NOVARTIS

Drug Regulatory Affairs

ZOMETA® (zoledronic acid)

4 mg/100 mL solution for infusion

Summary of Product Characteristics (SmPC)

Version 4.0

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1 Tradename

ZOMETA® 4 mg/100 mL solution for infusion

2 Description and composition

Pharmaceutical forms

Solution for infusion.

The solution is sterile, clear and colorless.

Active substance

Zoledronic acid (anhydrous).

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.

Information might differ in some countries.

3 Indications

Adults

- Treatment of hypercalcemia of malignancy (HCM) defined as albumin-corrected serum calcium (cCa) ≥12.0 mg/dL [3.0 mmol/L] [1-4].
- Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy that includes a Gonadotropin Releasing Hormone (GnRH) agonist [122,130].
- Prevention of skeletal-related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumor-induced hypercalcemia) in patients with advanced malignancies involving bone [56-60].
- Prevention of fracture and bone loss in postmenopausal women with early breast cancer (EBC) treated with aromatase inhibitors (AIs) [104-106,108].

Pediatric population (1 to <18 years)

- Treatment of severe osteogenesis imperfecta (OI) in pediatric patients [116-120].

4 Dosage regimen and administration

The Zometa® 4 mg powder and solvent for solution for infusion should be reconstituted in the vial using 5 mL water for injection from the supplied ampoule. The reconstituted solution should be further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution before infusion (see section 14 Pharmaceutical information/Instructions for use and handling).

The final Zometa solution for infusion, should be given as an intravenous infusion in no less than 15 minutes [56-60,91,104-106,108,122].

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 14 Pharmaceutical information/Instructions for use and handling). The final Zometa solution for infusion, should be given as an intravenous infusion of no less than 15 minutes [56-60,91,104-106,108,122].

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 [56-60,91,104-106,108,122].

Dosage regimen

Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women, in conjunction with hormonal therapy that includes a GnRH agonist

The recommended Zometa dose is a 4 mg infusion given every 6 months [122].

Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily [122].

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

In adult and elderly patients, the recommended Zometa dose is a 4 mg infusion given every 3 to 4 weeks [56-60,91].

Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily [57-60].

Prevention of fracture and bone loss in postmenopausal women with early breast cancer (EBC) treated with aromatase inhibitors (AIs)

The recommended Zometa dose is a 4 mg infusion given every 6 months [104-106,108].

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 is a single 4 mg infusion [91]. Patients must be maintained well hydrated prior to and following administration of Zometa [1-6].

Treatment of severe osteogenesis imperfecta (OI) in pediatric patients

The "ready-to-use" presentation of Zometa 4 mg/100 mL solution for infusion should not be used in this population.

Special populations

Pediatric patients

Children aged 1 year to <3 years

The recommended dose is 0.025 mg/kg zoledronic acid every 3 months. Clinical trial data are only available up to a dose of 0.35 mg (See section 12 Clinical studies). A stock solution must be prepared from the reconstituted solution or the concentrate and further diluted with 50 mL 0.9% w/v sodium chloride or 5% w/v glucose solution, given as an intravenous infusion over 30 to 45 minutes (See section 14 Pharmaceutical information/Instructions for use and handling) [116,118].

Children and adolescents (3 years to <18 years)

The recommended dose is 0.05 mg/kg zoledronic acid (up to a maximum of 4 mg) every 3 months. A stock solution must be prepared from the reconstituted solution or the concentrate and further diluted with 100 mL 0.9% w/v sodium chloride or 5% w/v glucose solution, given as an intravenous infusion over 30 minutes (See section 14 Pharmaceutical information/Instructions for use and handling) [116,118].

Administration of supplements in pediatric patients

Pediatric patients with severe OI should also be administered an oral calcium supplement and vitamin D daily starting at least 2 weeks prior to the first administration of zoledronic acid.

The following calcium and vitamin D doses are recommended [118].

Age	Calcium	Vitamin D
1 to 3 years	500 mg daily	5 micrograms daily (200 IU)
4 to 8 years	800 mg daily	5 micrograms daily (200 IU)
9 to 17 years	1,300 mg daily	5 micrograms daily (200 IU)

Treatment of patients with renal impairment

Patients with hypercalcemia of 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 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 6 Warnings and precautions) [61-63,91].

All other adult patients

When initiating treatment with Zometa, 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 [56-60,104-106,108].

In all patients except patients with HCM presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for these populations as CLcr 30 to 60 mL/min, the following Zometa dose is recommended (see also section 6 Warnings and precautions) [91]:

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 [57-60,107,122] (see section 6 Warnings and precautions). Zometa should be resumed at the same dose as that prior to treatment interruption [91,122].

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 [110].

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 Dosage regimen sub-section).

To prepare reduced doses of Zometa 4 mg powder or Zometa 4 mg/5 mL concentrate, withdraw an appropriate volume of the reconstituted solution (4 mg/ 5 mL) or of the concentrate 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 14 Pharmaceutical information/Instructions for use and handling. The withdrawn amount of the reconstituted solution or 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 [91].

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.

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

5 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 9 Pregnancy, lactation, females and males of reproductive potential).

6 Warnings and precautions

General

All patients, including pediatric patients and 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 (see section 3 Indications), phosphate and magnesium as well as serum creatinine should be carefully monitored after initiating Zometa therapy. If hypocalcemia, hypophosphatemia, 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 [91].

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. The safety and efficacy of zoledronic acid in adult patients with severe OI have not been established.

While not observed in clinical trials with Zometa, there have been reports of bronchoconstriction in acetylsalicylic acid sensitive asthmatic patients receiving bisphosphonates [8].

Pediatric patients

Symptomatic hypocalcemia has occurred with zoledronic acid being administered to children with severe OI aged 1 to 17 years. It is recommended that adequate oral daily intake of calcium and vitamin D be initiated at least 2 weeks before the first dose of Zometa and continued throughout the treatment period. The recommended doses of oral calcium and vitamin D are provided in section 4 Dosage and administration - Pediatric patients. Patients should be informed of the symptoms of hypocalcemia. Pre-existing hypocalcemia must be effectively treated by adequate intake of calcium and vitamin D before initiating therapy with Zometa. Physicians should consider clinical monitoring of serum calcium and mineral levels (phosphorus and magnesium) for patients at risk, especially during the 3 days following the first infusion of Zometa [117,119].

The safety and efficacy of Zometa in pediatric patients with severe OI under the age of 1 year have not been established.

Renal impairment

Adult patients with HCM and evidence of impairment in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with Zometa outweighs the possible risk (see Section 4 Dosage 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 [91].

Bisphosphonates have been associated with reports of renal function deterioration. 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 [91]. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of Zometa [99]. 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 4 Dosage and administration) [57-60,91,107].

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 Pharmacokinetics, section 4 Dosage and administration).

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

Hepatic impairment

As only limited clinical data are available in patients with severe hepatic impairment, no specific recommendations can be given for this patient population [1,2].

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been reported predominantly in adult cancer patients treated with bisphosphonates, including Zometa [95,98]. 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) [111].

Patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates [112].

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 an individual benefit/risk assessment [90].

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 [140].

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 [131].

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 [131].

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 7 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 [92,93].

Hypocalcemia

Hypocalcemia has been reported in patients treated with Zometa. Cardiac arrhythmias and neurologic adverse events (seizures, tetany, and numbness) have been reported secondary to cases of severe hypocalcemia. In some instances, the hypocalcemia may be life-threatening [135]. Caution is advised when Zometa is administered with other hypocalcemia causing drugs, as they may have a synergistic effect, resulting in severe hypocalcemia (see section 8 Interactions) [138]. Serum calcium should be measured and hypocalcemia must be corrected before initiating Zometa therapy. Patients should be adequately supplemented with calcium and vitamin D [137].

7 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 7-1 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 [133,136] (see subsection Description of selected adverse reaction). Cases of arthralgia and myalgia have commonly been reported [1,2,4,6,64].

In premenopausal women with hormone receptor-positive EBC treated with hormonal therapy that includes a GnRH agonist and in postmenopausal women with EBC who are taking adjuvant

aromatase inhibitor, the additive effect of the concomitant treatment may lead to a higher frequency of musculoskeletal pain [123].

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 [1,2,4,6,64].

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 [1,2,4,6,64,123,126].

Anorexia was commonly reported in patients treated with Zometa 4 mg [64].

Rash or pruritus has been uncommonly observed.

As with other bisphosphonates, cases of conjunctivitis have been commonly reported [1,2,4,6,64,123,126].

Based on pooled analysis of placebo-controlled studies, severe anemia (Hb < 8.0 g/dL) was commonly reported in patients receiving Zometa [57,58].

Adverse drug reactions from clinical trials (Table 7-1) 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 7-1 Adverse drug reactions from clinical trials

Blood and lymphatic system disorders		
	Common:	Anaemia
	Uncommon:	Thrombocytopenia, leukopenia
	Rare:	Pancytopenia
Immune system disorders		
	Uncommon:	Hypersensitivity reaction
	Rare:	Angioedema
Nervous system disorders		
	Common:	Headache, paraesthesia [123]
	Uncommon:	Dizziness, Dysgeusia, hypoaesthesia, hyperaesthesia, tremor
	Very rare:	Convulsion, Hypoaesthesia and tetany (secondary to hypocalcaemia) [137,138]
Psychiatric disorders		
	Common:	Sleep disorder [123]
	Uncommon:	Anxiety
	Rare:	Confusional state
Eye disorders		
	Common:	Conjunctivitis
	Uncommon:	Blurred vision
	Rare	Uveitis [77-81,138]

Gastrointestinal disorders		
	Common:	Nausea, vomiting, decreased appetite, constipation
	Uncommon:	Diarrhoea, abdominal pain, dyspepsia, stomatitis, dry mouth
Respiratory, thoracic and mediastinal disorders:		
	Uncommon:	Dyspnoea, cough
	Rare:	Interstitial lung disease (ILD) [132,138]
Skin and subcutaneous tissue disorders		
	Common:	Hyperhidrosis [123]
	Uncommon:	Pruritus, rash (including erythematous and macular rash)
Musculoskeletal and connective tissue disorders		
	Common:	Bone pain*, myalgia*, arthralgia*, generalised body pain, joint stiffness [123]
	Uncommon:	Osteonecrosis of jaw (ONJ) [133], muscle spasms*
Cardiac disorders		
	Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcemia) [137]
Vascular disorders		
	Common:	Hypertension [92,93,123]
	Uncommon:	Hypotension [92,93]
Renal and urinary disorders		
	Common:	Renal impairment
	Uncommon:	Acute renal failure, haematuria, proteinuria
	Rare:	Acquired Fanconi syndrome [141]
General disorders and administration site conditions		
	Common:	Acute phase reaction [133], pyrexia, influenza-like illness (including: fatigue, chills, malaise and flushing), peripheral oedema, asthenia [123]
	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 [136]
Investigations		
	Very common:	Hypophosphataemia
	Common:	Blood creatinine and blood urea increased, hypocalcemia
	Uncommon:	Hypomagnesaemia, hypokalaemia
	Rare:	Hyperkalaemia, hypernatraemia

** a higher frequency may be observed in premenopausal women with hormone receptor-positive EBC treated with hormonal therapy that includes a GnRH agonist and in postmenopausal women with EBC who are concomitantly taking aromatase inhibitor.*

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 7-2 Adverse drug reactions from spontaneous reports and literature (frequency not known)

Immune system disorders
Anaphylactic reaction/shock [114]
Nervous system disorders
Somnolence [101]
Eye disorders
Episcleritis [77-81], scleritis and orbital inflammation [121]
Cardiac disorders
Atrial fibrillation [102]
Vascular disorders
Hypotension leading to syncope or circulatory collapse, primarily in patients with underlying risk factors [92,93]
Respiratory, thoracic and mediastinal disorders
Bronchospasm [100]
Skin and subcutaneous tissue disorders
Urticaria [115]
Musculoskeletal and connective tissue disorders
Severe and occasionally incapacitating bone, joint, and/or muscle pain [132], atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction, including Zometa) [131].

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%) [133]. 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 6 Warnings and precautions, see section 8 Interactions).

In premenopausal women with EBC, there were 1.1% of patients with renal function deterioration (based on analysis of serum creatinine as defined in section 4.2 Posology and method of administration) in the Zometa group vs. 0.8% of patients in the control (no Zometa) group. In postmenopausal women with EBC, there were 2.4% of patients with renal function deterioration in the Zometa group vs. 2.0% of patients in the control (no Zometa) group [122,123,126].

Osteonecrosis

Cases of osteonecrosis (primarily of the jaw but also of other anatomical sites including hip, femur and external auditory canal) [140] have been reported predominantly in cancer patients treated with bisphosphonates, including Zometa [94,98]. Many patients with osteonecrosis of the jaw had signs of local infection including osteomyelitis [90], 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 [140], radiotherapy, corticosteroids) and co-morbid conditions (e.g. anemia, 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 6 Warnings and precautions) [78,82,83-90]. Data suggests a greater frequency of reports of ONJ based on tumor type (advanced breast cancer, multiple myeloma) [111].

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 [133,136].

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 [113].

Adjuvant treatment of hormone receptor-positive early breast cancer (EBC) in premenopausal women in conjunction with hormonal therapy that includes a GnRH agonist and in postmenopausal women, treated with aromatase inhibitor

The safety profile of Zometa was studied in one non active-controlled trial (ABCSG-12) and in three active-controlled trials (AIBL studies) conducted in 1,954 pre- and postmenopausal women, respectively, treated with Zometa 4 mg throughout their study drug treatment period, infused over no less than 15 minutes every 6 months [122,126]. The median duration of exposure for the safety analysis of Zometa 4 mg was 36 months in premenopausal women, and 42 months in postmenopausal women (pooled from three studies). The premenopausal women were also receiving goserelin (3.6 mg s.c.) every 28 days in combination with either tamoxifen (20 mg/day p.o.) or anastrozole (1 mg/day po), while the postmenopausal women received letrozole (2.5 mg/day p.o.) (see section 12 Clinical studies).

The types of adverse reactions (ADRs) observed in this population were generally consistent with those previously seen in patients with advanced cancer involving bone [123,126] and are included in Table 7-1. In concomitant therapy, the assessment of the adverse reaction (ADR) frequency may be biased by the additive effect of the different drugs.

Osteonecrosis of the jaw (ONJ), as an adverse event (AE) to Zometa therapy, was observed in the three trials conducted in postmenopausal women with EBC with an overall incidence of 0.5%. The causal relationship of this AE with Zometa has not been established [122,123,126].

Special populations

Pediatric population with severe OI

The safety of Zometa was studied in a one-year active-controlled trial [118] conducted in 74 children aged 1 to 17 years treated with zoledronic acid for severe OI (see section 12 Clinical studies). The types of adverse events (AEs) observed in this population were generally consistent with those previously seen in adults with advanced cancer involving bone.

Adverse drug reactions (ADRs) seen very commonly in pediatric patients with severe OI included pyrexia (54%), hypocalcemia (22%), vomiting (18%), fatigue (12%) and nausea (11%). ADRs commonly occurring with a frequency of at least 5% were (with decreased order of incidence): headache, pain in extremity, tachycardia, acute-phase reaction, pain, arthralgia, musculoskeletal pain, hypophosphatemia, nasopharyngitis and upper abdominal pain [117-120].

Fracture AEs were reported. Interpretation of the risk of fracture is confounded by the fact that fractures are common events in patients with severe OI as part of the disease process. Long bone fracture AEs occurred in approximately 24% (femur) and 14% (tibia) of zoledronic acid-treated patients with severe OI regardless of OI type and causality [117,118,119].

8 Interactions

Anticipated interactions to be considered

Caution is advised when bisphosphonates like Zometa are administered with aminoglycosides [8] or calcitonin or loop diuretics [128], since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section 6 Warnings and precautions).

Caution is indicated when Zometa is used with other potentially nephrotoxic drugs (see section 7 Adverse drug reactions) [6].

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 [134,137].

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 [1,2,107].

No dose adjustment for Zometa is needed when co-administered with thalidomide, except in patients with mild to moderate renal impairment at baseline (see Section 4 Dosage and administration). Co-administration of thalidomide (100 or 200 mg once daily) with Zometa (4 mg given as a 15 minute infusion) did not significantly change the pharmacokinetics of zoledronic acid and the creatinine clearance of patients with multiple myeloma [128,134].

9 Pregnancy, lactation, females and males of reproductive potential

9.1 Pregnancy

Risk Summary

Zometa should not be used during pregnancy (see section 5 Contraindications).

There may be a risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant (see section 5 contraindication) while receiving bisphosphonate therapy [138]. 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. The potential risk in humans is unknown [138].

Data

Human Data

There are no adequate and well-controlled studies of Zometa in pregnant women [142].

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 [139] [142].

9.2 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 5 Contraindications).

9.3 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. There are no data available in humans [138] [142].

10 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 [103].

11 Clinical pharmacology

Pharmacotherapeutic group, ATC

Bisphosphonate, M05 BA08

Pharmacodynamics (PD)

Mechanisms of action (MOA)

Adjuvant treatment in early breast cancer: Non-clinical data indicate that zoledronic acid exerts anti-cancer effects not only within bone, but also at extra-skeletal sites, without the direct involvement of osteoclast inhibition. Available data indicate that the anti-cancer effects of zoledronic acid are predominantly due to inhibition of a key enzyme (farnesyl pyrophosphate synthase) in the mevalonate pathway in a variety of cell types. Anti-cancer actions may include: induction of cancer cell apoptosis, reduced proliferation of tumor cells, synergistic effects with hormonal therapy or chemotherapy, decreased tumor cell adhesion, invasion, and migration, altered macrophage function, inhibition of angiogenesis and activation of the immune system through enhanced proliferation of human gamma-d-T cells and cytokine secretion. Through these mechanisms and inhibition of bone resorption, zoledronic acid alters the bone and bone marrow micro-environment which may prevent the growth of micro-metastases and impair their survival in bone and soft tissues. Clinical data from translational studies indicate that zoledronic acid targets and reduces the number of disseminated tumor cells in the bone marrow of breast

cancer patients [124,125]. In addition, other translational studies provide evidence of inhibition of angiogenesis and immune activation of gamma-d-T cells [125].

Hypercalcemia of Malignancy and Bone Metastases from Solid Tumors: Zoledronic acid is a highly potent drug that belongs to the bisphosphonate class of drugs, which act primarily on bone [16-26]. It is one of the most potent inhibitors of osteoclastic bone resorption known to date [16-18,20,65].

The selective action of bisphosphonates on bone is based on their high affinity for mineralized 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 [22-26,66].

In addition to being a very potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumor properties that could contribute to its overall efficacy in the treatment of metastatic bone disease [27-31]. The following properties have been demonstrated in preclinical studies:

- *In vivo*: Inhibition of osteoclastic bone resorption, which alters the bone marrow micro-environment making it less conducive to tumor cell growth [67], anti-angiogenic activity [68], anti-pain activity [69].
- *In vitro*: inhibition of osteoblast proliferation [70], direct cytostatic and pro-apoptotic activity on tumor cells [71-73], synergistic cytostatic effect with other anti-cancer drugs [74,75], anti-adhesion/invasion activity [76].

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 [5,32,33].

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 5,000 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 [38,134,138].

Biotransformation/Metabolism

Zoledronic acid is not metabolized 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 t½alpha 0.24 and t½beta 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of t½gamma 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 [5,32,33].

Linearity/non-linearity

The zoledronic acid pharmacokinetics were found to be dose-independent [5,32,33]. 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

Pediatric patients

Limited pharmacokinetic data in children with severe OI suggest that the zoledronic acid pharmacokinetics in children 3 to 17 years of age is similar to that in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure [116,118].

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* [7], 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 [34-37].

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 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 impairment (creatinine clearance <30 mL/min) [62,63]. The use of Zometa is not recommended in patients with severe renal impairment (see section 6 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 [64].

12 Clinical studies

Clinical trial results in the adjuvant treatment of premenopausal women with hormone receptor-positive early stage breast cancer, in conjunction with hormonal therapy

The efficacy of adding Zometa (zoledronic acid 4 mg IV every 6 months) to adjuvant hormonal therapy for prevention of disease recurrences was evaluated in an open-label, randomized, controlled, multi-center study (ABCSG-12) of 1,803 premenopausal women with hormone receptor-positive early breast cancer. Patients were randomly assigned to receive goserelin (3.6 mg s.c. every 4 weeks) in combination with either tamoxifen (20 mg/day p.o.) or anastrozole (1 mg/day p.o.), with or without Zometa 4 mg infusion every 6 months for a period of 3 years or until disease recurrence [122,125].

Disease-free survival (DFS), the primary outcome, was defined as the time from randomization to the first appearance of a local, regional, or distant recurrence, of a second primary carcinoma, or of death due to any cause. The protocol-specified timing of evaluation procedures was the same for patients in all treatment groups. DFS events were confirmed by radiography or histology [122,125].

Demographic and other baseline characteristics were balanced among the treatment groups in the intent-to-treat (ITT) population (Table 12-1). Patients treated with adjuvant chemotherapy were excluded, but those with preoperative (neo-adjuvant) chemotherapy or adjuvant radiation therapy were allowed to enroll. Approximately 30% of patients had positive lymph nodes. Patients were treated for a median duration of 36 months [122,125].

Table 12-1: Demographic and baseline disease characteristics in the ITT population (premenopausal EBC patients receiving adjuvant hormonal therapy)

	Zometa (N=900) n (%)	Control (N=903) n (%)
Age (median, years)	44.5	45.0
Age group		
≤ 40	199 (22.1)	213 (23.6)
> 40	701 (77.9)	689 (76.3)
Nodal status		
Negative	602 (66.9)	609 (67.4)
Positive	275 (30.6)	275 (30.5)
Unknown	23 (2.6)	19 (2.1)
Cancer T-stage (pT) category		
= T1	682 (75.8)	693 (76.7)
≥ T2	195 (21.7)	191 (21.2)
Prior neo-adjuvant chemotherapy	49 (5.4)	48 (5.3)

Zometa 4 mg significantly reduced the relative risk of DFS events by 34% compared to adjuvant endocrine therapy alone, at a median follow-up time of 53 months. The primary efficacy analysis results are provided in Table 12-2. The Kaplan-Meier plot of DFS for the ITT population is shown in Figure 12-1. The Zometa effect on DFS was consistently observed in both anastrozole and tamoxifen treated patients. At 5 years, the absolute improvement in the DFS rate by Kaplan-Meier estimate was 3.8% for Zometa compared to control in the ITT population. The type and anatomical location of DFS events and deaths are summarized in Table 12-3 [122,125].

Table 12-2: DFS efficacy results (premenopausal women with early breast cancer receiving adjuvant hormonal therapy), ITT population

			Cox model [1]			
All patients [5]		**Number of events/ censored times**	**Hazard ratio [2]**	**95%CI**	**p-value [3]**	**Log-rank test p-value [4]**
Zometa	N= 900	65/835	0.66	(0.48,0.90)	0.009	0.008
Control	N= 903	97/806				

[1] Cox model is stratified by hormonal therapy and includes zoledronic acid therapy [0: control vs. 1: zoledronic acid]

[2] Hazard ratio of Zometa over control

[3] Based on a Wald test from Cox model

[4] p-value based on stratified log rank test

[5] All patients received goserelin

Figure 12-1: DFS by treatment group (zoledronic acid vs. control) in premenopausal EBC patients receiving hormonal therapy

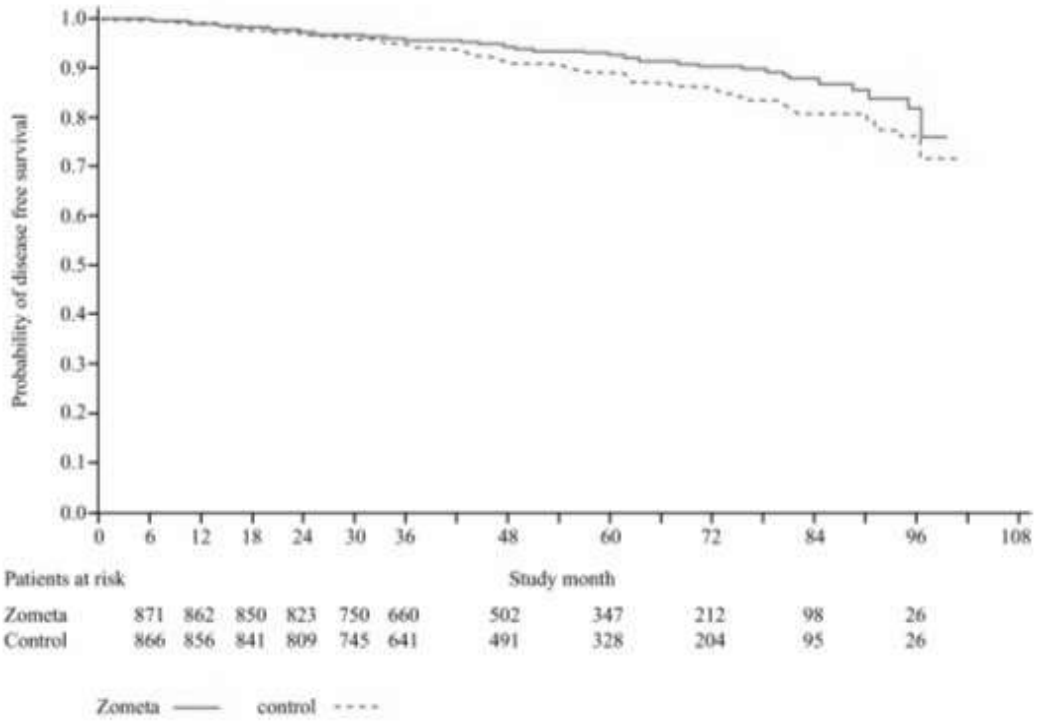


Table 12-3: DFS events and deaths (premenopausal women with EBC receiving hormonal therapy)

	Zometa N=900 n (%)	Control* N=903 n (%)
All events	65 (7.2%)	97 (10.7%)
Locoregional recurrences	13 (1.4%)	26 (2.9%)
Distant recurrences	38 (4.2%)	48 (5.3%)
Second primary carcinomas	14 (1.6%)	22 (2.4%)
Deaths without recurrence or second primary carcinoma	0	1 (0.1%)
Total deaths	21 (2.3%)	34 (3.8%)

**Control patients received either tamoxifen or anastrozole without Zometa. All patients received goserelin.*

Secondary endpoints from this study included recurrence-free survival (RFS) and overall survival (OS). For Zometa compared to control patients in the ITT population, there was a statistically significant improvement in RFS (HR 0.66; 95% CI: 0.49, 0.91; log-rank p = 0.01)

and a numerical trend towards improved OS (HR 0.65; 95% CI: 0.37, 1.12; log-rank p = 0.11) [122,125].

The trial also included a prospectively designed bone sub-study (n=415), with a change in lumbar spine bone mineral density (BMD) from baseline to 12 months as the primary endpoint. BMD at the lumbar spine (at 36 and 60 months) and hip trochanter (at 12, 36 and 60 months) were also measured in the sub-study. All BMD measurements were analyzed by dual x-ray absorptiometry (DEXA). Study drug treatment was administered during the first 36 months [122,125].

Relative to baseline there was a statistically significant difference in the mean percentage change in BMD at the lumbar spine (L1-L4) in the Zometa-treated patients compared to the control patients (1.2%, 0.7%, 5.0%, vs. -6.3%, -10.0%, -3.1% for 12, 36 and 60 months, respectively; $p<0.001$ using 2-sample t-test analysis at each time point). Similarly, relative to baseline, there was a statistically significant difference in the mean percentage change in BMD at the hip trochanter, in the Zometa-treated patients compared to the control patients (1.0%, 1.4%, 3.1%, vs. -4.2%, -7.0%, -2.7% for 12, 36 and 60 months, respectively; $p<0.001$ using 2-sample t-test analysis at each time point). Results of BMD analyses were also consistent with three other studies of adjuvant Zometa therapy in postmenopausal women (n=2194 total patients) with early breast cancer [122,125].

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 12-4 [57].

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 12-5 [58].

Table 12-4: 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 12-5: Efficacy results (solid tumors 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 12-6 [59,60].

Table 12-6: 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

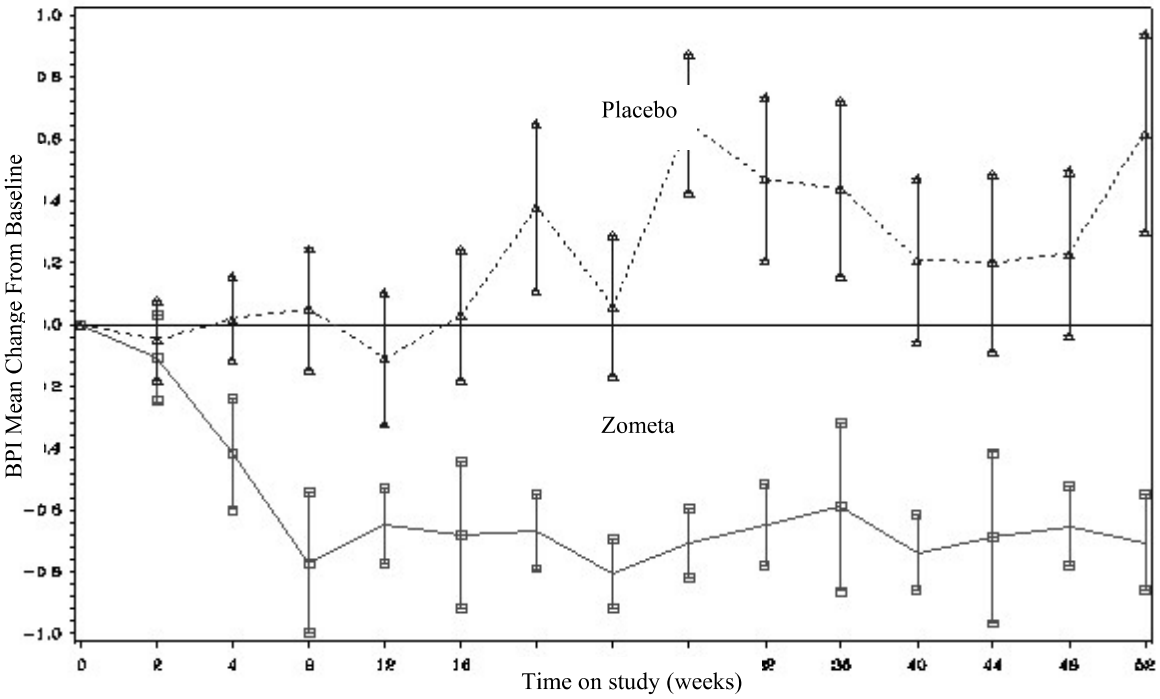
In clinical trials performed in adult patients with bone metastases or osteolytic lesions, the overall safety profile amongst all treatment groups (zoledronic acid 4 mg, and pamidronate 90 mg and placebo) was similar in types and severity [64].

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 4mg Zometa or placebo every four weeks for one year. Patients were evenly distributed between Zometa-treated and placebo groups [96,97].

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 [96,97].

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 12-2). 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 [96,97].

Figure 12-2: 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 [1,2,4].

To assess the effects of Zometa versus pamidronate 90 mg, the results of two pivotal multicenter studies in adult patients with HCM were combined in a pre-planned analysis [3]. 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 [3]. 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 12-7:

Table 12-7: Proportion of complete responders by day in the combined HCM studies [3]

	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 normocalcemia 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 [3].

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.

Clinical trial results in the prevention of fracture and bone loss in postmenopausal women with early breast cancer (EBC) treated with aromatase inhibitors (AIs)

The efficacy of Zometa (zoledronic acid 4 mg IV every 6 months) in the prevention of fracture and bone loss in postmenopausal women with EBC treated with AIs, a population with higher fracture rate than an age matched general population of postmenopausal women, was assessed in two parallel designed studies, with 600 and 1,065 patients, respectively. Patients in one trial were assessed at 24 months (n=391). In a pooled analysis of efficacy at 12 months, patients initiated on adjuvant Femara (letrozole) 2.5 mg daily were randomized to Zometa 4 mg IV every six months administered either upfront (832 patients) or delayed start treatment (833 patients). Patients in the upfront treatment group began Zometa at the same time as Femara, while patients in the delayed start group began Zometa when post-baseline BMD (bone mineral density) T-score was below -2.0 SD at either the lumbar spine or total hip, or when any new clinical fracture unrelated to trauma occurred.

The primary efficacy endpoint assessed was BMD. Lower bone mass (BMD) is associated with a higher fracture risk in postmenopausal women. Over 24 months, upfront treatment with Zometa consistently correlated with a progressive increase in BMD while delayed start treatment resulted in a progressive decrease in BMD. Beginning at month 6 and at all subsequent time points, Zometa (4mg IV every 6 months) upfront treatment demonstrated a statistically significant ($p<0.0001$) improvement over delayed treatment on the mean percent change from baseline for (BMD) at the lumbar spine (L1-L4) and at the total hip. Efficacy results are provided in Table 12-8 [104-106,108]. A comparable increase in BMD was observed

in a study of zoledronic acid (5 mg IV once annually) in the treatment of postmenopausal osteoporosis, which corresponded to relative risk reductions of 70% and 40%, respectively, in new vertebral and hip fractures over 3 years [109]. Zometa treatment significantly prevented BMD loss in postmenopausal EBC patients on AI therapy, consequently reducing fracture risk in this population.

Table 12-8: LS Mean Percent change from baseline in lumbar spine and total hip BMD at 12 and 24 months [108]

Month	Upfront Group#29(N)	Delayed Group## (N)	LS mean difference (95% CI)
Month 12 Lumbar Spine	+2.03 (715)	-3.11 (719)	5.2* (4.8, 5.6)
Month 12 Hip	+1.23 (713)	-2.20 (723)	3.5* (3.2, 3.8)
Month 24 Lumbar Spine	+3.06 (200)	-2.89 (191)	5.9* (5.0, 6.8)
Month 24 Hip	+1.47 (201)	-3.24 (190)	4.7* (4.1, 5.3)

#Upfront treatment: all patients initiated on Zometa 4 mg IV every 6 months

Delayed treatment: patients were initiated on treatment with Zometa 4 mg IV every 6 months when post-baseline BMD T-score was below -2.0 SD, or when any new clinical fracture unrelated to trauma occurred.

** p < 0.0001*

Bone turnover Markers

Bone specific alkaline phosphatase (BSAP) (n=464) and serum N-telopeptide (NTX) (n=182) were evaluated in a subset of patients at month 12. Treatment with Zometa 4 mg IV every 6 months significantly reduced markers of bone turnover in the upfront treated patients and maintained the markers within the normal pre-menopausal range through 12 months, thus indicating sufficient, but not excessive, suppression of bone turnover [108].

Clinical trial results in the treatment of severe osteogenesis imperfecta (OI) in pediatric patients 1 to 17 years of age

The efficacy of zoledronic acid (i.v.) in the treatment of pediatric patients (1 to 17 years) with severe OI (type I, III and IV) was assessed compared to pamidronate (i.v.) in one international, multicenter, randomized, open-label study [Study H2202] with 74 and 76 patients in each treatment group, respectively. One infant/toddler aged 1 to <2 years, 6 children aged 2 to <3 years, 30 children aged 3 to <9 years and 37 children/adolescents aged 9 to 17 years were exposed to zoledronic acid. The study treatment period was 12 months preceded by a 4 to 9-week screening period when vitamin D and elemental calcium supplements were taken for at least 2 weeks. Patients aged 1 to <3 years received 0.025 mg/kg of zoledronic acid every 3 months; the highest single administered dose was 0.35 mg. Patients aged 3 to 17 years received 0.05 mg/kg of zoledronic acid every 3 months; the highest single administered dose was 0.85 mg [116,118].

The study primary endpoint was a percentage change in lumber spine (LS) bone mineral density (BMD) after 12 months of treatment. The study demonstrated that zoledronic acid was non-

inferior and superior to the active control pamidronate for the primary endpoint (at 0.05 significance level since the lower limit of the 95% CI exceeds 0), and provided sustained reductions in biomarkers of bone resorption and formation. The percentage change from baseline in LS BMD at month 12 and corresponding 95% CI are presented in Table 12-9. This superiority result was confirmed by analyses in the per-protocol and completers populations and by a non-parametric ANCOVA model in the intent-to-treat (ITT) population (p-value=0.0132) [116,118,119].

Table 12-9: Change (%) from baseline in lumbar spine BMD at month 12 [116,118,119]

Population	Treatment	N	Mean (SE) [1]	Mean difference [1]	95% CI [1]
ITT	Zoledronic acid	63	42.71 (2.798)	8.06	0.42, 15.71
	Pamidronate	68	34.65 (2.669)		

N = patients with measurements at both baseline and month 12 visit, as determined by visit window after imputation by LOCF, if applicable. LOCF applied to ITT population only.
[1] Mean, mean difference (zoledronic acid - pamidronate) and 95% CI are based on t-distribution.

In pediatric patients treated with zoledronic acid in study [H2202], the mean (SD) reduction in the number of fractures per patient per year from 12 months prior to baseline to the 12-month period of the core study was 1.96 (3.84) [116,118,119].

An extension study [H2202E1] was conducted in order to examine the long-term general and renal safety of once yearly or twice yearly zoledronic acid over the 12 month extension treatment period in children who had completed one year of treatment with either zoledronic acid or pamidronate in the core study [H2202]. There were no new safety findings beyond those observed in the core study [117,119].

13 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 [42,43]. 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 [44,45].

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 [139].

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 2 to 3-week intervals were well tolerated in dogs [139].

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 [46-54,139].

Carcinogenicity

In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential [139].

14 Pharmaceutical information

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

Zometa reconstituted 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 [110].

Special precautions for storage

The unopened pharmaceutical forms do not require any special precautions for storage.

Information might differ in some countries.

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

Instructions for use and handling

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

The 4 mg 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).

The 4 mg/5 mL 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 4 Dosage 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 (including the stock solution for pediatric use) immediately. If not used immediately, the reconstituted solution should be stored at 2 to 8ºC. 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 4 Dosage and administration).

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

Pediatric use

The "ready-to-use" presentation of Zometa 4 mg/100 mL solution for infusion **should not be used** for administration of reduced Zometa dosages. For administration of reduced Zometa doses, Zometa 4 mg powder and solvent for solution for infusion or Zometa 4 mg/5 mL concentrate for solution for infusion should be used.

In order to prepare infusion solutions for pediatric patients with severe OI the Zometa 4 mg/5 mL reconstituted solution or 4 mg/5 mL concentrate must be further diluted with 75 mL of calcium-free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution) to obtain a diluted solution containing 0.05 mg/mL zoledronic acid in a total volume of 80 mL. This stock solution is used to prepare the individual final infusion solution (multiple amounts of 0.025 mg or 0.05 mg zoledronic acid) which is diluted to a total final volume of 50 mL or 100 mL for pediatric patients below and beyond the age of 3 years, respectively (See also section 4 Dosage and administration).

Preparation of pediatric infusion solutions	Pediatric patients <3 years	Pediatric patients ≥3 years
Amount of stock solution	0.5 mL (0.025 mg) per kg bodyweight	1 mL (0.05 mg) per kg bodyweight
Final volume to be infused	50 mL	100 mL
Infusion time	30 to 45 minutes	30 minutes

Special precautions for disposal

Zometa 4 mg powder for solution for infusion is supplied as packs containing 1, 4 or 10 vials and 1, 4 or 10 ampoules of water for injection, respectively. Powder vial: 6 mL colorless glass vial, hydrolytic glass type I. Solvent ampoule: 5 mL colorless glass ampoule.

Zometa 4 mg/5 mL concentrate for solution for infusion is supplied as packs containing 1, 4 or 10 vials. Vial: 5 mL colorless plastic vial container with rubber stopper and flip-off cap.

Zometa 4 mg/100 mL solution for infusion in a colorless plastic vial closed with a grey rubber stopper and an aluminum cap with deep purple flip-off component [129] is supplied in packs containing 1 bottle as a unit pack or in multi-packs comprising 4 or 5 packs each containing 1 bottle. Not all pack sizes may be marketed.

Any unused product or waste material should be disposed of in accordance with local requirements.

Not all pack sizes may be marketed in all countries.

15 Marketing Authorization Holder

Novartis Nigeria Limited

52/53 Isaac John Street,

Ikeja GRA,

Lagos.

Zometa Intravenous Infusion- NAFDAC Reg No: A4-5636