ZOLDRIA Infusion (Zoledronic acid)

**Composition**

ZOLDRIA Infusion
Each vial contains:
Zoledronic Acid monohydrate equivalent to Zoledronic acid anhydrous ................. 4 mg
As sterile freeze-dried powder for reconstitution with 5ml of Sterile Water for Injection IP

**Pharmacology**

> Pharmacodynamics

Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In 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 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 and 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, and anti-adhesion/invasion activity.

Clinical studies in patients with hypercalcaemia of malignancy showed that single-dose infusions of zoledronic acid are associated with decreases in serum calcium and phosphorus and increases in urinary calcium and phosphorus excretion.

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

Patients who have hypercalcaemia of malignancy can generally be divided into two groups according to the pathophysiologic mechanism involved: humoral hypercalcaemia and hypercalcaemia due to tumor invasion of bone. In humoral hypercalcaemia, osteoclasts are activated and bone resorption is stimulated by factors such as the parathyroid hormone-related protein; which are elaborated by the tumour and circulate systemically. Humoural hypercalcaemia usually occurs in squamous cell malignancies of the lungs or head and neck or in genitourinary tumours such as renal
cell carcinoma or ovarian cancer. Skeletal metastases may be absent or minimal in these patients.

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

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

### Pharmacokinetics

Pharmacokinetic data in patients with hypercalcaemia are not available.

**Distribution**

Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 patients with cancer and bone metastases. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at the end of infusion to max at 24 hours post-infusion, with population half-lives of $t_{1/2alpha}$ at 0.24 hours and $t_{1/2beta}$ at 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post-infusion, and a terminal elimination half-life $t_{1/2gamma}$ of 146 hours. The area under the plasma concentration versus time curve ($AUC_{0-24h}$) of zoledronic acid was dose-proportional from 2-16 mg.

The accumulation of zoledronic acid measured over three cycles was low, with mean $AUC_{0-24h}$ ratios for cycles 2 and 3 versus 1 of $1.13 \pm 0.30$ and $1.16 \pm 0.36$, respectively.

*In vitro* and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5,000 ng/mL. *In vitro*, the plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2,000 ng/mL of zoledronic acid.

**Metabolism**

Zoledronic acid does not inhibit the human cytochrome (CY) P450 enzymes *in vitro*. Zoledronic acid does not undergo biotransformation *in vivo*. In animal studies, 14C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in the urine, which suggests that zoledronic acid is not metabolized.

**Excretion**

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

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

**Paediatric**
Zoledronic acid is not indicated for use in children.

**Geriatric**
The pharmacokinetics of zoledronic acid was not affected by age in patients with cancer and bone metastases who ranged in age from 38 years to 84 years.

**Race**
Population pharmacokinetic analyses did not indicate any differences in pharmacokinetics among Japanese and North-American (Caucasian and African-American) patients with cancer and bone metastases.

**Hepatic Impairment**
No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid.

**Renal Impairment**
The pharmacokinetic studies conducted in 64 cancer patients represented typical clinical populations with normal-to-moderately impaired renal function. Compared to patients with normal renal function (n=37), patients with mild renal impairment (N=15) showed an average increase in plasma AUC of 15%, whereas patients with moderate renal impairment (N=11) showed an average increase (43%) in plasma AUC. Limited pharmacokinetic data are available for zoledronic acid in patients with severe renal impairment (CrCl less than 30 mL/min). Based on population pharmacokinetics/pharmacodynamics modelling, the risk of renal deterioration appears to increase with the AUC, which is doubled at a CrCl of 10 mL/min. The CrCl is calculated by the Cockcroft-Gault formula:

\[
\text{CrCl} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 0.85 \text{ for female patients}}{[72 \times \text{serum creatinine (mg/dL)}]}
\]

Zoledronic acid systemic clearance in individual patients can be calculated from the population clearance of zoledronic acid, CL (L/h) = 6.5(CLcr/90)^0.4. These formulae can be used to predict the zoledronic acid AUC in patients, where CL = Dose/AUC_{0\text{infinity}}. The average AUC_{0.24} in patients with normal renal function was 0.42 mg.h/L and the calculated AUC_{0\text{infinity}} for a patient with a CrCl of 75 mL/min was 0.66 mg.h/L following a 4 mg dose of zoledronic acid. However, efficacy and safety of adjusted dosing based on these formulae have not been prospectively assessed.

**Indications**

ZOLDRIA Infusion is indicated for the treatment of tumour-induced hypercalcaemia (hypercalcaemia of malignancy).

**Dosage And Administration**

The maximum recommended dose of ZOLDRIA Infusion in hypercalcaemia of malignancy (albumin-corrected serum calcium greater than or equal to 12 mg/dL) is 4 mg. The 4 mg dose must be given as a single-dose I.V. infusion over no less than 15 minutes. Patients who receive ZOLDRIA Infusion should have serum creatinine assessed prior to each treatment.

Dose adjustments of ZOLDRIA Infusion are not necessary in treating patients for hypercalcaemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine less than 400 mol/L or less than 4.5 mg/dL).

Patients should be adequately rehydrated prior to the administration of ZOLDRIA Infusion.

Consideration should be given to the severity of, as well as the symptoms of, tumour-induced hypercalcaemia when
considering the use of ZOLDRIA Infusion. Vigorous saline hydration, an integral part of hypercalcaemia therapy, should be initiated promptly and an attempt should be made to restore the urine output to about 2 L/day throughout treatment. Mild or asymptomatic hypercalcaemia may be treated with conservative measures (i.e. saline hydration, with or without loop diuretics). Patients should be hydrated adequately throughout the treatment, but overhydration, especially in those patients who have cardiac failure, must be avoided. Diuretic therapy should not be employed prior to correction of hypovolaemia.

Re-treatment with ZOLDRIA Infusion 4 mg may be considered if serum calcium does not return to normal or remain normal after initial treatment. It is recommended that a minimum of 7 days elapse before re-treatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving ZOLDRIA Infusion and serum creatinine must be assessed prior to re-treatment with ZOLDRIA Infusion.

ZOLDRIA Infusion 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 I.V. solution in a separate infusion line.

Preparation of the Solution
Vials of ZOLDRIA Infusion concentrate for infusion contain overfill, allowing for the withdrawal of 5 mL of concentrate (equivalent to 4 mg zoledronic acid). This concentrate should immediately be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP, following the proper aseptic technique, and administered to the patient by infusion. To avoid inadvertent injection, do not store undiluted concentrate in a syringe.

To prepare reduced doses for patients with baseline CrCl less than or equal to 60 mL/min, withdraw the specified volume of the ZOLDRIA Infusion concentrate from the vial for the dose required.

### Preparation of Reduced Doses ZOLDRIA Concentrate

<table>
<thead>
<tr>
<th>Remove and Use ZOLDRIA Volume (mL)</th>
<th>Dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.4</td>
<td>3.5</td>
</tr>
<tr>
<td>4.1</td>
<td>3.3</td>
</tr>
<tr>
<td>3.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

The withdrawn concentrate must be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2-8°C (36-46°F). The refrigerated solution should then be equilibrated to room temperature prior to administration. The total time between dilution, storage in the refrigerator and the end of administration must not exceed 24 hours.

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

**Method of Administration**

Due to the risk of clinically significant deterioration in renal function, which may progress to renal failure, single doses of zoledronic acid should not exceed 4 mg and the duration of infusion should be no less than 15 minutes. In the trials and in postmarketing experience, renal deterioration, progression to renal failure and dialysis have occurred in patients, including those treated with the approved dose of 4 mg infused over 15 minutes. There have been instances of this occurring after the initial zoledronic acid dose.

### Contraindications

**Hypersensitivity to Zoledronic Acid or Any Components of Zoledronic Acid**

Hypersensitivity reactions, including rare cases of urticaria and angio-oedema, and very rare cases of anaphylactic
reaction/shock have been reported.

Lactation
Zoledronic acid is contraindicated in lactating women.

### Warnings And Precautions

**Important Limitation of Use**
The safety and efficacy of zoledronic acid in the treatment of hypercalcaemia associated with hyperparathyroidism or with other non-tumour-related conditions have not been established.

#### Drug Interactions

*In vitro* studies indicate that the plasma protein binding of zoledronic acid is low, with the unbound fraction ranging from 60% to 77%. *In vitro* studies also indicate that zoledronic acid does not inhibit microsomal CYP450 enzymes. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as an intact drug.

**Aminoglycosides**
Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.

**Loop Diuretics**
Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcaemia.

**Nephrotoxic Drugs**
Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

**Thalidomide**
No dose adjustment for zoledronic acid 4 mg is needed when co-administered 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). Co-administration of thalidomide with zoledronic acid did not significantly change the pharmacokinetics of zoledronic acid or CrCl. In multiple myeloma patients, the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide.

Reports of osteonecrosis of jaw (ONJ) have been received in patients treated with zoledronic acid and concomitant anti-angiogenic medicinal products.

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

**Drugs with the Same Active Ingredient or in the Same Drug Class**
ZOLDRIA Infusion contains the same active ingredient as found in Rokfos (zoledronic acid). Patients being treated with ZOLDRIA Infusion should not be treated with Rokfos or other bisphosphonates.

**Hydration and Electrolyte Monitoring**
Patients with hypercalcaemia of malignancy must be adequately rehydrated prior to the administration of zoledronic acid. Loop diuretics should not be used until the patient is adequately rehydrated and should be used with caution in combination with zoledronic acid in order to avoid hypocalcaemia. Zoledronic acid should be used with caution with other nephrotoxic drugs.

Overhydration should be avoided in patients at risk of cardiac failure.
Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, as well as serum creatinine, should be carefully monitored following initiation of therapy with zoledronic acid. If hypocalcaemia, hypophosphataemia or hypomagnesaemia occur, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment; therefore, careful renal function monitoring should be considered.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with Zoledronic acid. Cardiac arrhythmias and neurologic adverse events (including seizures, numbness and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening.

Hypocalcemia must be corrected before initiating Zoledronic acid. Adequately supplement patients with calcium and vitamin D.

ONJ

ONJ has been reported predominantly in cancer patients treated with I.V. bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids, which may be risk factors for ONJ. Postmarketing 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). Many reports of ONJ involved patients with signs of local infection, including osteomyelitis.

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose.
- Cancer, chemotherapy, radiotherapy, corticosteroids, and smoking.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures and poorly fitting dentures.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors.

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

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop ONJ 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 ONJ. The clinical judgement of the treating physician should guide the management plan of each patient, based on individual benefit-risk assessment.

Musculoskeletal Pain

In postmarketing experience, severe and occasionally incapacitating bone, joint and/or muscle pain has been reported in patients taking bisphosphonates, including zoledronic acid. The time to onset of the symptoms varied from 1 day to several months after starting the drug. Most patients had relief of symptoms after stopping treatment. Discontinue use if severe symptoms develop. A subset had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, including zoledronic acid. These fractures can occur anywhere in the femoral shaft from just below the lesser trochanter to just above the supracondylar flare and are transverse or short-oblique in orientation without evidence of comminution. These fractures occur after minimal or no trauma. Patients may experience thigh or groin pain weeks to
months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. A number of case reports noted that patients were also receiving treatment with glucocorticoids (such as prednisone or dexamethasone) at the time of fracture. Causality with bisphosphonate therapy has not been established.

Any patient with a history of bisphosphonate exposure who presents with thigh or groin pain in the absence of trauma should be suspected of having an atypical fracture and should be evaluated. 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. It is unknown whether the risk of atypical femur fracture continues after stopping therapy.

### Patients with Asthma

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

### Renal Impairment

Zoledronic acid is excreted intact primarily via the kidneys, and the risk of adverse reactions, in particular renal adverse reactions, may be greater in patients with impaired renal function. Safety and pharmacokinetic data are limited in patients with severe renal impairment and the risk of renal deterioration is increased. Pre-existing renal impairment and multiple cycles of zoledronic acid and other bisphosphonates are risk factors for subsequent renal deterioration with zoledronic acid. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine also occur in some patients with continual administration of zoledronic acid at recommended doses for the prevention of skeletal-related events, although less frequently.

Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild-to-moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption.

Zoledronic acid treatment in patients with hypercalcaemia of malignancy with severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine greater than 400 mol/L or greater than 4.5 mg/dL were excluded.

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. Zoledronic acid treatment is not recommended in patients with bone metastases with severe renal impairment. In the clinical studies, patients with serum creatinine greater than 265 mol/L or greater than 3.0 mg/dL were excluded and there were only 8 of 564 patients treated with zoledronic acid 4 mg by a 15-minute infusion with a baseline creatinine greater than 2 mg/dL. Limited pharmacokinetic data exists in patients with CrCl less than 30 mL/min and, hence, the use of zoledronic acid is not recommended in patients with severe renal impairment.

### Hepatic Impairment

Only limited clinical data are available for the use of zoledronic acid to treat hypercalcaemia of malignancy in patients with hepatic insufficiency, and these data are not adequate to provide guidance on dosage selection or how to safely use zoledronic acid in these patients.
Fertility

Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F<sub>1</sub> generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolization, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus, these results precluded determining a definitive effect of zoledronic acid on fertility in humans.

Pregnancy

Pregnancy Category D

Bisphosphonates, such as zoledronic acid, are incorporated into the bone matrix, from where they are gradually released over periods of weeks to years. There may be a risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. Zoledronic acid may cause foetal harm when administered to a pregnant woman. In reproductive studies in pregnant rats, subcutaneous doses equivalent to 2.4 or 4.8 times the human systemic exposure resulted in pre- and post-implantation losses, decreases in viable foetuses and foetal skeletal, visceral and external malformations. There are no adequate and well-controlled studies in pregnant women. The extent of bisphosphonate incorporation into adult bone and, hence, the amount available for release back into the systemic circulation, is directly related to the total dose and duration of bisphosphonate use. Although there are no data on foetal risk in humans, bisphosphonates do cause foetal harm in animals, and animal data suggest that uptake of bisphosphonates into foetal bone is greater than into maternal bone. Therefore, there is a theoretical risk of foetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant after completing a course of bisphosphonate therapy. The impact of variables such as time between the cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration (I.V. versus oral) on this risk has not been established. Zoledronic acid should not be used during pregnancy.

Lactation

It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in lactating women.

Paediatric Use

Zoledronic acid is not indicated for use in children. The safety and effectiveness of zoledronic acid was studied in a 1-year, active-controlled trial of 152 paediatric subjects (74 receiving zoledronic acid). The enrolled population was subjects with severe osteogenesis imperfecta, aged 1-17 years, 55% male, 84% Caucasian, with a mean lumbar spine bone mineral density (BMD) of 0.431 gm/cm<sup>2</sup>, which is 2.7 standard deviations below the mean for age-matched controls (BMD Z-score of -2.7). At 1 year, increases in the BMD were observed in the zoledronic acid treatment group. However, changes in the BMD in individual patients with severe osteogenesis imperfecta did not necessarily correlate with the risk for fracture or the incidence or severity of chronic bone pain. The adverse events observed with zoledronic acid use in children did not raise any new safety findings beyond those previously seen in adults treated for hypercalcaemia of malignancy or bone metastases. However, adverse reactions seen more commonly in paediatric patients included pyrexia (61%), arthralgia (26%), hypocalcaemia (22%) and headache (22%). These reactions, excluding arthralgia, occurred most frequently within 3 days after the first infusion and became less common with repeat dosing. Because of long-term retention in bone, zoledronic acid should only be used in children if the potential benefit outweighs the potential risk. Plasma zoledronic acid concentration data was obtained from 10 patients with severe osteogenesis imperfecta (4 in the age group of 3-8 years and 6 in the age group of 9-17 years) infused with a 0.05 mg/kg dose over 30 minutes. Mean $C_{max}$...
and \( \text{AUC}_{\text{0-last}} \) were 167 ng/mL and 220 ng.h/mL, respectively. The plasma concentration time profile of zoledronic acid in paediatric patients represents a multi-exponential decline, as observed in adult cancer patients at an approximately equivalent mg/kg dose.

### Geriatric Use

Clinical studies of zoledronic acid in hypercalcaemia of malignancy included 34 patients who were 65 years of age or older. No significant differences in response rate or adverse reactions were seen in geriatric patients receiving zoledronic acid as compared to younger patients. Controlled clinical studies of zoledronic acid in the treatment of multiple myeloma and bone metastases of solid tumours in patients aged over 65 years revealed similar efficacy and safety in older and younger patients. Because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

### Effects on the 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.

### Undesirable Effects

#### Summary of the Safety Profile

Within 3 days after zoledronic acid administration, an acute-phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia and rigors; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following are the important identified risks with zoledronic acid in the approved indications: renal function impairment, ONJ, acute-phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, and anaphylaxis. The frequencies for each of these identified risks are shown in Table 1.

#### Tabulated List of Adverse Reactions

The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and postmarketing reports following predominantly long-term treatment with 4 mg zoledronic acid:

**Table 1**

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to ≥1/10), uncommon (≥1/1,000 to ≥1/100), rare (≥1/10,000 to ≥1/1,000), and very rare (≥1/10,000), not known (cannot be estimated from the available data).

**Blood and Lymphatic System Disorders?**

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Anaemia</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Neutropenia, thrombocytopenia, leucopenia</td>
</tr>
<tr>
<td>Rare</td>
<td>Pancytopenia, granulocytopenia</td>
</tr>
</tbody>
</table>

**Immune System Disorders**

Uncommon: Hypersensitivity reaction

Rare: Angioneurotic oedema

**Psychiatric Disorders**
Uncommon Anxiety, sleep disturbance, insomnia
Rare Confusion, depression

**Nervous System Disorders**

Common Headache
Uncommon Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare Seizures, numbness and tetany (secondary to hypocalcaemia)

**Eye Disorders**

Common Conjunctivitis
Uncommon Blurred vision, scleritis and orbital inflammation
Very rare Uveitis, episcleritis, iritis

**Cardiac Disorders**

Uncommon Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare Bradycardia
Very rare Cardiac arrhythmia (secondary to hypocalcaemia).

**Respiratory, Thoracic and Mediastinal Disorders**

Uncommon Dyspnoea, cough, bronchoconstriction
Rare Interstitial lung disease, upper respiratory tract infection

**Gastrointestinal Disorders**

Common Nausea, vomiting, anorexia
Uncommon Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth, mucositis, dysphagia, sore throat

**Skin and Subcutaneous Tissue Disorders**

Uncommon Pruritus, rash (including erythematous and macular rash), increased sweating, dermatitis

**Musculoskeletal and Connective Tissue Disorders**

Common Bone pain, myalgia, arthralgia, generalized pain, back pain
Uncommon Muscle cramps, ONJ

**Renal and Urinary Disorders**

Common Renal impairment
Uncommon  Acute renal failure, haematuria, proteinuria, urinary tract infection

General Disorders and Administration Site Conditions

Common  Fever, flu-like syndrome (including fatigue, rigors, malaise, weakness and flushing), lower limb oedema

Uncommon  Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria, progression of cancer, moniliasis, nonspecific infection, dehydration, weight decreased, appetite decreased, alopecia

Investigations

Very common  Hypophosphataemia

Common  Blood creatinine and blood urea increased, hypocalcaemia

Uncommon  Hypomagnesaemia, hypokalaemia, hypocalcaemia

Rare  Hyperkalaemia, hypernatraemia

Description of Selected Adverse Reactions

Renal Function Impairment
Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving the bone, the frequency of renal 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%), and 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 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 4 mg zoledronic acid.

ONJ
Cases of osteonecrosis (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. ONJ has multiple documented risk factors, including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and comorbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged.

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with Zoledronic acid in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an association between Zoledronic acid therapy, the reported event of hypocalcaemia, and the secondary development of cardiac arrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including; seizures, numbness and tetany.

Atrial Fibrillation
In one 3-year, randomized, double-blind, controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg
once-yearly versus placebo in the treatment of postmenopausal osteoporosis, 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 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

Acute Phase Reaction

This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, fatigue, headache, extremity pain, bone pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is 3 days post-zoledronic acid infusion, and the reaction is also referred to using the terms, “influenza like”, “flu-like” or “post-dose” symptoms; these symptoms usually resolve within a few days. Pyrexia has been the most commonly associated symptom, occurring in 44% of patients.

Atypical Fractures of the Femur

During postmarketing experience, the following reactions have been reported (frequency being rare):

- Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

Injection Site Reactions

Local reactions at the infusion site, such as redness or swelling, were observed infrequently. In most cases, no specific treatment is required and the symptoms subside after 24-48 hours.

Postmarketing 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.

ONJ

Cases of osteonecrosis (primarily involving the jaws) have been reported predominantly in cancer patients treated with I.V. bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids, which may be a risk factor for ONJ. Data suggests a greater frequency of reports of ONJ in certain cancers, such as advanced breast cancer and multiple myeloma. The majority of the reported cases are in cancer patients following invasive dental procedures, such as tooth extraction. It is therefore prudent to avoid invasive dental procedures as recovery may be prolonged.

Acute Phase Reaction

Within three days after zoledronic acid administration, an acute phase reaction has been reported, with symptoms including pyrexia, fatigue, bone pain and/or arthralgias, myalgias, chills, and influenza-like illness; these symptoms usually resolve within 3 days of onset, but resolution could take up to 7-14 days. However, some of these symptoms have been reported to persist for a longer duration.

Musculoskeletal Pain

Severe and occasionally incapacitating bone, joint and/or muscle pain has been reported with bisphosphonate use.

Atypical Subtrochanteric and Diaphyseal Femoral Fractures

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, including zoledronic acid.

Ocular Adverse Events

Cases of uveitis, scleritis, episcleritis, conjunctivitis, iritis, and orbital inflammation, including orbital oedema, have been reported during postmarketing use. In some cases, the symptoms resolved with topical steroids.

Hypersensitivity Reactions

There have been rare reports of allergic reaction with I.V. zoledronic acid, including angio-oedema and
bronchoconstriction. Very rare cases of anaphylactic reaction/shock have also been reported.

Additional Adverse Reactions Reported in Postmarketing Use include:

**Central Nervous System:** Taste disturbance, hyperaesthesia, tremor

**Special Senses:** Blurred vision

**Gastrointestinal:** Dry mouth

**Skin:** Increased sweating

**Musculoskeletal:** Muscle cramps

**Cardiovascular:** Hypertension, bradycardia, hypotension (associated with syncope or circulatory collapse, primarily in patients with underlying risk factors)

**Respiratory:** Bronchospasms, interstitial lung disease with positive re-challenge

**Renal:** Haematuria, proteinuria

**General Disorders and Administration Site Conditions:** Weight increase, influenza-like illness (pyrexia, asthenia, fatigue or malaise) persisting for greater than 30 days

**Laboratory Abnormalities:** Hyperkalaemia, hypernatraemia

### Overdosage

Clinical experience with acute overdose of zoledronic acid is limited. The administration of doses up to 48 mg of zoledronic acid in error has been reported. 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. Clinically relevant reductions in serum levels of calcium, phosphorus and magnesium should be corrected by I.V. administration of calcium gluconate, potassium or sodium phosphate, and magnesium sulphate, respectively.

### Incompatibility

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

### Shelf-Life

3 years

### Storage And Handling Instructions

Only a clear solution free from particles and discolouration should be used. Healthcare professionals are advised not to dispose of unused zoledronic acid via the domestic sewage system. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

**Stability**

After dilution, from a microbiological point of view, the diluted solution for infusion 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 2-8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.
Packaging Information

ZOLDRIA Infusion:
Each carton contains
4 mg zoledronic acid in a vial of 10 ml
5 ml Sterile Water for Injection IP
Last updated: Nov 2013
Last reviewed: Nov 2013

ZOLDRIA Infusion

Source URL: https://ciplamed.com/content/zoldria-infusion