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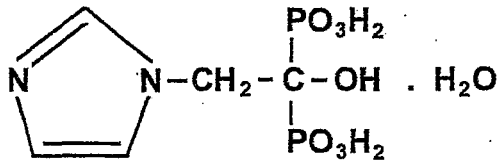
ZOMETA®
(zoledronic acid)

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 g/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 a sterile lyophilised powder 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. An ampoule containing 5 mL water for injections is provided as the diluent. Zometa, after reconstitution and appropriate dilution, 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.

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, and plasma protein binding is low (approximately 22 %) 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.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic or renal 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.

Clinical trials

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

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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:

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.

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

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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 %.

INDICATIONS

Treatment of tumour-induced hypercalcaemia.

CONTRAINDICATIONS

Clinically significant hypersensitivity to zoledronic acid, other bisphosphonates or any of the excipients in the formulation of Zometa.

PRECAUTIONS

Patient monitoring:
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.

Use in patients with renal impairment:
Zoledronic acid, in common with other bisphosphonates, has been associated with the development of renal impairment in some subjects. Patients who receive Zometa should have periodic evaluations of standard laboratory and clinical parameters of renal function. In any patient requiring repeated administration, serum creatinine should be evaluated prior to each dose.

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. Ongoing 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.

Limited clinical data are available in patients with pre-existing renal impairment. Zometa is excreted exlusively 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) were excluded from the pivotal clinical studies and therefore use of Zometa cannot be recommended in this group unless the benefits outweigh the risks.

Use in patients requiring repeated administration of Zometa:
In any patients requiring repeated administration of Zometa, serum creatinine should be evaluated prior to each dose. Patients with evidence of renal function deterioration should be appropriately evaluated and consideration should be given as to whether the potential benefit outweighs the possible risk.

Rehydration:
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.

Hypocalcaemia:
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.

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.

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 unless the benefits to the mother outweigh the risks to the fetus.

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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.

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 preimplantation 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 no appreciable binding to plasma proteins and human P450 enzymes *in vitro* (see "PHARMACOLOGY-Pharmacokinetics"), but no formal clinical interaction studies have been performed.

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.

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ADVERSE REACTIONS

Adverse reactions to Zometa are usually mild and transient and similar to those reported for other bisphosphonates. Intravenous administration has been most commonly associated with a rise in body temperature. Occasionally, a flu-like syndrome consisting of fever, chills, and bone and/or muscle ache was reported. 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 not requiring treatment. The serum calcium may fall to asymptomatic hypocalcaemic levels.

Occasionally, gastrointestinal reactions such as nausea and vomiting have been reported following intravenous infusion of Zometa.

Local reactions at the infusion site such as redness or swelling were also observed.

Some cases of rash, pruritus and chest pain have been observed.

As with other bisphosphonates, isolated cases of conjunctivitis and hypomagnesaemia have been reported.

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 table lists the adverse experiences reported in >15 % of patients irrespective of trial drug relationship in the tumour-induced hypercalcaemia clinical trials.

Adverse Experiences Reported in >15 % of patients Irrespective of Trial Drug Relationship in the Tumour-Induced Hypercalcaemia Clinical Trials

Percent of Patients

	Zometa 4 mg n = 86	**Zometa 8 mg** n = 98	**AREDIA 90 mg** n = 103
Fever	44.2	34.7	33.0
Progression of cancer	16.3	29.6	20.4
Anaemia	22.1	27.6	17.5
Nausea	29.1	21.4	27.2

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Constipation	26.7	19.4	12.6
Dyspnoea	22.1	18.4	19.4
Confusion	12.8	15.3	12.6
Insomnia	15.1	15.3	9.7
Vomiting	14.0	15.3	16.5
Hypokalaemia	11.6	12.2	15.5
Diarrhoea	17.4	10.2	16.5
Abdominal pain	16.3	7.1	12.6

In addition to the above, the following adverse events (%) were also reported in the tumour-induced hypercalcaemia clinical trials in patients receiving 4 mg Zometa, 8 mg Zometa or 90 mg Aredia, respectively: arthralgia/arthritis/myalgia (10.5, 7.1, 2.9), hypocalcaemia (5.8, 8.2, 1.9), hypomagnesaemia (10.5, 6.1, 4.9), hypophosphataemia (12.8, 5.1, 1.9), renal function abnormalities (4.7, 3.1, 1.0) and uraemia (2.3, 4.1, 1.0).

Adverse experiences that were considered related to 4 mg or 8 mg Zometa treatment reported in the tumour induced hypercalcaemia clinical trials are shown in the table below.

Treatment-Related Adverse Experiences Reported in Tumour-Induced Hypercalcaemia Clinical Trials

Percent of Patients

	Zometa 4 mg N= 86	**Zometa 8 mg** N=98	**Aredia 90 mg** N=103
Fever	7.0	10.2	9.7
Hypocalcaemia	5.8	6.1	1.9
Hypophosphataemia	3.5	3.1	1.0
Nausea	1.2	3.1	1.0
Pruritus	1.2	1.0	0
Skeletal pain	1.2	1.0	1.0
Hypomagnesaemia	1.2	0	0
Taste perversion	1.2	0	0
Vomiting	1.2	1.0	0
Chest pain	1.2	1.0	0
Erythematous rash	0	1.0	1.0
Conjunctivitis	0	1.0	1.0
Headache	0	1.0	0
Thrombocytopenia	0	0	1.0

DOSAGE AND ADMINISTRATION

For information on the reconstitution and dilution of Zometa, see "Instructions for use and handling".

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 50 mL 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. 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:

Studies performed to date show that no adjustment of dosage or infusion time is required in patients with mild or moderate renal impairment (serum creatinine < 400 micromol/L) [see "PRECAUTIONS"].

In patients requiring repeated administration of Zometa, serum creatinine should be measured prior to each dose (see "PRECAUTIONS").

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. Limited clinical data are available in patients with renal impairment and monitoring of renal function is recommended in such cases (see "PRECAUTIONS").

Instructions for Use and Handling

Reconstitution and further dilution:

Each vial of Zometa contains 4 mg zoledronic acid (anhydrous) as a sterile lyophilised powder for intravenous use only (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

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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 50 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), 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 50 mL 0.9 % sodium chloride solution or 5 % glucose solution.

Stability after reconstitution and dilution:
The reconstituted solution is chemically and physically stable for 24 hours at room temperature.

After aseptic reconstitution of Zometa powder for injection and subsequent aseptic addition of the reconstituted 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 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 reconstituted solution is to be diluted with 0.9 % sodium chloride solution or 5 % glucose solution.

Zometa reconstituted 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

Each vial of Zometa contains 4 mg zoledronic acid (calculated as the anhydrous form, corresponding to 4.264 mg zoledronic acid monohydrate). An ampoule containing 5 mL water for injections is provided as the diluent.

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

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