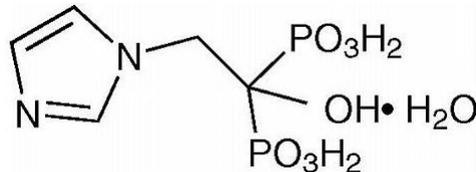


APO-Zoledronic Acid 4 mg/100 mL injection solution for infusion
APO-Zoledronic Acid 4 mg/5 mL concentrated injection for infusion**NAME OF THE MEDICINE**

Zoledronic acid (as monohydrate)

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

Structural Formula:

Molecular Formula: $C_5H_{10}N_2O_7P_2H_2O$

Molecular Weight: 290.11

CAS Registry Number: 165800-06-6 (zoledronic acid monohydrate)
118072-93-8 (zoledronic acid anhydrous)**DESCRIPTION**

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.

4 mg zoledronic acid is available in two forms: zoledronic acid 4 mg/100 mL injection solution for infusion and zoledronic acid 4 mg/5 mL concentrated injection for infusion

Zoledronic acid 4 mg/100 mL injection solution for infusion and zoledronic acid 4 mg/5 mL concentrated injection for infusion are a clear, colourless sterile solution, practically free from visible particles.

Zoledronic acid 4 mg/100 mL and Zoledronic acid 4 mg/5 mL are intended for i.v. administration. Each injection solution contains zoledronic acid 4mg calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate. In addition, the solution contains the following inactive ingredients: mannitol, sodium citrate and water for injections.

PHARMACOLOGY**Pharmacodynamics**

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.

Pharmacokinetics

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.

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

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 insufficiency

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 ± 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 **PRECAUTIONS**).

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 4 mg/5 mL 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 1**.

Table 1: 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] ¹	-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 multiple to SRE [95% CI] ²	0.68 [0.51, 0.91]		0.60 [0.39, 0.92]		0.71 [0.50, 1.01]	
Hazard ratio of multiple to SRE [95% CI] ³	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 2**.

Table 2: 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] ¹	-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 multiple to SRE [95% CI] ²	0.89 [0.75, 1.06]		0.96 [0.79, 1.16]		0.75 [0.58, 0.97]	
Hazard ratio of multiple to SRE [95% CI] ³	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

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 4 mg 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 3**.

Table 3: 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] ¹	-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] ²	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] ³	0.72 [0.56, 0.92]					

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 4 mg 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 4 mg 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 zoledronic acid 4 mg or placebo every four weeks for one year. Patients were evenly distributed between zoledronic acid 4 mg-treated and placebo groups.

The SRE rate ratio at one year was 0.61, indicating that treatment with zoledronic acid 4 mg 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 4 mg-treated group versus 49.6% in the placebo group (p=0.003). Zoledronic acid 4 mg significantly delayed the time of onset of the first SRE compared with placebo (median not reached versus 364 days; p=0.007). Zoledronic acid 4 mg 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 4 mg-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 4 mg was consistently below baseline.

Tumour-induced hypercalcaemia (TIH)

Two identical multicentre, 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 ≥ 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 ≤ 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 multicentre TIH studies were combined in a pre-planned analysis. The results showed that zoledronic acid 4 mg and 8 mg were statistically superior to pamidronate 90 mg for the proportion of complete responders at day 7 and day 10. 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 4: Proportion of complete responders by day in the combined TIH studies

	Day 4	Day 7	Day 10
Zoledronic Acid 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zoledronic acid 8 mg (N=90)	55.6% (p=0.021)	83.3% (p=0.010)*	86.7% (p=0.015)*
pamidronate 90 mg (N=99)	33.3%	63.6%	69.7%
P-values 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 ≤ 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 ≤ 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 5: Results for secondary efficacy variables in the combined TIH studies

	Zoledronic Acid 4 mg			Zoledronic Acid 8 mg			Aredia 90 mg	
	N	Median (days)	P-value	N	Median (days)	P-value	N	Median (days)
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 4mg and should not be administered over less than 15 minutes (see **PRECAUTIONS**).

INDICATIONS

- 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.

CONTRAINDICATIONS

Hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients in the formulation of zoledronic acid; pregnancy and breast-feeding.

PRECAUTIONS

Administration of zoledronic acid

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 20 minutes.

Rehydration

Patients must be maintained in a well hydrated state prior to and following administration of zoledronic acid. Patients must be assessed prior to administration of 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 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.

Zoledronic acid is also marketed in 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 being treated with zoledronic acid for these conditions should not be treated with other strengths of zoledronic acid nor any other bisphosphonate concomitantly.

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.

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 4 mg 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 TIH. 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 zoledronic acid 4 mg 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.

Use in patients with pre-existing renal impairment

Upon initiation of treatment of bone metastases in patients with mild to moderate renal impairment at baseline, dosage reductions are recommended (see **DOSAGE AND ADMINISTRATION**). The use of zoledronic acid is not recommended in patients with severe renal impairment (creatinine clearance < 30 mL/min).

Use in patients with severe renal impairment

Limited clinical data are available in patients with pre-existing renal impairment. Zoledronic acid is excreted exclusively via the kidney and the risk of renal deterioration may be greater in patients with pre-existing impairment of renal function. Patients with severe renal impairment were excluded from the pivotal clinical studies. The use of zoledronic acid is not recommended in patients with severe renal impairment because there are limited clinical safety and pharmacokinetic data in this population, and there is a risk of renal function deterioration in patients treated with bisphosphonates, including zoledronic acid. In clinical trials, patients with severe renal impairment were defined as those with baseline serum creatinine > 400 micromol/L for patients with TIH and > 265 micromol/L for premenopausal patients with EBC and patients with bone metastases, respectively. In pharmacokinetic studies, patients with severe renal impairment were defined as those with baseline creatinine clearance < 30 mL/min.

Use in patients with 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.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in patients treated with bisphosphonates, including zoledronic acid 4 mg. 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.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in patients receiving bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in zoledronic acid-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of zoledronic acid therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. Reports of atypical femoral fracture have been received in patients treated with zoledronic acid; however causality with zoledronic 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 have been reported in patients taking bisphosphonates. This category of drugs includes zoledronic acid (see **ADVERSE 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 rechallenged with the same drug or another bisphosphonate.

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 zoledronic acid is administered with other hypocalcaemia causing drugs, as they may have synergistic effect resulting in severe hypocalcaemia (see **INTERACTIONS WITH OTHER MEDICINES**). Serum calcium should be measured and hypocalcaemia must be corrected before initiating zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

Effect 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 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 (Category B3)

Zoledronic acid was administered subcutaneously to rats and rabbits during the foetal 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 postimplantation loss occurred at 0.4 mg/kg/day

(3 times the human exposure). No embryofoetal 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 body surface area [BSA]). Maternal toxicity was apparent in rabbits at these doses. In the absence of adequate available experience in human pregnancy, zoledronic acid should not be used during pregnancy.

Women of child-bearing potential

Women of child-bearing potential should be advised to avoid becoming pregnant and advised of the potential hazard to the foetus while receiving zoledronic acid. There may be risk of foetal 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

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.

Paediatric Use

The safety and efficacy of zoledronic acid 4 mg in paediatric patients have not been established.

Effect on ability to drive or use machinery

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

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 4 mg 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 4 mg in both species at all doses.

INTERACTIONS WITH OTHER MEDICINES

Absence of interactions

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics (except for loop diuretics, see **Anticipated interactions to be considered**), antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows moderate binding to plasma proteins and human P450 enzymes *in vitro* (see **PHARMACOLOGY-Pharmacokinetics**), but no formal clinical interaction studies have been performed.

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

Anticipated interactions to be considered

Caution is advised when bisphosphonates are administered with aminoglycosides and loop diuretics, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

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

Observed interactions to be considered

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

ADVERSE EFFECTS**Overview of Clinical Trial Data**

The most serious adverse drug reactions reported in patients receiving zoledronic acid in the approved indications are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute phase reaction, and hypocalcaemia. The frequencies of these adverse reactions are shown in Table 6 or shown as adverse reactions from 'Spontaneous reports and literature cases' with "not known" frequency.

Frequencies of adverse reactions to zoledronic acid 4 mg are mainly based on data collected from chronic treatment. Adverse reactions to zoledronic acid 4 mg 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 after zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including pyrexia, fatigue, bone pain, rigors, influenza-like illness, arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection **Description of selected adverse reactions**). 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 4 mg. 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.

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.

Table 6: Adverse drugs reactions

Blood and lymphatic system disorders	
Common:	anaemia
Uncommon:	thrombocytopenia, leukopenia
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, decreased appetite, constipation
Uncommon:	diarrhoea, abdominal pain, dyspepsia, stomatitis, dry mouth
General disorders and administration site conditions	
Common:	acute phase reaction, fever, flu-like syndrome (including fatigue, rigors, malaise and flushing), peripheral oedema, asthenia
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:	angioedema
Laboratory abnormalities	
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:	osteonecrosis of the jaw (ONJ), muscle cramps
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
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)

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

The following adverse reactions have been reported during post approval use of zoledronic acid 4 mg via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency (which is therefore categorised as not known) or establish a causal relationship to drug exposure.

Immune system disorders: anaphylactic reaction/shock

Nervous system disorders: somnolence

Eye disorders: uveitis, episcleritis, scleritis and orbital inflammation

Cardiac disorders: atrial fibrillation

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

Respiratory, thoracic and mediastinal disorders: bronchospasm, interstitial lung disease (ILD)

Skin and subcutaneous tissue disorders: urticaria

Musculoskeletal and connective tissue disorders; severe and occasionally incapacitating bone, joint, and/or muscle pain, atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including zoledronic acid).

Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been associated with reports of renal function impairment.

In a pooled analysis of safety data from zoledronic 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 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, has been reported in patients after the initial dose or a single dose of zoledronic acid (see **PRECAUTIONS**).

Osteonecrosis of the jaw

Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid (uncommon). 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. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see **PRECAUTIONS**). 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 on-set is ≤ 3 days post zoledronic acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms; these symptoms usually resolve within a few days.

DOSAGE AND ADMINISTRATION

For information on the dilution of zoledronic acid 4 mg/100 mL solution, see **Instructions for Use and Handling**.

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

Dosage regimen for adults (including elderly patients)

The recommended dose for the prevention of skeletal-related events in patients with advanced malignancies involving bone is 4 mg lasting no less than 20 minutes given as an intravenous infusion every 3 to 4 weeks. The zoledronic acid 4 mg/5 mL concentrated injection should be diluted before use – see **Instructions for Use and Handling**. The zoledronic acid 4 mg/100 mL injection solution requires no further dilution. 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)

Dosage regimen for adults (including elderly patients)

The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 3.0 mmol/L) is 4 mg given as a single intravenous infusion of no less than 20 minutes. The zoledronic acid 4 mg/5 mL concentrated injection should be diluted before use – see **Instructions for Use and Handling**. The zoledronic acid 4 mg/100 mL injection solution requires no further dilution. The hydration status of patients must be assessed prior to administration of zoledronic acid 4 mg to assure that patients are

adequately hydrated prior to and following administration of zoledronic Acid 4 mg. Following an initial dose of 4 mg, the median time to relapse is 30 days.

Patients with Impaired Renal Function

The use of zoledronic acid 4 mg is not recommended in patients with severe renal impairment (calculated creatinine clearance by Cockcroft-Gault formula of ≤ 30 mL/min) (see **PRECAUTIONS** and **Pharmacokinetics**).

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 ≥ 30 mL/min) as there are insufficient data to support the efficacy of doses less than 4 mg.

When initiating treatment with zoledronic acid 4 mg 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 zoledronic acid 4 mg dose is recommended (see **PRECAUTION**):

Baseline Creatinine Clearance (mL/min)	Zoledronic Acid Recommended Dose
>60	4.0mg
50-60	3.5mg*
40-49	3.3mg*
30-39	3.0mg*

*Doses have been calculated assuming target AUC of 0.66 (mg•hr/L) (CrCl=75 mL/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 zoledronic acid 4 mg should have serum creatinine assessed prior to each dose (see **PRECAUTIONS**). 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 zoledronic acid 4 mg outweighs the possible risk. Patients being treated for bone metastases should have the dose of zoledronic acid 4 mg 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 4 mg treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zoledronic acid 4 mg 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 zoledronic acid 4 mg therapy.

Instructions for use and handling

Zoledronic acid 4 mg/5 mL concentrated injection for infusion and zoledronic acid 4 mg/100 mL injection solution for infusion contain no antimicrobial agent. The injection solution is for single use in one patient on one occasion only. Discard any remaining residue.

1. Zoledronic Acid 4 mg/5 mL concentrate for intravenous injection:

Zoledronic acid 4 mg/5 mL concentrate vial contains an overfill of 4% to permit the withdrawal of the labelled amount of zoledronic acid from the vial. Prior to administration, the required amount of concentrate from one vial must be further diluted with 100 mL of calcium-free infusion solution (0.9 % w/v sodium chloride solution or 5% w/v glucose solution). If refrigerated, the solution must be allowed to reach room temperature before administration.

2. Zoledronic Acid 4 mg/100 mL injection solution for infusion:

Zoledronic acid 4 mg/100 mL injection solution is a “ready to use” presentation and must not be further diluted or mixed with other infusion solutions, except for patients with renal impairment.

3. Instructions on preparing reduced doses of zoledronic acid 4 mg/5 mL concentrated solution and 4 mg/100 mL solution:

In patients with mild to moderate renal impairment, which is defined as CL_{cr} 30 to 60 mL/min, reduced zoledronic acid dosages are recommended, except in patients with TIH (see **DOSAGE AND ADMINISTRATION – Patients with Impaired Renal Function**).

To prepare reduced doses from zoledronic acid 4 mg/5 mL concentrated solution, withdraw an appropriate volume of the concentrate 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

To prepare reduced doses from zoledronic acid 4 mg/100 mL injection solution, remove the corresponding volume of the solution as indicated below and replace with an equal volume of sterile 0.9% w/v sodium chloride or sterile 5% w/v glucose solution.

Baseline Creatinine clearance (mL/min)	Remove the following amount of zoledronic acid solution (mL)	Replace with the same volume of sterile 0.9% w/v sodium chloride or 5% w/v glucose solution (mL)	Zoledronic acid adjusted dose (mg/100 mL)
50 - 60	12.0	12.0	3.5
40 - 49	18.0	18.0	3.3
30 – 39	25.0	25.0	3.0

Stability after dilution

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 of the infusion solution is necessary, hold at 25°C or between 2° - 8°C for not more than 24 hours.

Incompatibilities

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% sodium chloride injection or 5% glucose injection), showed no incompatibility with zoledronic acid 4 mg/100 mL.

To avoid potential incompatibilities, zoledronic acid 4 mg solution is to be diluted with 0.9% sodium chloride injection or 5% glucose injection.

Zoledronic acid 4 mg/100 mL 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.

OVERDOSAGE

Clinical experience with acute overdosage of zoledronic acid 4 mg/100 mL 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.

Contact the Poisons Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

APO-Zoledronic Acid 4 mg/5 mL and APO-Zoledronic Acid 4 mg/100 mL are intended for injection by infusion.

Each vial contains 4 mg Zoledronic Acid as the active ingredient.

APO-Zoledronic Acid 4 mg/5 mL concentrated injection for infusion

APO-Zoledronic Acid 4 mg/5 mL concentrated injection for infusion is a clear, colourless, sterile solution. Clear plastic vials, rubber stoppers and aluminium seals with polypropylene flip off caps of 1, 4 or 10 vials*.

(AUST R 190337).

APO-Zoledronic Acid 4 mg/100 mL injection solution for infusion

APO-Zoledronic Acid 4 mg/100 mL injection solution for infusion is a colourless, sterile solution. Clear glass vials, rubber stoppers and aluminium seals with polypropylene flip off caps of 1, 4 or 5 vials.*

(AUST R 205927).

* Not all pack sizes may be available.

Storage

Store below 25°C.

NAME AND ADDRESS OF THE SPONSOR

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POISONS SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):

APO-Zoledronic Acid 4 mg/100 mL injection solution for infusion: **30 April 2014**

APO-Zoledronic Acid 4 mg/5 mL concentrated injection for infusion: **09 November 2014**

DATE OF LAST AMENDMENT:

23 June 2015