ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zometa 4 mg/100 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One bottle contains 4 mg zoledronic acid, corresponding to 4.264 mg zoledronic acid monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion

Clear and colourless solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

4.2 Posology and method of administration

Zometa must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated with Zometa should be given the package leaflet and the patient reminder card.

Posology

Prevention of skeletal related events in patients with advanced malignancies involving bone
Adults and older people
The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.

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

The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

Treatment of TIH
Adults and older people
The recommended dose in hypercalcaemia (albumin-corrected serum calcium ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment
TIH:
Zometa treatment in TIH patients 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 µmol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl (see section 4.4).

Prevention of skeletal related events in patients with advanced malignancies involving bone:
When initiating treatment with Zometa in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine 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 µmol/l or > 3.0 mg/dl were excluded.

For patients with normal renal function (defined as CLcr > 60 ml/min), zoledronic acid 4 mg/100 ml solution for infusion may be administered directly without any further preparation. In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, reduced Zometa doses are recommended (see also section 4.4).

Baseline creatinine clearance (ml/min)	**Zometa recommended dose***
> 60	4.0 mg zoledronic acid
50–60	3.5 mg* zoledronic acid
40–49	3.3 mg* zoledronic acid
30–39	3.0 mg* zoledronic acid

***** Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/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 or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l;
- For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l.

In the clinical studies, Zometa treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zometa treatment should be resumed at the same dose as that given prior to treatment interruption.

Paediatric population
The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Intravenous use.
Zometa 4 mg/100 ml solution for infusion should be given as a single intravenous infusion in no less than 15 minutes.

In patients with normal renal function, defined as CLcr > 60 ml/min, zoledronic acid 4 mg/100 ml solution for infusion must not be further diluted.

In patients with mild to moderate renal impairment, reduced Zometa doses are recommended (see section “Posology” above and section 4.4).

To prepare reduced doses for patients with baseline CLcr ≤ 60 ml/min, refer to Table 1 below. Remove the volume of Zometa solution indicated from the bottle and replace with an equal volume of

sterile sodium chloride 9 mg/ml (0,9%) solution for injection, or 5% glucose solution for injection.

Table 1 Preparation of reduced doses of Zometa 4 mg/100 ml solution for infusion

Baseline creatinine clearance (ml/min)	Remove the following amount of Zometa solution for infusion (ml)	Replace with the following volume of sterile sodium chloride 9 mg/ml (0,9%), or 5% glucose solution for injection (ml)	Adjusted dose (mg zoledronic acid in 100 ml)
50-60	12.0	12.0	3.5
40-49	18.0	18.0	3.3
30-39	25.0	25.0	3.0

Zometa 4 mg/100 ml solution for infusion must not be mixed with other infusion solutions and should be administered as a single intravenous solution in a separate infusion line.

Patients must be maintained well hydrated prior to and following administration of Zometa.

4.3 Contraindications

- Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients listed in section 6.1.
- Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

General

Patients must be assessed prior to administration of Zometa to ensure 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, should be carefully monitored after initiating Zometa therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, 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 substance as found in Aclasta (zoledronic acid). Patients being treated with Zometa should not be treated with Aclasta or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Renal insufficiency

Patients with TIH and 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 2–3 months.

Zometa has 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 and other bisphosphonates as well as use of other nephrotoxic medicinal products. While

the risk is reduced with a dose of 4 mg zoledronic acid administered over 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 4 mg zoledronic acid. 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 patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, Zometa should be withheld. Zometa should only be resumed when serum creatinine returns to within 10% of baseline. Zometa treatment should be resumed at the same dose as that given prior to treatment interruption.

In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/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.

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

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical trials in patients receiving Zometa. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). A study showed that ONJ was higher in myeloma patients when compared to other cancers (see section 5.1).

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth, except in medical emergency situations. A dental examination with appropriate preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with bisphosphonates in patients with concomitant risk factors.

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:
- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with Zometa. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to zoledronic acid administration. 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.

The management plan for patients who develop ONJ should be set up in close collaboration between the treating physician and a dentist or oral surgeon with expertise in ONJ. Temporary interruption of zoledronic acid treatment should be considered until the condition resolves and contributing risk factors are mitigated where possible.

Osteonecrosis of other anatomical sites
Osteonecrosis of the external auditory canal has been reported with bisphosphonates, mainly in association with long-term therapy. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy and/or local risk factors such as infection or trauma. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who present with ear symptoms including chronic ear infections.

Additionally, there have been sporadic reports of osteonecrosis of other sites, including the hip and femur, reported predominantly in adult cancer patients treated with Zometa.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking Zometa. However, such reports have been infrequent. 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 rechallenged with Zometa or another bisphosphonate.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with 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 bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate 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.

During bisphosphonate 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.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with Zometa. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening (see section 4.8). Caution is advised when Zometa is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5). Serum calcium should be measured and hypocalcaemia must be corrected before initiating Zometa therapy. Patients should be adequately supplemented with calcium and vitamin D.

Zometa contains sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially “sodium free”. However, if a solution of common salt (0.9% w/v sodium chloride solution) is used for the dilution of Zometa prior to administration then the dose of sodium received would be higher.

4.5 Interaction with other medicinal products and other forms of interaction

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 5.2), but no formal clinical interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics, since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section 4.4).

Caution is indicated when Zometa is used with other potentially nephrotoxic medicinal products. 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 Zometa is used in combination with thalidomide.

Caution is advised when Zometa is administered with anti-angiogenic medicinal products, as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zometa should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

It is not known whether zoledronic acid is excreted into human milk. Zometa is contraindicated in breast-feeding women (see section 4.3).

Fertility

Zoledronic acid was evaluated in rats for potential adverse effects on fertility of the parental and F1 generation. This resulted in exaggerated pharmacological effects considered to be related to the compound's inhibition of skeletal calcium metabolisation, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Thus these results precluded determining a definitive effect of zoledronic acid on fertility in humans.

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of Zometa along with driving and operating of machinery.

4.8 Undesirable effects

Summary of the safety profile

Within three days after Zometa administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following are the important identified risks with Zometa in the approved indications:
Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 2.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 2, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid:

Table 2

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders		
	Common:	Anaemia
	Uncommon:	Thrombocytopenia, leukopenia
	Rare:	Pancytopenia
Immune system disorders		
	Uncommon:	Hypersensitivity reaction
	Rare:	Angioneurotic oedema
Psychiatric disorders		
	Uncommon:	Anxiety, sleep disturbance
	Rare:	Confusion
Nervous system disorders		
	Common:	Headache
	Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
	Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)
Eye disorders		
	Common:	Conjunctivitis
	Uncommon:	Blurred vision, scleritis and orbital inflammation
	Rare:	Uveitis
	Very rare:	Episcleritis
Cardiac disorders		
	Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
	Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders		
	Uncommon:	Dyspnoea, cough, bronchoconstriction
	Rare:	Interstitial lung disease
Gastrointestinal disorders		
	Common:	Nausea, vomiting, decreased appetite
	Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Skin and subcutaneous tissue disorders		
	Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating

Musculoskeletal and connective tissue disorders		
	Common:	Bone pain, myalgia, arthralgia, generalised pain
	Uncommon:	Muscle spasms, osteonecrosis of the jaw
	Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Renal and urinary disorders		
	Common:	Renal impairment
	Uncommon:	Acute renal failure, haematuria, proteinuria
	Rare:	Acquired Fanconi syndrome
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, anaphylactic reaction/shock, urticaria
	Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
Investigations		
	Very common:	Hypophosphataemia
	Common:	Blood creatinine and blood urea increased, hypocalcaemia
	Uncommon:	Hypomagnesaemia, hypokalaemia
	Rare:	Hyperkalaemia, hypernatraemia

Description of selected adverse reactions

Renal function impairment
Zometa has been associated with reports of renal dysfunction. In a pooled analysis of safety data from Zometa registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal 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 tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zometa or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).

Osteonecrosis of the jaw
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as Zometa (see section 4.4). Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries.

Atrial fibrillation
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 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single

clinical trial is unknown.

Acute phase reaction
This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea arthralgia and 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.

Atypical fractures of the femur
During post-marketing experience the following reactions have been reported (frequency rare): Atypical subtrochanteric and diaphyseal femoral fractures (bisphopsphonate class adverse reaction).

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with Zometa in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an association between Zometa therapy, the reported event of hypocalcaemia, and the secondary development of cardiac arrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including; convulsions, hypoaesthesia and tetany (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Clinical experience with acute overdose of Zometa is limited. The administration of doses up to 48 mg of zoledronic acid in error has been reported. Patients who have received doses higher than those recommended (see section 4.2) 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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08

Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclastic bone resorption.

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, mineralisation or mechanical properties of bone.

In addition to being a 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 and 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

The first randomised, double-blind, placebo-controlled study compared zoledronic acid 4 mg to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients. Zoledronic acid 4 mg significantly reduced the proportion of patients experiencing at least one skeletal related event (SRE), delayed the median time to first SRE by > 5 months, and reduced the annual incidence of events per patient - skeletal morbidity rate. Multiple event analysis showed a 36% risk reduction in developing SREs in the zoledronic acid 4 mg group compared with placebo. Patients receiving zoledronic acid 4 mg reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. Fewer zoledronic acid 4 mg 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 including solid tumours other than breast or prostate cancer, zoledronic acid 4 mg significantly reduced the proportion of patients with an SRE, delayed the median time to first SRE by > 2 months, and reduced the skeletal morbidity rate. Multiple event analysis showed 30.7% risk reduction in developing SREs in the zoledronic acid 4 mg group compared with placebo. Efficacy results are provided in Table 4.

Table 3 Efficacy results (prostate cancer patients receiving hormonal therapy)

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	zoledronic acid 4 mg	Placebo	zoledronic acid 4 mg	Placebo	zoledronic acid 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 (+TIH)		Fractures*		Radiation therapy to bone	
	zoledronic acid 4 mg	Placebo	zoledronic acid 4 mg	Placebo	zoledronic acid 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, zoledronic acid 4 mg or 90 mg pamidronate every 3 to 4 weeks were compared in patients with multiple myeloma or breast cancer with at least one bone lesion. The results demonstrated that zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of SREs. The multiple event analysis revealed a significant risk reduction of 16% in patients treated with zoledronic acid 4 mg in comparison with patients receiving pamidronate. Efficacy results are provided in Table 5.

Table 5 Efficacy results (breast cancer and multiple myeloma patients)

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	zoledronic acid 4 mg	Pam 90 mg	zoledronic acid 4 mg	Pam 90 mg	zoledronic acid 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

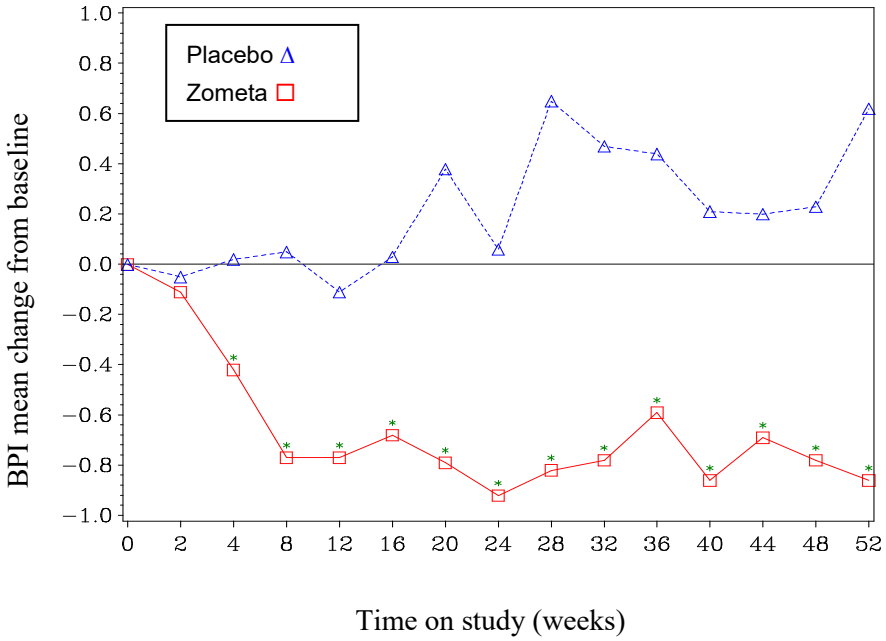
NA Not Applicable

Zoledronic acid 4 mg was also studied in a double-blind, randomised, placebo-controlled trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of 4 mg zoledronic acid 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 4 mg zoledronic acid or placebo every four weeks for one year. Patients were evenly distributed between zoledronic acid-treated and placebo groups.

The SRE rate (events/person year) was 0.628 for zoledronic acid and 1.096 for placebo. The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the zoledronic acid-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 zoledronic acid-treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid 4 mg reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo.

In the zoledronic acid-treated group, statistically significant improvement in pain scores (using the Brief Pain Inventory, BPI) was seen at 4 weeks and at every subsequent time point during the study, when compared to placebo (Figure 1). The pain score for zoledronic acid was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score.

Figure 1 **Mean changes from baseline in BPI scores. Statistically significant differences are marked (*p<0.05) for between treatment comparisons (4 mg zoledronic acid vs. placebo)**



CZOL446EUS122/SWOG study

The primary objective of this observational study was to estimate the cumulative incidence of osteonecrosis of the jaw (ONJ) at 3 years in cancer patients with bone metastasis receiving zoledronic acid. The osteoclast inhibition therapy, other cancer therapy, and dental care was performed as clinically indicated in order to best represent academic and community-based care. A baseline dental examination was recommended but was not mandatory.

Among the 3491 evaluable patients, 87 cases of ONJ diagnosis were confirmed. The overall estimated cumulative incidence of confirmed ONJ at 3 years was 2.8% (95% CI: 2.3-3.5%). The rates were 0.8% at year 1 and 2.0% at year 2. Rates of 3-year confirmed ONJ were highest in myeloma patients (4.3%) and lowest in breast cancer patients (2.4%). Cases of confirmed ONJ were statistically significantly higher in patients with multiple myeloma (p=0.03) than other cancers combined.

Clinical trial results in the treatment of TIH

Clinical studies in tumour-induced hypercalcaemia (TIH) demonstrated that the effect of zoledronic acid is characterised by decreases in serum calcium and urinary calcium excretion. In Phase I dose finding studies in patients with mild to moderate tumour-induced hypercalcaemia (TIH), effective doses tested were in the range of approximately 1.2–2.5 mg.

To assess the effects of 4 mg zoledronic acid versus pamidronate 90 mg, the results of two pivotal multicentre studies in patients with TIH were combined in a pre-planned analysis. There was faster normalisation of corrected serum calcium at day 4 for 8 mg zoledronic acid and at day 7 for 4 mg and 8 mg zoledronic acid. The following response rates were observed:

Table 6 Proportion of complete responders by day in the combined TIH studies

	Day 4	Day 7	Day 10
Zoledronic acid 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zoledronic acid 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 compared to pamidronate.			

Median time to normocalcaemia was 4 days. Median time to relapse (re-increase of albumin-corrected serum calcium ≥ 2.9 mmol/l) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg (p-values: 0.001 for 4 mg and 0.007 for 8 mg zoledronic acid). There were no statistically significant differences between the two zoledronic acid doses.

In clinical trials 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg) were retreated with 8 mg zoledronic acid. The response rate in these patients was about 52%. Since those patients were retreated with the 8 mg dose only, there are no data available allowing comparison with the 4 mg zoledronic acid dose.

In clinical trials performed in patients with tumour-induced hypercalcaemia (TIH), 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.

Paediatric population

Clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years

The effects of intravenous zoledronic acid in the treatment of paediatric patients (age 1 to 17 years) with severe osteogenesis imperfecta (types I, III and IV) were compared to intravenous pamidronate in one international, multicentre, randomised, open-label study with 74 and 76 patients in each treatment group, respectively. The study treatment period was 12 months preceded by a 4- to 9-week screening period during which vitamin D and elemental calcium supplements were taken for at least 2 weeks. In the clinical programme patients aged 1 to < 3 years received 0.025 mg/kg zoledronic acid (up to a maximum single dose of 0.35 mg) every 3 months and patients aged 3 to 17 years received 0.05 mg/kg zoledronic acid (up to a maximum single dose of 0.83 mg) every 3 months. An extension study 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.

The primary endpoint of the study was the percent change from baseline in lumbar spine bone mineral density (BMD) after 12 months of treatment. Estimated treatment effects on BMD were similar, but the trial design was not sufficiently robust to establish non-inferior efficacy for zoledronic acid. In particular there was no clear evidence of efficacy on incidence of fracture or on pain. Fracture adverse events of long bones in the lower extremities were reported in approximately 24% (femur) and 14% (tibia) of zoledronic acid-treated patients vs 12% and 5% of pamidronate-treated patients with severe osteogenesis imperfecta, regardless of disease type and causality but overall incidence of fractures was comparable for the zoledronic acid and pamidronate-treated patients: 43% (32/74) vs 41% (31/76). Interpretation of the risk of fracture is confounded by the fact that fractures are common events in patients with severe osteogenesis imperfecta as part of the disease process.

The type of adverse reactions observed in this population were similar to those previously seen in adults with advanced malignancies involving the bone (see section 4.8). The adverse reactions ranked

under headings of frequency, are presented in Table 7. The following conventional classification is used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 7 Adverse reactions observed in paediatric patients with severe osteogenesis imperfecta[1]

Nervous system disorders		
	Common:	Headache
Cardiac disorders		
	Common:	Tachycardia
Respiratory, thoracic and mediastinal disorders		
	Common:	Nasopharyngitis
Gastrointestinal disorders		
	Very common:	Vomiting, nausea
	Common:	Abdominal pain
Musculoskeletal and connective tissue disorders		
	Common:	Pain in extremities, arthralgia, musculoskeletal pain
General disorders and administration site conditions		
	Very common:	Pyrexia, fatigue
	Common:	Acute phase reaction, pain
Investigations		
	Very common:	Hypocalcaemia
	Common:	Hypophosphataemia

[1] Adverse events occurring with frequencies < 5% were medically assessed and it was shown that these cases are consistent with the well established safety profile of Zometa (see section 4.8)

In paediatric patients with severe osteogenesis imperfecta, zoledronic acid seems to be associated with more pronounced risks for acute phase reaction, hypocalcaemia and unexplained tachycardia, in comparison to pamidronate, but this difference declined after subsequent infusions.

The European Medicines Agency has waived the obligation to submit the results of studies with zoledronic acid in all subsets of the paediatric population in the treatment of tumour-induced hypercalcaemia and prevention of skeletal-related events in patients with advanced malignancies involving bone (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 zoledronic acid 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 zoledronic acid on day 28.

Intravenously administered zoledronic acid is eliminated by 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 zoledronic acid in plasma after multiple doses 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.

The interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as seen with other bisphosphonates.

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).

In an *in vitro* study, zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

Special populations

Paediatric patients
Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those 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.

5.3 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 intravenously once every 2–3 days in dogs for up to 52 weeks was also well tolerated.

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

The safety margins relative to renal effects were narrow in the long-term repeat-dose parenteral animal studies but the cumulative no adverse event levels (NOAELs) in the single dose (1.6 mg/kg) and multiple dose studies of up to one month (0.06–0.6 mg/kg/day) did not indicate renal effects at doses equivalent to or exceeding the highest intended human therapeutic dose. Longer-term repeat administration at doses bracketing the highest intended human therapeutic dose of zoledronic acid produced toxicological effects in other organs, including the gastrointestinal tract, liver, spleen and

lungs, and at intravenous injection sites.

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. Dystocia was observed at the lowest dose (0.01 mg/kg bodyweight) tested in the rat.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium citrate
Water for injections

6.2 Incompatibilities

This medicinal product must not be allowed to come into contact with any calcium-containing solutions and it must not be mixed or given intravenously with any other medicinal product in the same infusion line.

6.3 Shelf life

Unopened bottle: 3 years.

After first opening: From a microbiological point of view, the solution for infusion should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C – 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

100 ml solution in a transparent, colourless, plastic (cycloolefinic copolymer) bottle closed with a fluorocarbon polymer coated bromobutyl rubber stopper and an aluminum cap with a flip-off component of polypropylene.

Unit packs containing 1 bottle.

Multi-packs containing 4 (4x 1) or 5 (5x 1) bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Additional information on handling of Zometa, including guidance on the preparation of reduced

doses using the Zometa ready-to-use bottle, is provided in section 4.2.

Aseptic techniques must be followed during the preparation of the infusion. For single use only.

Only clear solution free from particles and discolouration should be used.

Healthcare professionals are advised not to dispose of unused Zometa via the domestic sewage system.

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

7. MARKETING AUTHORISATION HOLDER

Phoenix Labs Unlimited Company
Suite 12, Bunkilla Plaza
Bracetown Business Park
Clonee, County Meath
Ireland

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/176/007-9

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20.03.2001
Date of latest renewal: 20.03.2006

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu