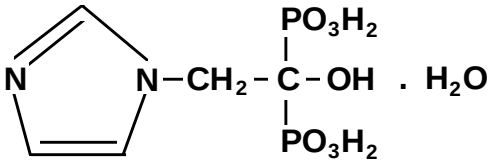
ZOMETA®
(zoledronic acid)

NAME OF THE MEDICINE

The active ingredient of Zometa is a bisphosphonate, zoledronic acid, or 1-hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diphosphonic acid monohydrate.

The chemical structure of zoledronic acid is:



Empirical formula: $C_5H_{10}N_2O_7P_2 \cdot H_2O$
Relative molecular mass: 290.11
CAS 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.

Zometa is available in three forms: a sterile lyophilised powder for injection, a sterile liquid concentrate for injection and an injection solution. Each vial contains 4 mg zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate) and the excipients, mannitol and sodium citrate. Zometa liquid concentrate for injection and Zometa injection solution, also contain water for injections. An ampoule containing 5 mL water for injections is provided as the diluent for the powder for injection. After further dilution, Zometa is administered by intravenous infusion (see "DOSAGE AND ADMINISTRATION").

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 hypercalcemia 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.

Elimination:
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 hypercalcemia 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 ± 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, Zometa was compared to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients with 214 men receiving Zometa 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. Zometa 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 Zometa group compared with placebo (p=0.002). Pain was measured at baseline and periodically throughout the trial. Patients receiving Zometa 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	
	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo	Zometa 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 time 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 event analysis [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 hypercalcemia
** includes vertebral and non-vertebral fractures
*** NR = not reached

In a second phase III randomised, double-blind trial (Study 010) comparing Zometa 4 mg to pamidronate 90 mg, 1,116 patients (561 Zometa 4 mg, 555 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg Zometa 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 Zometa 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	
	Zometa 4 mg	Pam 90 mg	Zometa 4 mg	Pam 90 mg	Zometa 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% C.I][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 time to SRE [95% C.I.][2]	0.89 [0.75, 1.06]		0.96 [0.79, 1.16]		0.75 [0.58, 0.97]	
Hazard ratio of multiple event analysis [95% CI] [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 hypercalcemia
** includes vertebral and non-vertebral fractures
*** NR = not reached

In the third trial (Study 011), Zometa 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. Zometa 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 Zometa 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	
	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo	Zometa 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 hypercalcemia
** includes vertebral and non-vertebral fractures
*** NR = not reached

Zometa 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 Zometa on the skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (adjusted for the presence of prior pathological fracture), divided by the total risk period. Patients received either 4 mg Zometa or placebo every four weeks for one year. Patients were evenly distributed between Zometa-treated and placebo groups.

The SRE rate ratio at one year was 0.61, indicating that treatment with Zometa reduced the rate of occurrence of SREs by 39% compared with placebo (p=0.027). The proportion of patients with at least one SRE (excluding hypercalcemia) was 29.8% in the Zometa-treated group versus 49.6% in the placebo group (p=0.003). Zometa significantly delayed the time of onset of the first SRE compared with placebo (median not reached versus 364 days; p=0.007). Zometa reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo.

In the Zometa-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 Zometa was consistently below baseline.

Tumour-induced hypercalcemia (TIH):

Two identical multicenter, randomised, double-blind, double-dummy studies of Zometa 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 hypercalcemia (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 Zometa 4 mg and 8 mg groups in each study, but not for the pamidronate 90 mg group. To assess the effects of Zometa versus those of pamidronate, the two multicenter TIH studies were combined in a pre-planned analysis. The results showed that Zometa 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 Zometa 8 mg and by day 7 for Zometa 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
Zometa 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zometa 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 Zometa 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 Zometa doses had a statistically longer time to relapse than pamidronate. There was no statistically significant difference between the Zometa doses.

Table 5: Results for secondary efficacy variables in the combined TIH studies

	Zometa 4 mg			Zometa 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 Zometa 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 Zometa for hypercalcemia. 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 Zometa should not exceed 4 mg 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 hypercalcemia.

CONTRAINDICATIONS

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

PRECAUTIONS

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

Rehydration:
Patients must be maintained in a well hydrated state prior to and following administration of Zometa. Patients must be assessed prior to administration of Zometa to ensure that they are adequately hydrated. It is essential in the initial treatment of tumour-induced hypercalcemia 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 hypercalcemia-related metabolic parameters, such as serum levels of calcium, phosphate, magnesium and potassium, as well as serum creatinine, should be carefully monitored after initiating Zometa therapy. If hypocalcemia, hypophosphatemia or

hypomagnesemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

Zometa contains the same active ingredient as in Aclasta (zoledronic acid). Patients being treated with Zometa should not be treated with Aclasta concomitantly. Patients treated with Zometa should also not be treated with any other bisphosphonate concomitantly.

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

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

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 Zometa 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 Zometa is not recommended in patients with severe renal impairment (creatinine clearance < 30mLs/min).

Use in patients with severe renal impairment:
Limited clinical data are available in patients with pre-existing renal impairment. Zometa 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 Zometa 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 Zometa. 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 (see Dosage and Administration).

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
Osteonecrosis of the jaw:
Osteonecrosis of the jaw (ONJ) has been reported predominantly in patients treated with bisphosphonates, including Zometa. 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 osteomyletitis. The condition may result in chronic pain, may be resistant to treatment, and in serious cases may result in disfigurement.

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

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

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

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

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 Zometa-treated patients, who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of Zometa 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 Zometa; however causality with Zometa therapy has not been established.

During Zometa 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 Zometa (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.

Hypocalcemia:

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

Effect on ability to drive or use machinery

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

Effects on fertility

The fertility was decreased in rats dosed SC with 0.1 mg/kg/day zoledronic acid (0.1 times the maximum human exposure of 8 mg, based on 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 fetal organogenesis period. In rats, increased malformations were seen at 0.2 mg/kg/day (1.5 times the expected human exposure at 8 mg, based on AUC), and increased postimplantation loss occurred at 0.4 mg/kg/day (3 times the human exposure). No embryofetal 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, Zometa 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 fetus while receiving Zometa. There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant while receiving bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk has not been established.

Use in Lactation

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 Zometa administration.

Paediatric Use

The safety and efficacy of Zometa in paediatric patients have not been established.

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, Zometa 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 Zometa in both species at all doses.

INTERACTIONS WITH OTHER MEDICINES

Absence of interactions

In clinical studies, Zometa 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 like Zometa are administered with aminoglycosides or calcitonin or and loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

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

Observed interactions to be considered

Caution is advised when Zometa 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 Zometa in the approved indications are: anaphylactic reaction, ocular adverse events, osteonecrosis of the jaw, atypical femoral fracture, atrial fibrillation, renal function impairment, acute phase reaction, and hypocalcemia. The frequencies of these adverse reactions are shown in Table 6 or shown as adverse reactions from 'Spontaneous reports and literature cases' with "not known" frequency.

Frequencies of adverse reactions to Zometa 4 mg are mainly based on data collected from chronic treatment. Adverse reactions to Zometa 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 Zometa 4 mg or pamidronate 90 mg.

Within three days after Zometa 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 reaction"). Arthralgia and myalgia have been reported in approximately 3% of patients. In most cases no specific treatment is required and the symptoms subside after a couple of hours/days.

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

Gastrointestinal reactions such as nausea (5.8%) and vomiting (2.6%) have been reported following intravenous infusion of Zometa. Anorexia was reported in 1.5% of patients treated with Zometa 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 hypercalcemia, Grade 3 (NCI Common Toxicity Criteria [CTC]) elevations of serum creatinine were seen in 2.3%, 3.1% and 3.0% of patients receiving Zometa 4 mg, Zometa 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 drug reactions from clinical trials are listed by MedDRA system organ class. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse drug reaction is based on the following convention (CIOMS III): Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000).

Table 6 Adverse drug reactions

Blood and lymphatic system disorders:	
Common:	anemia
Uncommon:	thrombocytopenia, leukopenia
Rare:	pancytopenia
Vascular disorders:	
Common:	hypertension
Uncommon:	hypotension
Cardiac disorders:	
Rare:	Bradycardia, Cardiac arrhythmia (secondary to hypocalcemia)
Eye disorders:	
Common:	conjunctivitis
Uncommon:	blurred vision
Rare:	Uveitis
Very rare:	episcleritis
Gastrointestinal disorders:	
Common:	nausea, vomiting, decreased appetite, constipation
Uncommon:	diarrhea, 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 increased
Rare:	Arthritis and joint swelling as a symptom of Acute phase reaction
Immune system disorders:	
Uncommon:	hypersensitivity reaction
Rare:	angioedema

Laboratory abnormalities:	
Very common:	hypophosphatemia
Common:	blood creatinine and blood urea increased, hypocalcemia
Uncommon:	hypomagnesemia, hypokalemia
Rare:	hyperkalemia, hypernatremia
Musculoskeletal, connective tissue and bone disorders:	
Common:	bone pain, myalgia, arthralgia, generalised body pain, joint stiffness
Uncommon:	osteonecrosis of jaw (ONJ), muscle spasms
Nervous system disorders:	
Common:	headache, paresthesia
Uncommon:	dizziness, dysgeusia, hypoesthesia, hyperesthesia, tremor
Very rare:	Convulsion, hypoesthesia and tetany (secondary to hypocalcemia)
Psychiatric disorders:	
Common:	sleep disorder
Uncommon:	anxiety
Rare:	Confusional state
Renal and urinary disorders:	
Common:	renal impairment
Uncommon:	acute renal failure, hematuria, proteinuria
Rare:	Acquired Fanconi syndrome
Respiratory, thoracic and mediastinal disorders:	
Uncommon:	dyspnea, 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-marketing experience with Zometa 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: episcleritis, scleritis and orbital inflammation

Cardiac disorders: atrial fibrillation

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

Respiratory, thoracic and mediastinal disorders: bronchospasms

Skin and subcutaneous tissue disorders: urticaria

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

Description of selected adverse reactions

Renal function impairment

Zometa has been associated with reports of renal function impairment.

In a pooled analysis of safety data from Zometa 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 Zometa (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 Zometa 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 Zometa (see "PRECAUTIONS").

Osteonecrosis

Cases of osteonecrosis (primarily of the jaw but also of other anatomical sites including hip, femur and external auditory canal) have been reported predominantly in cancer patients treated with bisphosphonates, including Zometa. Many patients with osteonecrosis of the jaw had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic drugs, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see "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 onset time is $\leq$ 3 days post-Zometa 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 reconstitution and dilution of Zometa, 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, given as an intravenous infusion lasting no less than 15-minutes every 3 to 4 weeks. The Zometa 4 mg/5 mL concentrate should be reconstituted and further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution. The 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 hypercalcemia (TIH)

Dosage regimen for adults (including elderly patients):
The recommended dose in hypercalcemia (albumin-corrected serum calcium ≥ 3.0 mmol/L) is 4 mg, given as a single intravenous infusion of no less than 15 minutes (see "Instructions for Use and Handling"). The Zometa 4 mg/5 mL concentrate should be reconstituted and further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution. The 4 mg/100 mL injection solution requires no further dilution. The hydration status of patients must be assessed prior to administration of Zometa to assure that patients are adequately hydrated prior to and following administration of Zometa. Following an initial dose of 4 mg, the median time to relapse is 30 days.

Patients with Impaired Renal Function

The use of Zometa 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 Zometa 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 Zometa dose is recommended [see "PRECAUTIONS"]:

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

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

Following initiation of therapy, patients who receive Zometa 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 Zometa outweighs the possible risk. Patients being treated for bone metastases should have the dose of Zometa 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, Zometa treatment was resumed only when the creatinine returned to within 10% of the baseline value. Zometa should be resumed at the same dose administered prior to treatment interruption.

Monitoring Advice

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

Instructions for Use and Handling

Zometa powder for injection and Zometa liquid concentrate for injection contain no antimicrobial agent. Zometa is for single use in one patient only. Discard any remaining residue.

1. Zometa powder for intravenous injection:

Each vial contains 4 mg zoledronic acid (anhydrous) as a sterile lyophilised powder (the vial contains an overfill of 4% to permit the withdrawal of the labelled amount of zoledronic acid

from the vial). The powder must first be reconstituted in the vial using 5 mL water for injections from the ampoule supplied (the ampoule contains a 6.2% overfill to permit the withdrawal of the nominal dose from the ampoule). Dissolution must be complete before the solution is withdrawn. The required amount of the reconstituted solution is then further diluted with 100 mL of calcium-free infusion solution (0.9% sodium chloride solution or 5% glucose solution). If refrigerated, the solution must be allowed to reach room temperature before administration.

Stability after reconstitution and dilution:
The reconstituted solution should be used immediately or as soon as practicable after preparation. If storage is necessary hold at 2-8ºC .

After subsequent aseptic addition of the reconstituted solution to the infusion media, the infusion solution should also be used as soon as practicable to reduce the risk of microbiological hazard. If storage of the solution is necessary, hold at 2º - 8ºC. The total storage time from reconstitution of the powder to administration of the Zometa infusion solution should not be longer than 24 hours.

2. Zometa liquid concentrate for intravenous injection:

Zometa is also available as a 4 mg/5 mL liquid concentrate (the liquid concentrate vial contains an overfill of 6% 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.

3. Zometa injection solution:

Zometa is also available as a 4 mg/100 mL injection solution. The Zometa 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.

4. Instructions on preparing reduced doses of Zometa

In patients with mild to moderate renal impairment, which is defined as CLcr 30 to 60 mL/min, reduced Zometa dosages are recommended, except in patients with TIH (see Dosage and Administration – Patients with Impaired renal Function section).

To prepare reduced doses of Zometa® 4 mg powder for injection or Zometa® 4 mg/5 mL concentrate, withdraw an appropriate volume of the reconstituted solution or liquid concentrate (4 mg/ 5 mL) 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 of Zometa 4 mg/100 mL injection solution remove the corresponding volume of Zometa solution as indicated below and replace it with an equal volume of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Baseline Creatinine Clearance (mL/min)	Remove the following amount of Zometa solution (mL)	Replace with the same volume of sterile 0.9% w/v sodium chloride or 5% w/v glucose solution (mL)	Zometa adjusted dose (mg/100mL)
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 2º - 8ºC 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 solution or 5% glucose solution), showed no incompatibility with Zometa.

To avoid potential incompatibilities, Zometa solution is to be diluted with 0.9% sodium chloride solution or 5% glucose solution.

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

PRESENTATION AND STORAGE CONDITIONS

Zometa powder for injection contains 4mg zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate) as a lyophilised powder in glass vials. An ampoule containing 5 mL water for injections is provided as the diluent. Packs of 1 vial and 1 diluent ampoule. Novartis does not supply this presentation of Zometa in Australia.

Zometa concentrated injection contains 4mg zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate) as a liquid concentrate in plastic vials. Packs of 1, 4 or 10 vials. Packs of 4 or 10 vials are not available in Australia.

Zometa injection solution contains 4 mg zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate) as a ready to use injection solution. Packs of 1, 4 or 5 plastic vials. Packs of 4 or 5 vials are not available in Australia.

Storage: Store below 30 degrees C. Medicines should be kept out of the reach of children.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine (Schedule 4)

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

15 March 2001

DATE OF MOST RECENT AMENDMENT

27 June 2016

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