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Zometa®

4 mg/5 mL concentrate for solution for infusion
4 mg/100ml solution for infusion
Bisphosphonate

DESCRIPTION AND COMPOSITION

Pharmaceutical forms
Concentrate for solution for infusion.
Solution for infusion.
The solution is sterile, clear and colorless.

Active substance
Zoledronic acid (anhydrous)
Concentrate for solution for infusion: One vial with 5 mL concentrate contains 4 mg zoledronic acid (anhydrous), corresponding to 4.264 mg zoledronic acid monohydrate.
Solution for infusion: One bottle with 100 ml solution contains 4 mg zoledronic acid (anhydrous), corresponding to 4.264 mg zoledronic acid monohydrate.

Excipients
Mannitol, sodium citrate, water for injection
Pharmaceutical formulations may vary between countries.

INDICATIONS

- Treatment of osteolytic, osteoblastic, and mixed bone metastases of solid tumours and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy.
- Treatment of hypercalcemia of malignancy (HCM).

DOSAGE REGIMEN AND ADMINISTRATION

The Zometa 4 mg/5 mL concentrate for solution for infusion should be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution before infusion (see section INSTRUCTIONS FOR USE AND HANDLING). The final Zometa solution for infusion, should be given as an intravenous infusion of no less than 15 minutes.
The Zometa 4 mg/100 mL solution for infusion is a "ready to use" presentation and must not be further diluted or mixed with other infusion solutions except for patients with renal impairment. It should be administered as a single intravenous solution in a separate infusion line in no less than 15 minutes.

Dosage regimen
Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy
In adults and elderly patients, the recommended Zometa dose is a 4 mg infusion given every 3 to 4 weeks.
Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.

Treatment of hypercalcemia of malignancy (HCM)
In adult and elderly patients, the recommended Zometa dose in hypercalcemia (albumin-corrected serum calcium ≥ 12.0 mg/dL or 3.0 mmol/L) is a single 4 mg infusion. Patients must be maintained well hydrated prior to and following administration of Zometa.

Treatment of patients with renal impairment
Patients with hypercalcemia with malignancy (HCM)
Zometa treatment in adult patients with hypercalcemia of malignancy (HCM) who also have severe renal impairment should be considered only after evaluating the risks and benefit of treatment. In the clinical studies, patients with serum creatinine ~400 micromol/L or >4.5 mg/dL were excluded. No dose adjustment is necessary in HCM patients with serum creatinine < 400 micromol/L or < 4.5 mg/dL (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

Treatment of bone metastases and treatment of osteolytic lesions, in conjunction with standard antineoplastic therapy.
When initiating treatment with Zometa, serum creatinine levels and creatinine clearance (CL_{cr}) should be determined. CL_{cr} is calculated from serum creatinine levels using the Cockcroft-Gault formula. Zometa is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CL_{cr} < 30 mL/min. In clinical trials with Zometa, patients with serum creatinine > 265 micromol/L or > 3.0 mg/dL were excluded. 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 to 60 mL/min, the following Zometa dose is recommended (see also section SPECIAL WARNINGS AND PRECAUTIONS FOR USE):

Table 1

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, serum creatinine should be measured prior to each dose of Zometa and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:
- For patients with normal baseline serum creatinine (< 1.4 mg/dL), an increase of ≥ 0.5 mg/dL;
- For patients with an abnormal baseline creatinine (> 1.4 mg/dL), an increase of ≥ 1.0 mg/dL.

In the clinical studies, Zometa treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section WARNINGS AND PRECAUTIONS). Zometa should be resumed at the same dose as that prior to treatment interruption.

Method of administration
Zometa must only be administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.
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 in no less than 15 minutes..
Patients must be maintained in a well hydrated state prior to and following administration of Zometa.

Preparation of reduced Zometa doses
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 HCM (see section Dosage regimen sub-section).
To prepare reduced doses of Zometa 4 mg/5 mL concentrate, withdraw an appropriate volume of the liquid concentrate needed, as follows:
4.4 mL for 3.5 mg dose
4.1 mL for 3.3 mg dose
3.8 mL for 3.0 mg dose
For information on the reconstitution and dilution of Zometa (see section INSTRUCTIONS FOR USE AND HANDLING). The withdrawn amount of the concentrate must be diluted in 100 mL of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion of no less than 15 minutes.
To prepare reduced doses of Zometa 4 mg/100 mL solution for infusion, 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.

Table 2

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

CONTRAINDICATIONS

- Hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of Zometa.
- Pregnancy and breast-feeding women (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

WARNINGS AND PRECAUTIONS

General
All patients, including patients with mild to moderate renal impairment, must be assessed prior to administration of Zometa to assure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.
Standard hypercalcemia-related metabolic parameters, such as albumin-corrected serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating Zometa therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesemia occur, 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. Zometa should also not be given together with other bisphosphonates since the combined effects of these agents are unknown.
While not observed in clinical trials with Zometa, there have been reports of bronchoconstriction in acetylsalicylic acid sensitive asthmatic patients receiving bisphosphonates.

Renal impairment
Adult patients with HCM and 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 (see section DOSAGE REGIMEN AND ADMINISTRATION).
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 to 3 months.
Bisphosphonates have been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zometa or other bisphosphonates as well as use of nephrotoxic drugs or using a shorter infusion time than currently recommended. While the risk is reduced with a dose of Zometa 4 mg administered over no less than 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zometa. Increases in serum creatinine also occur in some patients with chronic administration of Zometa at recommended doses for prevention of skeletal related events, although less frequently.
Serum creatinine levels should be measured before each Zometa dose. In patients with mild to moderate renal impairment at the initiation of Zometa treatment, lower doses are recommended in all adult patients except patients with HCM. In patients who show evidence of renal deterioration during treatment, Zometa should only be resumed when creatinine level returns to within 10% of baseline value (see section DOSAGE AND ADMINISTRATION).
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 or ≥ 4.5 mg/dL for patients with HCM and ≥ 265 micromol/L or ≥ 3.0 mg/dL for all other patients, respectively.) In pharmacokinetic studies, patients with severe renal impairment were defined as those with baseline creatinine clearance <30 mL/min (see section CLINICAL PHARMACOLOGY, subsection Pharmacokinetics, see section DOSAGE REGIMEN AND ADMINISTRATION).

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 adult cancer patients treated with bisphosphonates, including Zometa. Many of these patients were also receiving chemotherapy and corticosteroids. Many had signs of local infection including osteomyelitis.
Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma), and dental status (dental extraction, periodontal disease, local trauma including poorly fitting dentures).
Patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates.
While on treatment with bisphosphonates, 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 an 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.

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking bisphosphonates, including Zometa (see section ADVERSE DRUG REACTIONS). 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 re-challenged with the same drug or another bisphosphonate.

Hypocalcemia
Hypocalcaemia 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 hypocalcaemia. In some instances, the hypocalcaemia may be life-threatening. Caution is advised when Zometa is administered with other hypocalcaemia causing drugs, as they may have a synergistic effect, resulting in severe hypocalcaemia (see section INTERACTIONS). Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zometa therapy. Patients should be adequately supplemented with calcium and vitamin D.

INTERACTIONS

Anticipated interactions to be considered
Caution is advised when bisphosphonates like Zometa are administered with aminoglycosides or calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section WARNINGS AND PRECAUTIONS).
Caution is indicated when Zometa is used with other potentially nephrotoxic drugs (see section ADVERSE DRUG REACTIONS).

Observed interactions to be considered
Caution is advised when Zometa is administered with anti-angiogenic drugs as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these drugs.

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.
No dose adjustment for Zometa 4 mg is needed when coadministered with thalidomide. In a pharmacokinetic study of 24 patients with multiple myeloma, Zometa 4 mg given as a 15- minute infusion was administered either alone or with thalidomide (100 mg once daily on days 1-14 and 200 mg once daily on days 15-28).
Coadministration of thalidomide with Zometa did not significantly change the pharmacokinetics of zoledronic acid or creatinine clearance.
Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes in vitro (see section PHARMACOKINETICS), but no formal clinical interaction studies have been performed.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk Summary
Zometa should not be used during pregnancy (see section CONTRAINDICATIONS).
There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section CONTRAINDICATION) 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.
Studies in rats have shown reproductive toxicological effects (see section NON-CLINICAL SAFETY DATA). The potential risk in humans is unknown.

Data

Human Data
There are no adequate and well-controlled studies of Zometa in pregnant women.

Animal Data
Teratogenicity studies were performed in two species, both via subcutaneous administration of zoledronic acid. In rats teratogenicity was observed at doses ≥ 0.2 mg/kg/day (2.4 fold the anticipated human exposure, based on AUC comparison) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats.
In rabbits no teratogenic or embryo/fetal effects were observed, although maternal toxicity was marked at 0.1 mg/kg/day. Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

Lactation

Risk summary
It is not known whether zoledronic acid is excreted into human milk. Zometa should not be used by breast-feeding women (see section CONTRAINDICATIONS).

Females and males of reproductive potential
Women of child-bearing potential should be informed of the potential hazard to the fetus and be advised to avoid becoming pregnant while receiving Zometa.

Infertility
The fertility was decreased in rats dosed subcutaneously with 0.01 mg/kg/day of zoledronic acid with systemic exposures of 0.12 times the human systemic exposure following an intravenous dose of 4 mg (based on AUC). The effects observed included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses. There are no data available in humans.

ADVERSE DRUG REACTIONS

Summary of the safety profile
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 3 or shown as adverse reactions from 'Spontaneous reports and literature cases' with 'not known' frequency.
Frequencies of adverse reactions for 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. Those reactions can be expected to occur in approximately one third of patients treated with Zometa. Within three days after Zometa administration, an acute phase reaction has commonly been reported, with symptoms including pyrexia, fatigue, bone pain, chills, influenza-like illness, arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see subsection Description of selected adverse reaction). Cases of arthralgia and myalgia have been reported. Very commonly, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels, which is asymptomatic not requiring treatment. Commonly, the serum calcium may fall to asymptomatic hypocalcemic levels. Gastrointestinal reactions, such as nausea and vomiting have been commonly reported following intravenous infusion of Zometa. Uncommonly, local reactions at the infusion site, such as redness or swelling and/or pain were also observed. Anorexia was commonly reported in patients treated with Zometa 4 mg. Rash or pruritus has been uncommonly observed.
As with other bisphosphonates, cases of conjunctivitis have been commonly reported.
Based on pooled analysis of placebo-controlled studies, severe anemia (Hb < 8.0 g/dL) was commonly reported in patients receiving Zometa. Adverse reactions (Table 3) 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 3 Adverse drug reactions from clinical trials

Blood and lymphatic system disorders	
Common:	Anemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
Immune system disorders	
Uncommon:	Hypersensitivity reaction
Rare:	Angioedema
Nervous system disorders	
Common:	Headache, paresthesia
Uncommon:	Dizziness, dysgeusia, hypoesthesia, hyperesthesia, tremor
Very rare:	Convulsion, hypoaesthesia and tetany (secondary to hypocalcemia)
Psychiatric disorders	
Common:	Sleep disorder
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusional state
Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision
Rare:	Uveitis, episcleritis
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite, constipation
Uncommon:	Diarrhea, abdominal pain, dyspepsia, stomatitis, dry mouth
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)
Musculoskeletal and connective tissue disorders	
Common:	Bone pain, myalgia, arthralgia, generalised body pain, joint stiffness
Uncommon:	Osteonecrosis of jaw (ONJ), muscle spasms
Cardiac disorders	
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcemia)
Vascular disorders	
Common:	Hypertension
Uncommon:	Hypotension
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
General disorders and administration site conditions	
Common:	Acute phase reaction, pyrexia, influenza-like illness (including: fatigue, chills, 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
Investigations	
Very common:	Hypophosphatemia
Common:	Blood creatinine and blood urea increased, hypocalcemia
Uncommon:	Hypomagnesemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatremia

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.Since 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 categorized as not known). Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 4 Adverse drug reactions from spontaneous reports and literature (frequency not known)

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
Bronchospasm
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 tumors (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 section WARNINGS AND PRECAUTIONS, see section INTERACTIONS).

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 section WARNINGS AND PRECAUTIONS). Data suggests a greater frequency of reports of ONJ based on tumor 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 ≤ 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.

Atrial fibrillation
In one 3 year, randomized, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with Zometa (zoledronic acid) 4 mg every 3 to 4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

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.

CLINICAL PHARMACOLOGY

Pharmacodynamics (PD)
Mechanisms of action (MOA)
Zoledronic acid is a highly potent drug that belongs to the bisphosphonates class of drugs, which act primarily on bone. It is one of the most potent inhibitors of osteoclastic bone resorption known to date.
The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralization or mechanical properties of bone.
In addition to being a very potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:
- *In vivo*: Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment making it less conducive to tumour cell growth, anti-angiogenic activity, anti-pain activity
- *In vitro*: inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

Pharmacokinetics (PK)
Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients with bone metastases yielded the following pharmacokinetic data.
No pharmacokinetic data for zoledronic acid are available in patients with hypercalcemia.
After initiating the infusion of zoledronic acid, the plasma concentrations of the drug rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to <10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of drug on day 28.

Distribution
Zoledronic acid shows low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/mL to 5000 ng/mL. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/mL to 77% at 2000 ng/mL of zoledronic acid.

Biotransformation/Metabolism
Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Zoledronic acid does not inhibit human P450 enzymes *in vitro*.

Elimination
Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2}$alpha 0.24 and t_{1}beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2}$gamma 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug given every 28 days. Over the first 24 hours, 39 ± 16% 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 very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 L/h, independent of dose, and unaffected by gender, age, race, and body weight.

Linearity/non-linearity
The zoledronic acid pharmacokinetics were found to be dose-independent. 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 populations
Hepatic impairment
No pharmacokinetic data for zoledronic acid are available in patients with hepatic impairment. 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 feces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

Renal impairment
The renal clearance of zoledronic acid was 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

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50 mL/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 72% 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). The use of Zometa is not recommended in patients with severe renal impairment (see section WARNINGS AND PRECAUTIONS).

Effect of gender, age and race

The three pharmacokinetic studies conducted in cancer patients with bone metastases reveal no effect by gender, race, age (range 38 to 84 years), and body weight on zoledronic acid total clearance.

CLINICAL STUDIES

Clinical trial results in the treatment of osteolytic, osteoblastic and mixed bone metastases and osteolytic lesions of multiple myeloma, in conjunction with standard antineoplastic therapy

Zometa was compared to placebo for the prevention of skeletal-related events (SREs) in adult prostate cancer patients with 214 men receiving Zometa 4 mg versus 208 receiving placebo. 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 demonstrated a significant advantage over placebo for the proportion of patients experiencing at least one skeletal-related event (SRE) (38% for Zometa 4 mg versus 49% for placebo, p=0.028), delayed the median time to first SRE (488 days for Zometa 4 mg versus 321 days for placebo, p=0.009), and reduced the annual incidence of event per patient - skeletal morbidity rate (0.77 for Zometa 4 mg versus 1.47 for placebo, p=0.005). Multiple event analysis showed 36% 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 3, 9, 21 and 24. Fewer Zometa patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 5.

In a second study, Zometa reduced the number of SREs and extended the median time to an SRE by over two months in the population of adult patients who had other solid tumors involving bone, which had a median survival of only six months (134 patients with non- small-cell lung cancer (NSCLC), 123 with other solid tumors treated with Zometa vs 130 patients with NSCLC, 120 with other solid tumors treated with placebo). After initial 9 months of treatment, 101 patients entered the 12 month extension study, and 26 completed the full 21 months. Zometa 4 mg reduced the proportion of patients with SREs (39% for Zometa 4 mg versus 48% for placebo, p=0.039), delayed the median time to first SRE (236 days for Zometa 4 mg versus 155 days for placebo, p=0.009), and reduced the annual incidence of events per patient-skeletal morbidity rate (1.74 for Zometa 4 mg versus 2.71 for placebo, p=0.012). Multiple event analysis showed 30.7% risk reduction in developing skeletal-related events in the Zometa group compared with placebo (p=0.003). The treatment effect in non- small cell lung cancer patients appeared to be smaller than in patients with other solid tumors. Efficacy results are provided in Table 6.

Table 5: Efficacy results (prostate cancer patients receiving hormonal therapy)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo
N	214	208	214	208	214	208
Proportion of patients with SREs (%)	38	49	17	25	26	33
p-value	0.028		0.052		0.119	
Median time to SRE (days)	488	321	NR	NR	NR	640
p-value	0.009		0.020		0.055	
Skeletal morbidity rate	0.77	1.47	0.20	0.45	0.42	0.89
p-value	0.005		0.023		0.060	
Risk reduction of suffering from multiple events** (%)	36	-	NA	NA	NA	NA
p-value	0.002		NA		NA	

* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable

Table 6: Efficacy results (solid tumours other than breast or prostate cancer)

	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo	Zometa 4 mg	Placebo
N	257	250	257	250	257	250
Proportion of patients with SREs (%)	39	48	16	22	29	34
p-value	0.039		0.064		0.173	
Median time to SRE (days)	236	155	NR	NR	424	307
p-value	0.009		0.020		0.079	
Skeletal morbidity rate	1.74	2.71	0.39	0.63	1.24	1.89
p-value	0.012		0.066		0.099	
Risk reduction of suffering from multiple events** (%)	30.7	-	NA	NA	NA	NA
p-value	0.003		NA		NA	

* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable

In a third phase III randomized, double-blind trial comparing Zometa 4 mg to pamidronate 90 mg, 1,122 adult patients (564 Zometa 4 mg, 558 pamidronate 90 mg) with multiple myeloma or breast cancer with at least one bone lesion were treated with 4 mg Zometa or 90 mg pamidronate every 3 to 4 weeks. Eight patients were excluded from the efficacy analysis because of good clinical practice non-compliance. 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 analyses revealed a significant risk reduction of 16% (p=0.030) in patients treated with Zometa 4 mg. Efficacy results are provided in Table 7.

Table 7: Efficacy results (breast cancer and multiple myeloma patients)

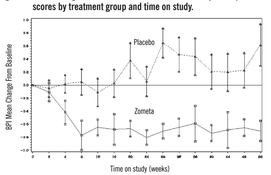
	Any SRE (+HCM)		Fractures*		Radiation therapy to bone	
	Zometa 4 mg	Pam 90 mg	Zometa 4 mg	Pam 90 mg	Zometa 4 mg	Pam 90 mg
N	561	555	561	555	561	555
Proportion of patients with SREs (%)	48	52	37	39	19	24
p-value	0.198		0.653		0.037	
Median time to SRE (days)	376	356	NR	714	NR	NR
p-value	0.151		0.672		0.026	
Skeletal morbidity rate	1.04	1.39	0.53	0.60	0.47	0.71
p-value	0.084		0.614		0.015	
Risk reduction of suffering from multiple events** (%)	16	-	NA	NA	NA	NA
p-value	0.030		NA		NA	

* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial.
NR Not Reached
NA Not Applicable

In clinical trials performed in adult patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity. Zometa was also studied in a double-blind, randomized, placebo-controlled trial in 228 adult patients with documented bone metastases from breast cancer to evaluate the effect of Zometa on the skeletal-related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcemia and adjusted for prior 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). Median time to onset of the first SRE was not reached in the Zometa-treated arm at the end of the study and was significantly prolonged compared to placebo (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, decreases in pain scores from baseline (using the Brief Pain Inventory, BPI) occurred from 4 weeks onwards and at every subsequent time point during the study, while the pain score in the placebo group remained unchanged or increased from baseline (Figure 1). Zometa inhibited the worsening of the analgesic score more than placebo. In addition, 71.8% of Zometa-treated patients versus 63.1% of placebo patients showed improvement or no change in the ECOG performance score at the final observation.

Figure 1: Mean change from baseline in Brief Pain Inventory (BPI) pain scores by treatment group and time on study.



Clinical trial results in the treatment of HCM

Clinical studies in hypercalcemia of malignancy (HCM) demonstrated that the effect of zoledronic acid is characterized by decreases in serum calcium and urinary calcium excretion.

To assess the effects of Zometa versus pamidronate 90 mg, the results of two pivotal multicentre studies in adult patients with HCM 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. There was faster normalization of corrected serum calcium at day 4 for Zometa 8 mg and at day 7 for Zometa 4 mg and 8 mg. The following response rates were observed Table 8:

Table 8: Proportion of complete responders by day in the combined HCM 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 denote statistical superiority over pamidronate.

Median time to normo-calcaemia was 4 days. By day 10, the response rate was 87 to 88 % for the Zometa treatment groups versus 70 % for pamidronate 90 mg. Median time to relapse (re- increase of albumin-corrected serum calcium ≥ 2.9 mmol/L) was 30 to 40 days for patients treated with Zometa versus 17 days for those treated with pamidronate 90 mg. The results showed that both Zometa doses were statistically superior to pamidronate 90 mg for time to relapse. There were no statistically significant differences between the two Zometa doses.

In clinical trials performed in adult patients with hypercalcemia of malignancy (HCM), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

NON-CLINICAL SAFETY DATA

Toxicity studies

In the bolus parenteral studies, zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2 to 3 days in dogs for up to 52 weeks was also well tolerated.

The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphysis of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

The kidney was identified as a major target organ for toxicity in parenteral studies with zoledronic acid. In the intravenous infusion studies, renal tolerability was observed in rats given six infusions at doses of up to 0.6 mg/kg at 3-day intervals, while five infusions of 0.25 mg/kg administered at 3-week intervals were well tolerated in dogs.

Reproduction toxicity

For reproductive toxicity see section 9 Pregnancy, lactation, females and males of reproductive potential.

Mutagenicity

Zoledronic acid was not mutagenic *in vitro* and *in vivo* in the mutagenicity tests performed.

Carcinogenicity

In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential.

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% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with Zometa.

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

Zometa concentrate and Zometa "ready-to-use" solution for infusion must not be mixed or come into contact 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.

STORAGE

See also folding box.

Zometa should not be used after the date marked "EXP" on the pack.

Zometa must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

Zometa 4 mg/5 mL concentrate for solution for infusion and Zometa 4mg/100mL solution for infusion are for intravenous use only.

The 4mg/5mL concentrate from one vial (or the volume of the concentrate withdrawn as required) 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).

The 4 mg/100 mL solution is a "ready-to-use" presentation which must not be further diluted or mixed with other infusion solutions except for patients with renal impairment. For reduced doses of this presentation in patients with mild and moderate renal impairment (see section DOSAGE REGIMEN AND ADMINISTRATION).

After aseptic reconstitution and dilution (or for reduced doses of the 'ready-to-use' presentation), it is preferable to use the reconstituted and diluted product immediately. If not used immediately, the reconstituted solution should be stored at 2 to 8°C. The duration and conditions of storage prior to use are under the healthcare provider's responsibility. The total time between reconstitution, dilution, storage in a refrigerator at 2 to 8°C and end of administration must not exceed 24 hours. If refrigerated, the solutions must be allowed to reach room temperature before administration. (See also section DOSAGE REGIMEN AND ADMINISTRATION).

Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used.

Manufacturer:

See folding box.

International Package Leaflet

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