NOVARTIS

Drug Regulatory Affairs

ZOMETA®

(zoledronic acid)

4 mg powder and solvent for solution for infusion

International Package Leaflet

(without prevention of fracture and bone loss in postmenopausal women with EBC treated with AIs & treatment of severe OI in paediatric patients)

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Zometa®

4 mg powder and solvent for solution for infusion

Bisphosphonate

COMPOSITION AND PHARMACEUTICAL FORM

One vial contains 4 mg zoledronic acid (anhydrous), corresponding to 4.264 mg zoledronic acid monohydrate.

For a full list of excipients, see EXCIPIENTS.

Powder and solvent for solution for infusion.

INDICATIONS

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in patients with advanced malignancies involving bone.
- Treatment of hypercalcaemia of malignancy (HCM).

DOSAGE AND ADMINISTRATION

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.

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

Adults and elderly

The recommended dose in 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 an intravenous infusion lasting no less than 15 minutes 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 HCM

Adults and elderly

The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥12.0 mg/dL or 3.0 mmol/L) 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 single

intravenous infusion of no less than 15 minutes. Patients must be maintained well hydrated prior to and following administration of Zometa.

Renal impairment

HCM:

Zometa treatment in adult patients with hypercalcaemia of malignancy (HCM) who also have severe renal impairment should be considered only after evaluating the risks and benefits 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).

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

When initiating treatment with Zometa in adult patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine levels and creatinine clearance (CLcr) should be determined. CLcr 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 CLcr <30 mL/min. In clinical trials with Zometa, patients with serum creatinine >265 micromol/L or >3.0 mg/dL were excluded.

In adult patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 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) (CLcr=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 SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Zometa should be resumed at the same dose as that prior to treatment interruption.

Instructions on preparing reduced doses of Zometa

Withdraw an appropriate volume of the reconstituted solution (4 mg/ 5 mL) as needed:

4.4 mL for 3.5 mg dose

4.1 mL for 3.3 mg dose

3.8 mL for 3.0 mg dose

For information on the reconstitution and dilution of Zometa, see section INSTRUCTIONS FOR USE AND HANDLING. The withdrawn amount of reconstituted solution 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.

CONTRAINDICATIONS

Zometa powder for solution for infusion is contraindicated in pregnancy, breast-feeding women, in patients with clinically significant hypersensitivity to zoledronic acid or other bisphosphonates or any of the excipients in the formulation of Zometa.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE

General

Patients 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 hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating Zometa therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occur, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

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

~~The safety of Zometa in paediatric patients with renal impairment has not been established.~~

Renal insufficiency

Adult patients with HCM with evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zometa outweighs the possible risk.

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.

Patients should have their serum creatinine levels assessed prior to each dose of Zometa. Upon initiation of treatment in adult patients with bone metastases with mild to moderate renal impairment, lower doses of Zometa are recommended. 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).

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 (in clinical trials defined as serum creatinine ≥400 micromol/L or ≥4.5 mg/dL for patients with HCM and ≥265 micromol/L or ≥3.0 mg/dL for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance <30 mL/min), the use of Zometa is not recommended in patients with severe renal impairment.

The safety of Zometa in paediatric patients with renal impairment has not been established.

Hepatic insufficiency

As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in 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 tumour 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, 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.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking bisphosphonates. However, such reports have been infrequent. This category of drugs includes Zometa (zoledronic acid). 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.

INTERACTIONS

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 does not inhibit human P450 enzymes *in vitro* (see section PHARMACOKINETICS), but no formal clinical interaction studies have been performed. Caution is advised when bisphosphonates like Zometa are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is indicated when Zometa is used with other potentially nephrotoxic drugs. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

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

PREGNANCY AND LACTATION

Pregnancy

In animal reproduction studies zoledronic acid was administered subcutaneously to rats and rabbits. It was found to be teratogenic at doses ≥ 0.2 mg/kg bodyweight in rats. In rabbits, there was no teratogenicity or foetotoxicity but maternotoxicity was found. Zometa should not be used during pregnancy.

Lactation

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

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

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

UNDESIRABLE EFFECTS

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 either for Zometa or for pamidronate 90 mg. Intravenous administration has been most commonly associated with a flu-like syndrome in about 9% of patients including bone pain, fever, fatigue and rigors. Occasionally cases of arthralgia and myalgia in approximately 3% of patients have been reported.

Frequently, the reduction in renal calcium excretion is accompanied by a fall in serum phosphate levels in approximately 20% of patients, which is asymptomatic not requiring 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. Occasionally local reactions at the infusion site such as redness or swelling and/or pain were also observed in less than 1% of the patients.

Anorexia was reported in 1.5% of patients treated with Zometa 4 mg.

Few cases of rash or pruritus, have been observed (below 1%).

As with other bisphosphonates, cases of conjunctivitis in approximately 1% have been reported.

There have been some reports of impaired renal function (2.3%) in the bone metastases population; however, other risk factors in this ill patient population may have contributed as well. Based on pooled analysis of placebo controlled studies, severe anaemia (Hb <8.0 g/dL) was reported in 5.2% of patients receiving Zometa 4 mg versus 4.2% on placebo.

The following adverse drug reactions, listed in Table 2, have been accumulated from clinical studies following predominantly chronic treatment with zoledronic acid:

Adverse reactions (Table 2) are ranked under headings of frequency, the most frequent first, 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.

Table 2

Blood and lymphatic system disorders		
	Common:	Anaemia
	Uncommon:	Thrombocytopenia, leucopenia
	Rare:	Pancytopenia
Nervous system disorders		
	Common:	Headache

	Uncommon:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor
Psychiatric disorders		
	Uncommon:	Anxiety, sleep disturbance
	Rare:	Confusion
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
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Dyspnoea, cough
Skin and subcutaneous tissue disorders		
	Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal, connective tissue and bone disorders		
	Common:	Bone pain, myalgia, arthralgia, generalised pain
	Uncommon:	Muscle cramps
Cardiovascular disorders		
	Uncommon:	Hypertension, hypotension
	Rare:	Bradycardia
Renal and urinary disorders		
	Common:	Renal impairment
	Uncommon:	Acute renal failure, haematuria, proteinuria
Immune system disorders		
	Uncommon:	Hypersensitivity reaction
	Rare:	Angioneurotic oedema
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
Laboratory abnormalities		
	Very common:	Hypophosphataemia
	Common:	Blood creatinine and blood urea increased, hypocalcaemia
	Uncommon:	Hypomagnesaemia, hypokalaemia
	Rare:	Hyperkalaemia, hypernatraemia

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

In one 3 year, randomised, 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.

Post-marketing experience

The following adverse reactions have been reported during postapproval use of Zometa. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of osteonecrosis (primarily of the jaws) have been reported predominantly in cancer patients treated with bisphosphonates, including Zometa (uncommon). Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged (see section SPECIAL WARNINGS AND PRECAUTIONS FOR USE). Data suggests a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma).

In very rare cases, the following events have been reported: hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors, atrial fibrillation, somnolence, bronchoconstriction, anaphylactic reaction/shock, urticaria, scleritis and orbital inflammation.

OVERDOSE

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 hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

PHARMACODYNAMICS

Zoledronic acid belongs to a new highly potent class of bisphosphonates 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.

Clinical trial results in the prevention of skeletal related events in patients with advanced malignancies involving bone

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 3.

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 tumours involving bone, which had a median survival of only six months (134 patients with non-small-cell lung cancer [NSCLC], 123 with other solid tumours treated with Zometa vs 130 patients with NSCLC, 120 with other solid tumours 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 tumours. Efficacy results are provided in Table 4.

Table 3: 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 4: 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 randomised, 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 5.

Table 5: 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.

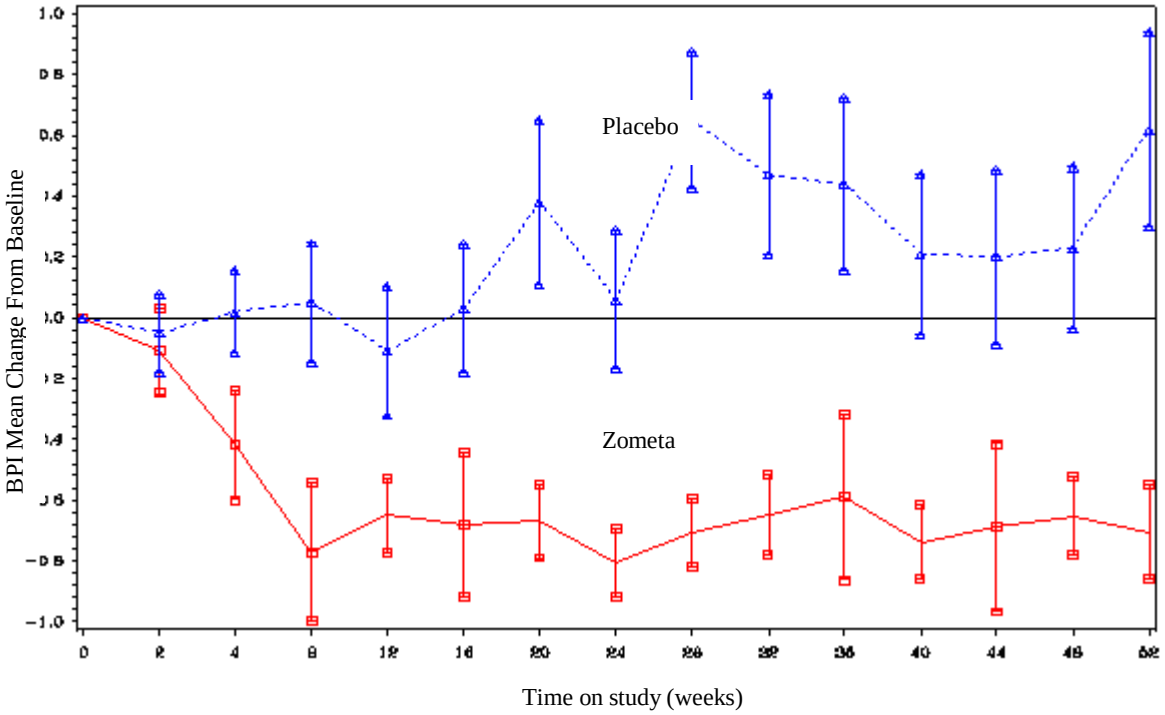
Zometa was also studied in a double-blind, randomized, placebo-controlled trial in 228 adult patients with documented bone metastases from breast cancer to evaluate the effect of Zometa on the skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcaemia and adjusted for prior fracture), divided by the total risk period. Patients received either 4mg 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 hypercalcaemia) 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 hypercalcaemia of malignancy (HCM) demonstrated that the effect of zoledronic acid is characterised 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 normalisation 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 6:

Table 6: 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 normocalcaemia 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 hypercalcaemia 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.

PHARMACOKINETICS

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, which were found to be dose independent.

After initiating the infusion of zoledronic acid, the plasma concentrations of 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.

Intravenously administered zoledronic acid is eliminated via a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½}$ alpha 0.24 and $t_{½}$ beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½}$ gamma 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. 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. 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 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.

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 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).

Zoledronic acid shows no affinity for the cellular components of blood and plasma protein binding is low (approximately 56%) and independent of the concentration of zoledronic acid.

PRECLINICAL SAFETY DATA

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/kg in rats.

Subchronic and chronic toxicity

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/day intravenously in dogs for up to 52 weeks was also well tolerated.

Reproduction toxicity

Zoledronic acid was teratogenic in the rat at subcutaneous doses ≥0.2 mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found.

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

Local tolerance

Local tolerance testing in rabbits showed that intravenous administration was well tolerated.

EXCIPIENTS

Zometa vial: Mannitol, sodium citrate

Solvent ampoule: Water for injection

Pharmaceutical formulations may vary between countries.

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 reconstituted solution is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Zometa reconstituted solution 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.

STORAGE

See also folding box.

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

Reconstituted solution:

The reconstituted solution is chemically and physically stable for 24 hours at room temperature.

After aseptic reconstitution and dilution, it is preferable to use the reconstituted and diluted product immediately. If not used immediately, the duration and conditions of storage prior to use are the care provider's responsibility. The total time between reconstitution, dilution, storage in a refrigerator at 2 to 8℃ and end of administration must not exceed 24 hours.

INSTRUCTIONS FOR USE AND HANDLING

Zometa 4 mg powder for solution for infusion is for intravenous use only. The powder must first be reconstituted in the vial using 5 mL water for injection from the ampoule supplied. Dissolution must be complete before the solution is withdrawn. The amount of reconstituted solution as required is then 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. See also section DOSAGE AND ADMINISTRATION.

Note: Zometa should be kept out of the reach and sight of children.

INFORMATION FOR THE HEALTHCARE PROFESSIONALS

How to prepare and administer Zometa

- To prepare an infusion solution containing 4 mg Zometa, add 5 mL of water for injections from the ampoule supplied in the pack to the vial containing the Zometa powder under aseptic conditions. Shake the vial gently to dissolve the powder.
- Further dilute the Zometa reconstituted solution (5 mL) with 100 mL of calcium-free infusion solution. If a lower dose of Zometa is required, first withdraw the volume of the reconstituted solution (4 mg/5 mL) as shown in table below, and dilute it further with 100 mL of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride or 5% w/v glucose solution.

  Do not mix Zometa reconstituted solution with calcium-containing or other divalent cation-containing solutions such as Lactated Ringer's solution.

Instructions on preparing reduced doses of Zometa

Withdraw an appropriate volume of the reconstituted solution (4 mg/ 5 mL) as needed:

4.4 mL	for 3.5 mg dose
4.1 mL	for 3.3 mg dose
3.8 mL	for 3.0 mg dose

- The Zometa infusion solution should preferably be used immediately. If the solution is not used immediately, storage prior to use is the responsibility of the care provider and should be in a refrigerator at 2° to 8℃. Allow the refrigerated solution to reach room temperature before administration.
- The total time between reconstitution, dilution, storage in the refrigerator and end of administration must not exceed 24 hours.
- The solution containing Zometa is given as a single intravenous infusion of no less than 15 minutes. The hydration status of patients must be assessed prior to and following administration of Zometa to assure that they are adequately hydrated.
- Studies with glass bottles, 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.
- Since no data are available on the compatibility of Zometa with other intravenously administered substances, Zometa must not be mixed with other medications/substances and should always be given through a separate infusion line.

Manufacturer:

See folding box.

International Package Leaflet

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