Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid or other bisphosphonates, as well as 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.

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as Zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries.

Acute phase reaction

This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea arthralgia and arthritis with subsequent joint swelling. The onset time is ≤ 3 days post-infusion, and the reaction is also referred to using the terms "flu-like" or "post-dose" symptoms.

Atypical fractures of the femur

During post-marketing experience the following reactions have been reported (frequency rare):

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

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: convulsions, hypoaesthesia and tetany.

Effects on ability to drive and use machines

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

DRUG INTERACTIONS

In-vitro studies indicate that zoledronic acid is approximately 22% bound to plasma proteins. 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 the intact drug. However, no in-vivo drug interaction studies have been performed.

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 hypocalcemia.

Nephrotoxic Drugs

Caution is indicated when Zoledronic acid is used with other potentially nephrotoxic drugs.

Thalidomide

No dose adjustment for Zoledronic acid 4 mg is needed when coadministered with thalidomide. Coadministration of thalidomide with Zoledronic acid did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.

USE IN SPECIFIC POPULATIONS

Pregnancy

ZOLEDRONIC ACID SHOULD NOT BE USED DURING PREGNANCY. There are no studies in pregnant women using Zoledronic acid. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Mothers

It is not known whether Zoledronic acid is excreted in human milk. Because many drugs are excreted in human milk, and because Zoledronic acid binds to bone long term, Zoledronic acid should not be administered to a nursing woman.

Pediatric Use

Zoledronic acid is not indicated for use in children.

Geriatric Use

Clinical studies of Zoledronic acid in hypercalcemia 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 tumors in patients over age 65 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.

OVERDOSAGE

Clinical experience with acute overdose 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.

Dosage and Packing Information

Zoledronic acid injection - 4mg/5ml is filled in 5 ml clear plastic vials stoppered with 20 mm rubber stoppers and sealed with 20 mm flip off aluminium seals.

Presentation

Clear Plastic Vial x 5mL with aluminum seal and magenta (Color code: PK-19) flip-off button in a box.

Storage

- Keep out of reach of children.
- Protect from light and moisture.
- Store at temperatures not exceeding 30°C.
- Do not freeze.

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

For suspected adverse drug reaction,
report to the FDA: **www.fda.gov.ph**

Reg. No. : DR-XY44082

MEGA We care

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Date of First Authorization: 28th January 2015
Date of Revision of Package Insert: March 2024

IZ6014403-0040

ZOLEDRONIC ACID

ZINVEL

4mg / 5ml
Concentrate Solution
for Intravenous Infusion
Bisphosphonate

℞

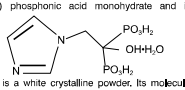
FORMULATION

Each 5ml vial contains:

Zoledronic acid Monohydrate equivalent to Zoledronic acid	4 mg
Water for injection USP	q.s.

DESCRIPTION

Zinvel 4 mg/5ml solution for Intravenous infusion contains zoledronic acid, a bisphosphonic acid which is an inhibitor of osteoclastic bone resorption. Zoledronic acid is designated chemically as (1-Hydroxy-2-imidazol-1-yl-phosphonoethyl) phosphonic acid monohydrate and its structural formula is



Zoledronic acid is a white crystalline powder. Its molecular formula is $C_5H_{10}N_2O_7P_2 \cdot H_2O$ and its molar mass is 290.1 g/Mol. Zoledronic acid is highly soluble in 0.1 N sodium hydroxide solution, sparingly soluble in water and 0.1 N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

Available form

It is available in vials as a sterile liquid concentrate solution for intravenous infusion. Each 5-mL vial contains 4.264 mg of zoledronic acid monohydrate, corresponding to 4 mg zoledronic acid as an anhydrous basis.

Inactive Ingredients: Mannitol USP, Sodium citrate USP, Water for injection USP

CLINICAL PHARMACOLOGY

Mechanism of Action

The principal pharmacologic action of zoledronic acid is inhibition of bone resorption. Although the antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action.

In vitro, zoledronic acid inhibits osteoclastic activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclastic activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Clinical studies in patients with hypercalcemia of malignancy (HCM) showed that single-dose infusions of Zometa 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 hypercalcemia of malignancy (HCM, tumor-induced hypercalcemia) 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 hypercalcemia. Reducing excessive bone resorption and maintaining adequate fluid administration are, therefore, essential to the management of hypercalcemia of malignancy.

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

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

Total serum calcium levels in patients who have hypercalcemia of malignancy may not reflect the severity of hypercalcemia, since concomitant hypoalbuminemia is commonly present. Ideally, ionized calcium levels should be used to diagnose and follow hypercalcemic 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, CSC) 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 hypercalcemia are not available. Distribution Single or multiple (every 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 end of infusion to less than 1% of C_{max} 24 hours post-infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between Days 2 and 28 post-infusion, and a terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 0-16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC0-24h ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively. In vitro and ex vivo studies showed low affinity of zoledronic acid for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5000 ng/mL. In vitro, the plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of zoledronic acid.

Metabolism

Zoledronic acid does not inhibit human P450 enzymes in vitro. Zoledronic acid does not undergo biotransformation in vivo. In animal studies, less than 3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney. Following an intravenous dose of 20 nCi ^{14}C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Excretion

In 64 patients with cancer and bone metastases, on average (± SD) 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 post-Day 2. The cumulative percent of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released, back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h. Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. 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 ([mean ± SD] 403 ± 118 ng/mL versus 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL versus 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations

Pediatrics

Zoledronic acid is not indicated for use in children

Geriatrics

The pharmacokinetics of zoledronic acid were 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 Insufficiency

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

Renal Insufficiency

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 in plasma AUC of 43%. Limited pharmacokinetic data are available for Zoledronic acid in patients with severe renal impairment (creatinine clearance less than 30 mL/min). Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, which is doubled at a creatinine clearance of 10 mL/min. Creatinine clearance is calculated by the Cockcroft-Gault formula: Males: $\frac{\text{(weight in kg)} \times (140 - \text{age})}{(72) \times \text{serum creatinine (mg/100 mL)}}$ Females: (0.85) x (above value)

Zoledronic acid systemic clearance in individual patients can be calculated from the population clearance of Zoledronic acid, CL (L/h)=6.5(CrCl90)0.4. These formulae can be used to predict the Zoledronic acid AUC in patients, where CL=Dose/$AUC_{0-\infty}$. The average $AUC_{0-\infty}$ in patients with normal renal function was 0.42 mgh/L and the calculated $AUC_{0-\infty}$ for a patient with creatinine clearance of 75 mL/min was 0.66 mgh/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 and USAGE

Zoledronic acid is a bisphosphonate indicated for the treatment of:

Hypercalcemia of Malignancy

Zoledronic acid is indicated for the treatment of hypercalcemia of malignancy defined as an albumin-corrected calcium (cCa) of > 12 mg/dL [3.0 mmol/L] using the formula: cCa in mg/dL=Ca in mg/dL + 0.8 (mid-range of measured albumin in mg/dL).

Multiple Myeloma and Bone Metastases of Solid Tumors

Zoledronic acid is indicated for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors, in conjunction with standard antineoplastic therapy. Prostate cancer should have progressed after treatment with at least one hormonal therapy.

Important Limitation of Use

The safety and efficacy of Zoledronic acid in the treatment of hypercalcemia associated with hyperparathyroidism or with other non tumor related conditions has not been established.

DOSAGE AND ADMINISTRATION

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

Hypercalcemia of Malignancy

The maximum recommended dose of Zoledronic acid in hypercalcemia of malignancy (albumin-corrected serum calcium ≥12 mg/dL [3.0 mmol/L]) is 4 mg. The 4-mg dose must be given as a single-dose intravenous infusion over no less than 15 minutes. Patients who receive Zoledronic acid should have serum creatinine assessed prior to each treatment.

Dose adjustments of Zoledronic acid are not necessary in treating patients for hypercalcemia of malignancy presenting with mild-to-moderate renal impairment prior to initiation of therapy (serum creatinine <400 µmol/L or <4.5 mg/dL). Patients should be adequately rehydrated prior to administration of Zoledronic acid. Consideration should be given to the severity of, as well as the symptoms of, tumor-induced hypercalcemia when considering use of Zoledronic acid. Vigorous saline hydration, an integral part of hypercalcemia 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 hypercalcemia 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 hypovolemia. Retreatment with Zoledronic acid 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 retreatment, to allow for full response to the initial dose. Renal function must be carefully monitored in all patients receiving Zoledronic acid and serum creatinine must be assessed prior to retreatment with Zoledronic acid.

Multiple Myeloma and Metastatic Bone Lesions of Solid Tumors

The recommended dose of Zoledronic acid in patients with multiple myeloma and metastatic bone lesions from solid tumors for patients with creatinine clearance >60 mL/min is 4 mg infused over no less than 15 minutes every 3-4 weeks. The optimal duration of therapy is not known. Upon treatment initiation, the recommended Zoledronic acid doses for patients with reduced renal function (mild and moderate renal impairment) are listed in Table 1. These doses are calculated to achieve the same AUC as that achieved in patients with creatinine clearance of 75 mL/min. Creatinine clearance (CrCl) is calculated using the Cockcroft-Gault formula.

Table 1: Reduced Doses for Patients with Baseline CrCl ≤ 60mL/min

Baseline Creatinine Clearance (ml/min)	Zinvel Recommended Dose*
> 60	4 mg
50 - 60	3,5 mg
40 - 49	3,3 mg
30 - 39	3 mg

*Doses calculated assuming target AUC of 0,66(mg*hr/L) (CrCl~75mL/min

During treatment, serum creatinine should be measured before each Zoledronic acid dose and treatment should be withheld for renal deterioration. In the clinical studies, renal deterioration was defined as follows:

For patients with normal baseline creatinine, increase of 0.5 mg/dL.

For patients with abnormal baseline creatinine, increase of 1.0 mg/dL.

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

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

Preparation of Solution

4 mg Dose

Vials of Zoledronic acid 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. Do not store undiluted concentrate in a syringe, to avoid inadvertent injection.

Preparing Reduced Doses for Patients with Baseline CrCl ≤ 60 mL/min

Withdraw the appropriate volume of the Zoledronic acid concentrate from the vial for the dose required (see Table 2).

Table 2: Preparation of Reduced Doses

Zinvel Volume (mL)	Dose (mg)
4,4	3,5
4,1	3,3
3,8	3,0

The withdrawn concentrate must be diluted in 100 mL of sterile 0,9% Sodium Chloride, USP, or 5% Dextrose Injection, USP.

For All Prepared Doses

If not used immediately after dilution with infusion media, for microbiological integrity, the solution should be refrigerated at 2°C-8°C (36°F-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 end of administration must not exceed 24 hours.

Zoledronic acid 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 line separate from all other drugs.

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.

CONTRAINDICATIONS

Hypersensitivity to Zoledronic Acid or Any Components of Zoledronic acid

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

WARNING AND PRECAUTIONS

Drugs with same active ingredient or in the same drug class

Zinvel contains the same active ingredient as found in Zoledronic acid 5mg strength. Patients being treated with Zinvel should not be treated with Zoledronic acid 5mg strength or other bisphosphonates.

Hydration and Electrolyte Monitoring

Patients with hypercalcemia of malignancy must be adequately rehydrated prior to 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 hypocalcemia. Zoledronic acid should be used with caution with other nephrotoxic drugs.

Standard hypercalcemia-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 Zinvel. If hypocalcemia, hypophosphatemia, or hypomagnesemia occur, short-term supplemental therapy may be necessary.

Renal Impairment

Zoledronic acid is excreted intact primarily via the kidney, 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

Preexisting renal insufficiency and multiple cycles of Zoledronic acid and other bisphosphonates are risk factors for subsequent renal deterioration with Zinvel. Factors predisposing to renal deterioration, such as dehydration or the use of other nephrotoxic drugs, should be identified and managed, if possible.

Zoledronic acid treatment in patients with hypercalcemia 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 >400 µmol/L or >4.5 mg/dL were excluded.

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

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in cancer patients treated with intravenous bisphosphonates, including Zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids which may be risk factors for ONJ. 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

Discontinue use if severe symptoms develop.

A typical 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.

Hepatic Impairment

Only limited clinical data are available for use of Zoledronic acid to treat hypercalcemia 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.

UNDESIRABLE EFFECTS

Summary of the safety profile

Within three days after Zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; 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, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 3.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 3, have been accumulated from clinical studies and post-marketing reports follow-ing predominantly chronic treatment with 4 mg zoledronic acid:

Table 3

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), very rare (<1/10,000), not known (cannot be estimated from the available data),

Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
Immune system disorders	
Uncommon:	Hypersensitivity reaction
Rare:	Angioneurotic oedema
Psychiatric disorders	
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusion
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision, scleritis and orbital inflammation
Rare:	Uveitis
Very rare:	Episcleritis
Cardiac disorders	
Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough, bronchoconstriction
Rare:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite
Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal and connective tissue disorders	
Common:	Bone pain, myalgia, arthralgia, generalised pain
Uncommon:	Muscle spasms, osteonecrosis of the jaw
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
General disorders and administration site conditions	
Common:	Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Uncommon:	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
Investigations	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia