003 mg/kg/day SC for 12 months (0.004 times the maximum human exposure of 8 mg, based on BSA).

In dogs, testicular and prostatic atrophy and oligospermia were observed at 0.2 mg/kg/day IV for 3 months (0.6 times the maximum human exposure of 8 mg, based on BSA), and testicular atrophy and/or mineralisation at 0.03 mg/kg IV dosed every 2-3 days for 6 months (0.1 times the maximum human exposure of 8 mg, based on BSA). Female dogs had decreased weights of ovaries and uterus, correlated with anoestrus and, in some animals, with vaginal epithelial

degeneration at 0.01 mg/kg/day IV (0.03 times the maximum human exposure of 8 mg, based on BSA).

### **Use in pregnancy – Australian Pregnancy Category B3**

DBL Zoledronic Acid is contraindicated during pregnancy (see section 4.3 Contraindications).

Zoledronic acid was administered subcutaneously to rats and rabbits during the fetal organogenesis period. In rats, increased malformations were seen at 0.2 mg/kg/day (1.5 times the expected human exposure at 8 mg, based on AUC) and increased post-implantation loss occurred at 0.4 mg/kg/day (3 times the human exposure). No embryo-fetal effects were observed at 0.1 mg/kg/day (0.7 times the human exposure). In rabbits, zoledronic acid increased late resorptions at 0.03 mg/kg/day and above (0.07 times the highest clinical dose, based on BSA). Maternal toxicity was apparent in rabbits at these doses. In the absence of adequate available experience in human pregnancy, DBL Zoledronic Acid should not be used during pregnancy.

Women of child-bearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the fetus while receiving DBL Zoledronic Acid. There may be a risk of fetal harm (e.g., skeletal and other abnormalities) if a woman becomes pregnant 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.

### **Use in lactation**

DBL Zoledronic Acid is contraindicated in breast-feeding women (see section 4.3 Contraindications).

Studies have not been performed in lactating animals, and the transfer of zoledronic acid into milk is unknown. Because many drugs are excreted in human milk, breast-feeding should be discontinued before administration with DBL Zoledronic Acid.

## **4.7 Effects on ability to drive and use machines**

No studies on the effects on the ability to drive and use machines have been performed.

## **4.8 Adverse effects (undesirable effects)**

### **Overview of clinical trial data**

The most serious adverse drug reactions reported in patients receiving DBL Zoledronic Acid in the approved indications are anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute phase reaction, and hypocalcaemia. The frequencies of these adverse reactions are shown below in this section.

Frequencies of adverse reactions to 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. These reactions can be expected to occur in approximately one third of patients who receive either zoledronic acid 4 mg or pamidronate 90 mg.

Within three days following intravenous administration, an acute phase reaction has commonly been reported including flu-like syndrome in bone pain, pyrexia, fatigue, rigors, influenza-like illness, arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection Description of selected adverse reaction). Arthralgia and myalgia have been reported in approximately 3% of patients. In most cases no specific treatment is required and the symptoms subside after a couple of hours/days.

Frequently, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels in approximately 20% of patients, which is asymptomatic and does not require treatment. The serum calcium may fall to asymptomatic hypocalcaemic levels in approximately 3% of patients.

Gastrointestinal reactions such as nausea (5.8%) and vomiting (2.6%) have been reported following intravenous infusion of zoledronic acid. Anorexia was reported in 1.5% of patients treated with zoledronic acid 4 mg.

Local reactions at the infusion site such as redness or swelling and/or pain were also observed in less than 1% of patients.

Some cases of rash, pruritus and chest pain have been observed.

As with other bisphosphonates, cases of conjunctivitis in approximately 1% of patients and cases of hypomagnesaemia have been reported.

There have been some reports of impaired renal function (2.3%) with chronic administration of zoledronic acid 4 mg. However, other risk factors in this severely ill patient population may have contributed as well.

In clinical trials of patients with tumour-induced hypercalcaemia, Grade 3 (NCI Common Toxicity Criteria [CTC]) elevations of serum creatinine were seen in 2.3%, 3.1 % and 3.0% of patients receiving zoledronic acid 4 mg, zoledronic acid 8 mg and pamidronate 90 mg, respectively, as expected in this disease state and with this class of compounds. However, other risk factors in this severely ill patient population may have contributed as well.

The following adverse drug reactions have been accumulated from clinical studies following predominantly chronic treatment with zoledronic acid:

Adverse reactions are ranked under headings of frequency, using the following convention:

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 ( $< 1/10,000$ ), including isolated reports.

### ***Blood and lymphatic system disorders***

Common: anaemia.

Uncommon: thrombocytopenia, leucopenia.

Rare: pancytopenia.

### ***Vascular disorders***

Common: hypertension.

Uncommon:, hypotension.

### ***Cardiac disorders***

Rare: bradycardia, cardiac arrhythmia (secondary to hypocalcaemia).

### ***Eye disorders***

Common: conjunctivitis.

Uncommon: blurred vision.

Rare: uveitis.

Very rare: episcleritis.

### ***Gastrointestinal disorders***

Common: nausea, vomiting, anorexia, decreased appetite, constipation.

Uncommon: diarrhoea, abdominal pain, dyspepsia, stomatitis, dry mouth.

### ***General disorders and administration site conditions***

Common: asthenia, peripheral oedema, acute phase reaction, fever, flu-like syndrome (including fatigue, rigors, malaise and flushing).

Uncommon: injection site reactions (including pain, irritation, swelling, induration, redness), chest pain, weight increase.

Rare: arthritis and joint swelling as a symptom of acute phase reaction.

### ***Immune system disorders***

Uncommon: hypersensitivity reaction.

Rare: angioneurotic oedema.

### ***Metabolism and nutrition disorders***

Very common: hypophosphataemia.

Common: blood creatinine and blood urea increased, hypocalcaemia.

Uncommon: hypomagnesaemia, hypokalaemia.

Rare: hyperkalaemia, hypernatraemia.

### ***Musculoskeletal, connective tissue and bone disorders***

Common: bone pain, myalgia, arthralgia, generalised pain, joint stiffness.

Uncommon: muscle spasms, osteonecrosis of jaw (ONJ).

### ***Nervous system disorders***

Common: headache, paraesthesia.

Uncommon: dizziness, dysgeusia, hypoaesthesia, hyperaesthesia, tremor.

Very rare: convulsion, hypoaesthesia and tetany (secondary to hypocalcaemia).

### ***Psychiatric disorders***

Common: sleep disorder.

Uncommon: anxiety.

Rare: confusional state.

### ***Renal and urinary disorders***

Common: renal impairment.

Uncommon: acute renal failure, haematuria, proteinuria.

Rare: acquired Fanconi syndrome.

### ***Respiratory, thoracic and mediastinal disorders***

Uncommon: dyspnoea, cough.

Rare: Interstitial lung disease (ILD).

### ***Skin and subcutaneous tissue disorders***

Common: hyperhidrosis.

Uncommon: pruritus, rash (including erythematous and macular rash).

## **Description of selected adverse reactions**

### ***Renal function impairment***

DBL Zoledronic Acid has been associated with reports of renal function impairment.

In a pooled analysis of safety data from 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 tumours (3.2%).

Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of DBL 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 DBL Zoledronic Acid (see Section 4.4 Special warnings and precautions for use).

### **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 DBL 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 comorbid 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 Special warnings and precautions for use). 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  $\leq 3$  days post DBL 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.

### **Post-marketing experience**

The following adverse reactions have been reported during post-approval use of zoledronic acid. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

**Immune system disorders:** anaphylactic reaction/shock.

**Nervous system disorders:** somnolence.

**Eye disorders:** episcleritis, scleritis and orbital inflammation.

**Cardiac disorders:** atrial fibrillation.

**Vascular disorders:** hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors.

**Respiratory, thoracic and mediastinal disorders:** bronchospasms.

**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).

### **Reporting suspected adverse effects**

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at [www.tga.gov.au/reporting-problems](http://www.tga.gov.au/reporting-problems).

## 4.9 Overdose

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

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

#### Mechanism of action

Zoledronic acid is a bisphosphonate, potently inhibiting osteoclastic bone resorption.

Bisphosphonates have a high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear.

In long-term studies in adult animals, zoledronic acid inhibits bone resorption and increases bone mineralisation without adversely affecting the formation or mechanical properties of bone.

Clinical studies in tumour-induced hypercalcaemia demonstrated that the effect of zoledronic acid is characterised by decreases in serum calcium and urinary calcium excretion.

Preclinical studies demonstrated that, in addition to its inhibitory activity against bone resorption, zoledronic acid possesses the following properties that could contribute to its overall efficacy in the treatment of metastatic bone disease:

- *In vivo*: anti-tumour activity in some animal models, anti-angiogenic activity, anti-pain activity.
- *In vitro*: inhibition of osteoclast proliferation, cytostatic and pro-apoptotic activity on tumour cells at concentrations greater than the clinical  $C_{max}$ , synergistic cytostatic effect with other anti-cancer drugs.

#### Clinical trials

##### ***Prevention of skeletal-related events in patients with advanced malignancies involving bone***

Three randomised, double-blind studies (039, 010, 011) were conducted to assess the efficacy of zoledronic acid in preventing skeletal-related events (SREs) in patients with advanced malignancies involving bone. The primary efficacy variable was the proportion of patients experiencing at least one SRE, defined as radiation therapy to bone, surgery to bone, pathological bone fracture or spinal cord compression.

In Study 039, zoledronic acid was compared to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients with 214 men receiving zoledronic acid 4 mg IV infusion every 3 weeks versus 208 receiving placebo (IV infusion of saline). 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 significantly reduced the proportion of patients with SRE ( $p=0.028$ ) and delayed the time to first SRE ( $p=0.009$ ). Multiple event analysis showed 36% relative 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 21 ( $p=0.014$ ) and 24 ( $p=0.024$ ). The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are summarised in Table 2.

**Table 2: Efficacy results (prostate cancer patients with biochemical progression of disease while receiving first-line hormonal therapy)**

	Any SRE (-TIH)*		Fractures**		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
Number of patients	214	208	214	208	214	208
Proportion of patients with SREs (%)	38	49	17	25	26	33
Difference [95% CI] <sup>1</sup>	-10.7 [-20.2, -1.3]		-7.7 [-15.4, 0.0]		-7.0 [-15.7, 1.7]	
Median time to SRE (days)	488	321	NR***	NR***	NR***	NR***
Hazard ratio of time to SRE [95% CI] <sup>2</sup>	0.68 [0.51, 0.91]		0.60 [0.39, 0.92]		0.71 [0.50, 1.01]	
Hazard ratio of multiple event analysis [95% CI] <sup>3</sup>	0.64 [0.49, 0.85]		NA		NA	

1 The 95% confidence intervals for the differences are based on the normal approximation of the differences.

2 The 95% confidence intervals for the hazard ratios are derived from the estimates of Cox regression analysis.

3 The 95% confidence intervals for the hazard ratios are derived from the estimates of robust variances.

\* SRE (-TIH) = skeletal related event excluding tumour-induced hypercalcaemia.

\*\* includes vertebral and non-vertebral fractures.

\*\*\* NR = not reached.

In a second phase III randomised, double-blind trial (Study 010) comparing zoledronic acid 4 mg to pamidronate 90 mg, 1,116 patients (561 zoledronic acid 4 mg, 555 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg zoledronic acid IV infusion every 3 to 4 weeks or 90 mg pamidronate IV infusion every 3 to 4 weeks. 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 analysis did not reveal a significant difference between the two treatments ( $p=0.059$ ). Efficacy results are provided in Table 3.

**Table 3: Efficacy results (breast cancer and multiple myeloma patients)**

	Any SRE (-TIH)*		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
Number of patients	561	555	561	555	561	555
Proportion of patients with SREs (%)	47	51	37	39	19	24
Difference [95% CI] <sup>1</sup>	-3.4 [-9.3, 2.5]		-1.1 [-6.8, 4.6]		-5.2 [-10.1, -0.4]	
Median time to SRE (days)	377	363	NR***	714	NR***	NR***
Hazard ratio of time to SRE [95% CI] <sup>2</sup>	0.89 [0.75, 1.06]		0.96 [0.79, 1.16]		0.75 [0.58, 0.97]	
Hazard ratio of multiple event analysis [95% CI] <sup>3</sup>	0.86 [0.74, 1.01]		NA		NA	

1 The 95% confidence intervals for the differences are based on the normal approximation of the differences.

2 The 95% confidence intervals for the hazard ratios are derived from the estimates of Cox regression analysis.

3 The 95% confidence intervals for the hazard ratios are derived from the estimates of robust variances.

\* SRE (-TIH) = skeletal related event excluding tumour-induced hypercalcaemia.

\*\* includes vertebral and non-vertebral fractures.

\*\*\* NR = not reached.

Pam = Pamidronate.

In the third trial (Study 011), zoledronic acid 4 mg IV infusion every 3 weeks (n=257) was compared with placebo (IV infusion of saline; n=250) in patients with other solid tumours involving bone. The tumours included non small cell lung cancer (approximately 50% of subjects), renal cell cancer, thyroid cancer, head and neck cancer and other solid tumours. These patients had a median survival of only 6 months. After initial 9 months of treatment, 101 patients entered the 12 month double-blind extension study, and 26 completed the full 21 months. Zoledronic acid 4 mg showed a trend to reduce the proportion of patients with SRE (p=0.127) and significantly delayed the time to first SRE (p=0.03). Multiple event analysis showed 28% relative risk reduction in developing skeletal related events in the zoledronic acid group compared with placebo (p=0.01). The treatment effect in non-small cell lung cancer patients appeared to be smaller than in patients with other solid tumours. Efficacy results are provided in Table 4.

**Table 4: Efficacy results (non small cell lung cancer and other tumours)**

	Any SRE (-TIH)*		Fractures**		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
Number of patients	257	250	257	250	257	250
Proportion of patients with SREs (%)	39	46	16	22	29	34
Difference [95% CI] <sup>1</sup>	-6.7 [-15.3, 1.9]		-6.4 [-13.2, 0.4]		-5.6 [-13.7, 2.5]	
Median time to SRE (days)	236	163	NR***	NR***	424	307
Hazard ratio of time to SRE [95% CI] <sup>2</sup>	0.74 [0.57, 0.97]		0.62 [0.41, 0.93]		0.76 [0.55, 1.03]	
Hazard ratio of multiple event analysis [95% CI] <sup>3</sup>	0.72 [0.56, 0.92]		NA		NA	

1 The 95% confidence intervals for the differences are based on the normal approximation of the differences.

2 The 95% confidence intervals for the hazard ratios are derived from the estimates of Cox regression analysis.

3 The 95% confidence intervals for the hazard ratios are derived from the estimates of robust variances.

\* SRE (-TIH) = skeletal related event excluding tumour-induced hypercalcaemia.

\*\* includes vertebral and non-vertebral fractures.

\*\*\* NR = not reached.

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

The SRE rate ratio at one year was 0.61, indicating that treatment with zoledronic acid reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the zoledronic acid-treated group versus 49.6% in the placebo group (p=0.003). Zoledronic acid significantly delayed the time of onset of the first SRE compared with placebo (median not reached versus 364 days; 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, statistically significant improvement (p<0.05) in pain scores, a complication of bone metastases, (using the Brief Pain Inventory, BPI) was seen at 4 weeks and at every subsequent time point during the study, when compared to placebo. The pain score for zoledronic acid was consistently below baseline.

### ***Tumour-induced hypercalcaemia (TIH)***

Two identical multicenter, randomised, double-blind, double-dummy studies of zoledronic acid 4 mg or 8 mg given as a 5-minute infusion or pamidronate 90 mg given as a 2-hour infusion were conducted in patients with tumour-induced hypercalcaemia (TIH). TIH was defined as corrected serum calcium (CSC) concentration of  $\geq 3.00$  mmol/L. The primary efficacy variable was the proportion of patients having a complete response, defined as the lowering of the CSC to  $\leq 2.70$  mmol/L within ten days after drug infusion. Each treatment group was considered efficacious if the lower bound of the 95% confidence interval for the proportion of complete responders was  $>70\%$ . This was achieved for the zoledronic acid 4 mg and 8 mg groups in each study, but not for the pamidronate 90 mg group. To assess the effects of zoledronic acid versus those of pamidronate, the two multicenter TIH studies were combined in a preplanned 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. The results also demonstrated a faster normalisation of CSC by day 4 for zoledronic acid 8 mg and by day 7 for zoledronic acid 4 and 8 mg doses.

The following response rates were observed:

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

	<b>Day 4</b>	<b>Day 7</b>	<b>Day 10</b>
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 vs pamidronate 90 mg based on Cochran-Mantel Haenszel adjusting for baseline CSC.			
* P-values denote statistical superiority over pamidronate.			

There were no statistically significant differences between the two zoledronic acid doses. Secondary efficacy variables, time to relapse and duration of complete response, were also assessed. Time to relapse was defined as the duration (in days) from study infusion until the last CSC value  $\leq 2.90$  mmol/L. Patients who did not have a complete response were assigned a time to relapse of 0 days. Duration of complete response was defined as the duration (in days) from the occurrence of a complete response until the last CSC  $\leq 2.70$  mmol/L. The results showed that both zoledronic acid doses had a statistically longer time to relapse than pamidronate. There was no statistically significant difference between the zoledronic acid doses.

**Table 6: Results for secondary efficacy variables in the combined TIH studies**

	<b>Zoledronic acid 4 mg</b>			<b>Zoledronic acid 8 mg</b>			<b>Aredia 90 mg</b>	
	<b>N</b>	<b>Median (days)</b>	<b>P-value</b>	<b>N</b>	<b>Median (days)</b>	<b>P-value</b>	<b>N</b>	<b>Median (days)</b>
Time to relapse	86	30	0.001*	90	40	0.007*	99	17
Duration of complete response	76	32	NA	78	43	NA	69	18
P-values vs pamidronate 90 mg based on Cox regression adjusted for baseline CSC.								
NA: Duration of complete response was not analysed in the subset of complete responders.								
*P-values denote statistical superiority over pamidronate.								

Retreatment with zoledronic acid 8 mg was allowed for patients in any of the treatment arms whose serum calcium did not return to normal or remain normal after initial treatment. A minimum of 7 days was allowed to elapse before retreatment to allow for full response to the initial dose. In clinical studies, 69 patients have received a second infusion of 8 mg zoledronic acid for hypercalcaemia. The complete response rate observed in these retreated patients was 52%.

Although these studies used doses of 8 mg and an infusion time of 5 minutes, subsequent safety data have indicated that such dosage regimens are associated with an increased risk of renal impairment. Therefore, doses of zoledronic acid should not exceed 4 mg and should not be administered over less than 15 minutes (see section 4.4 Special warnings and precautions for use).

## **5.2 Pharmacokinetic properties**

Single 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 32 patients with bone metastases yielded the following pharmacokinetic data, which were found to be dose independent.

### **Absorption**

Zoledronic acid is administered by intravenous infusion. By definition, absorption is complete at the end of the infusion.

### **Distribution**

Zoledronic acid shows no affinity for the cellular components of blood. Protein binding is dependent on calcium ions and, possibly, other cations present in plasma. Plasma protein binding in heparinised plasma from healthy subjects is moderate (approximately 60%) and independent of the concentration of zoledronic acid.

### **Metabolism**

Zoledronic acid is not metabolised and is excreted unchanged via the kidney.

### **Excretion**

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of 0.23 and 1.75 hours, followed by a long elimination phase with a terminal elimination half-life of 167 hours. Over the first 24 hours, 39 to 46% 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 slowly back into the systemic circulation and eliminated via the kidney with a half-life of at least 167 hours. The total body clearance is 3.7 - 4.7 L/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion but had no effect on the area under the plasma concentration versus time curve.

### **Special patient populations:**

#### ***Hepatic impairment***

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes

*in vitro*, shows no biotransformation and, in animal studies, < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

### ***Renal impairment***

The renal clearance of zoledronic acid was significantly positively correlated with creatinine clearance, renal clearance representing  $75 \pm 33\%$  of the creatinine clearance, which showed a mean of  $84 \pm 29$  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 20 mL/min (severe renal impairment) or 50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37%, or 72% respectively, of that of a patient showing creatinine clearance of 84 mL/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance <30 mL/min). See section 4.4 Special warnings and precautions for use.

## **5.3 Preclinical safety data**

### **Genotoxicity**

Zoledronic acid was not mutagenic in bacterial reverse mutation tests in *Salmonella typhimurium* and *Escherichia coli* or in cultured V79 Chinese hamster lung cells. Zoledronic acid did not induce chromosome aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* micronucleus test in rats.

### **Carcinogenicity**

In carcinogenicity studies, zoledronic acid was administered orally by gavage to rats and mice at daily doses of 0.1, 0.5 and 2.0 mg/kg and 0.1, 0.3 and 1.0 mg/kg, respectively, for at least 104 weeks without evidence of carcinogenic potential. Chronic parenteral administration was not feasible given the potential of the compound to cause severe local irritation. The pharmacological bone changes typically observed following long-term bisphosphonate administration to young animals with growing skeletons gave clear evidence of systemic exposure to zoledronic acid in both species at all doses.

## **6. PHARMACEUTICAL PARTICULARS**

### **6.1 List of excipients**

#### **DBL Zoledronic Acid Concentrated Injection**

Mannitol, sodium citrate dihydrate and water for injections.

### **6.2 Incompatibilities**

DBL Zoledronic Acid must not be mixed with calcium or other divalent cation-containing infusion solutions, such as Lactated Ringer's solution.

### 6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

### 6.4 Special precautions for storage

#### Concentrated Injection

Store below 30°C.

#### Diluted solution

After addition of the concentrated solution to the infusion media, the infusion solution should be used as soon as possible. If storage of the diluted solution is necessary, hold at 2° - 8°C for not more than 24 hours. The refrigerated solution must be allowed to reach room temperature before administration.

### 6.5 Nature and contents of container

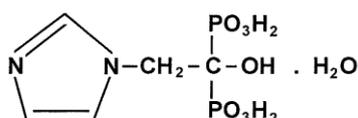
DBL Zoledronic Acid Concentrated Injection is supplied plastic vials in packs of 1, 4 or 10 vials.

### 6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

### 6.7 Physicochemical properties

#### Chemical structure



Chemical name: 1-hydroxy-2-(1H-imidazol-1-yl)ethane-1, 1-diphosphonic acid monohydrate.

Empirical formula: C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O<sub>7</sub>P<sub>2</sub>·H<sub>2</sub>O.

Molecular weight: 290.11.

Zoledronic acid monohydrate is a white, crystalline powder. It is soluble in water, most soluble at neutral pH (>290 mg/mL; pH=6.8) and practically insoluble in organic solvents.

#### CAS number

165800-06-6 (zoledronic acid monohydrate).

118072-93-8 (zoledronic acid anhydrous).

## **7. MEDICINE SCHEDULE (POISONS STANDARD)**

S4, Prescription Only Medicine.

## **8. SPONSOR**

Pfizer Australia Pty Ltd  
Level 17, 151 Clarence Street  
Sydney NSW 2000.

Toll Free Number: 1800 675 229.  
www.pfizer.com.au.

## **9. DATE OF FIRST APPROVAL**

11 May 2012.

## **10. DATE OF REVISION**

15 June 2021.

### **Summary Table of Changes**

<b>Section changed</b>	<b>Summary of new information</b>
2, 3, 4.2, 6.1, 6.4	Removal of information on DBL Zoledronic Acid IV Infusion following cancellation of ARTG entry

<sup>TM</sup> Trademark.