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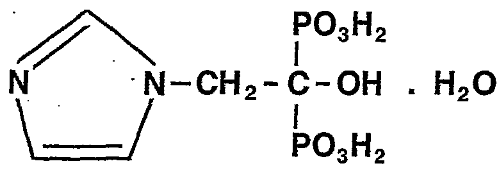
ZOMETA®
(zoledronic acid)

NAME OF THE DRUG

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:



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.

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)

Zometa is available in two forms: a sterile lyophilised powder for injection, and a sterile liquid concentrate for injection. 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 also contains 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 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.

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 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

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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.

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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 hypercalcaemia
** 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.

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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 hypercalcaemia
** 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.

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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] The95% 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

Tumour-induced hypercalcaemia (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 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 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.

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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 hypercalcaemia. The complete response rate observed in these retreated patients was 52%.

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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

Clinically significant 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 over a period of 15 minutes. A 5-minute infusion of Zometa 4 mg has proven to be effective and well tolerated in the treatment of tumour-induced hypercalcaemia. Repeated dose studies in cancer patients with bone metastases suggest that the 15-minute infusion of Zometa provides the same efficacy with an even greater safety margin. Accordingly, a 15-minute infusion rate of zoledronic acid 4 mg was chosen as the recommended schedule.

Rehydration:
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 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 Zometa therapy. If hypocalcaemia, hypophosphataemia or hypomagnesaemia occurs, short-term supplemental therapy may be necessary.

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.

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Monitoring of renal function:
Zoledronic acid, in common with other bisphosphonates, has been associated with the development of renal impairment in some subjects. Factors that may increase the potential for deterioration in renal function include pre-existing renal impairment, chronic administration of Zometa at the 8 mg dose, or using a shorter infusion time than currently recommended. Increases in serum creatinine also occur in some patients with chronic administration of Zometa at recommended doses, although less frequently.

Patients who receive Zometa should have serum creatinine assessed prior to each dose. 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, Zometa was resumed only when the creatinine level returned to within 10% of the baseline value (see "DOSAGE AND ADMINISTRATION").

Osteonecrosis of the jaw:
Osteonecrosis of the jaw has been reported in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

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.

Use in patients with pre-existing 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 adverse reactions may be greater in patients with pre-existing impairment of renal function. Patients with severe renal impairment (creatinine levels > 400 micromol/L for patients with TIH and >265 micromol/L for patients with bone metastases) were excluded from the pivotal clinical studies. In view of the potential impact of bisphosphonates, including Zometa, on renal function, the lack of extensive clinical safety data in patients with severe renal impairment (serum creatinine > 400 micromol/L) and only limited pharmacokinetic data in patients with severe renal

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impairment at baseline (creatinine clearance < 30 mL/min; see "Pharmacokinetics"), the use of Zometa is not recommended in this patient population.

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.

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

Onset of effect:
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.

Effect on ability to drive or use machinery:
No studies on the effects on the ability to drive and use machines have been performed.

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.

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.

Carcinogenicity, Mutagenicity, Impairment of Fertility
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.

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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.

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).

Interactions with Other Drugs

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

Caution is indicated when Zometa is used in combination with other potentially nephrotoxic drugs.
In multiple myeloma patients, the risk of renal dysfunction may be increased when intravenous bisphosphonates are used in combination with thalidomide.

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

ADVERSE REACTIONS

Overview of Clinical Trial Data

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.
Intravenous administration has been most commonly associated with a flu-like syndrome in approximately 9% of patients, consisting of bone pain, fever, fatigue and rigors. Arthralgia

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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.

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

In clinical trials of patients with tumour-induced hypercalcaemia, Grade 3 (NCI Common Toxicity Criteria [CTC]) elevations of serum creatinine were seen in 2.3%, 3.1% and 3.0% of patients receiving 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.

While not observed with Zometa, administration of other bisphosphonates has been associated with bronchoconstriction in acetylsalicylic acid-sensitive asthmatic patients.

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 (≥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), including isolated reports.

Blood and lymphatic system disorders:
Common: anaemia
Uncommon: thrombocytopenia, leukopenia

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Rare: pancytopenia

Cardiovascular disorders:
Uncommon: hypertension
Rare: bradycardia

Eye disorders:
Common: conjunctivitis
Uncommon: blurred vision
Very rare: Uveitis, episcleritis

Gastrointestinal disorders:
Common: nausea, vomiting, anorexia
Uncommon: diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth

General disorders and administration site conditions:
Common: fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Uncommon: asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase

Immune system disorders:
Uncommon: hypersensitivity reaction
Rare: angioneurotic oedema

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
Uncommon: muscle cramps

Nervous system disorders:
Common: headache
Uncommon: dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor

Psychiatric disorders:
Uncommon: anxiety, sleep disturbance
Rare: confusion

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Renal and urinary disorders:
Common: renal impairment
Uncommon: acute renal failure, haematuria, proteinuria

Respiratory, thoracic and mediastinal disorders:
Uncommon: dyspnoea, cough

Skin and subcutaneous tissue disorders:
Uncommon: pruritus, rash (including erythematous and macular rash), increased sweating

Postmarketing: Very rare cases of osteonecrosis (primarily of the jaws) have been reported in patients treated with bisphosphonates. Many had signs of local infection including osteomyelitis. 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 cannot be determined, it is prudent to avoid dental surgery as recovery may be prolonged (see "PRECAUTIONS").

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 reconstituted and further diluted Zometa solution for infusion (diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution), given as a 15-minute intravenous infusion every 3 to 4 weeks. 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)

Initial treatment:

The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 3.0 mmol/L) is 4 mg reconstituted and further diluted Zometa solution for infusion (diluted with 100 mL

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0.9% w/v sodium chloride or 5% w/v glucose solution), given as a single 15-minute intravenous infusion (see "Instructions for Use and Handling"). 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.

Repeated treatment:
Patients who show complete response (normalisation of serum calcium ≤ 2.7 mmol/L) and subsequently relapse or who are refractory to initial treatment may be retreated with Zometa 8 mg given as a single 15-minute intravenous infusion. However, at least one week must elapse before retreatment to allow for a full response to the initial dose. In clinical studies 69 such patients received retreatment with Zometa 8 mg. The response rate observed in these retreated patients was 52%. The 4 mg dose was not tested as a retreatment dose in refractory patients.

Patients with Impaired Renal Function
Dose adjustments are not necessary in patients 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). The use of Zometa is not recommended in patients with severe renal impairment [see "PRECAUTIONS" and "Pharmacokinetics"].

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, increase of > 44 micromol/L
- For patients with abnormal baseline creatinine, 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.

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 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 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.

If an 8 mg dose is required (re-treatment of TIH), two vials are each to be reconstituted with 5 mL water for injections as described above and the resulting 10 mL reconstituted solution further diluted with 100 mL 0.9% sodium chloride solution or 5% glucose solution.

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 2-8°C.

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 2° - 8°C. 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, 5.0 mL 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.

If an 8 mg dose is required (re-treatment), 10.0 mL concentrate corresponding to two vials must be further diluted with 100 mL 0.9 % w/v sodium chloride solution or 5 % w/v glucose solution.

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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 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 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 solution must not be mixed with calcium-containing solutions such as Ringer's solution.

OVERDOSAGE

There is no experience of acute overdosage with Zometa. Patients who have received doses higher than those recommended should be carefully monitored. In the event of clinically significant hypocalcaemia, reversal may be achieved with an infusion of calcium gluconate.

PRESENTATION

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.
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.

Storage: Store below 30 degrees C. Medicines should be kept out of the reach of children.
Poison schedule: 4

SPONSOR

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