

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic acid MCM PHARMA 4mg/5ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial with 5 ml concentrate contains 4 mg zoledronic acid (as monohydrate, corresponding to 4.264 mg zoledronic acid monohydrate).

One ml concentrate contains 0.8 mg zoledronic acid (as monohydrate).

This medicinal product contains 5.63 mg sodium per vial.

For a full list of excipients see section 6.1

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion

Clear and colourless solution.

Average values for pH = 6.0 and for osmolarity 300 mOsm/kg

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

Zoledronic acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

Posology

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

Adults and elderly

The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg 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 elderly

The recommended dose in hypercalcaemia (albumin-corrected serum calcium \geq 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment*TIH:*

Zoledronic Acid MCM PHARMA 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 Zoledronic Acid MCM PHARMA 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. Zoledronic Acid MCM PHARMA 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 Zoledronic Acid MCM PHARMA, patients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, reduced zoledronic acid doses are recommended (see also section 4.4).

Baseline Creatinine Clearance (ml/min)	Zoledronic Acid 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 Zoledronic Acid MCM PHARMA 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 an 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, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). zoledronic acid treatment should be resumed at the same dose as that 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 sections 5.1 but no recommendation on a posology can be made.

Method of administration

Intravenous use.

Zoledronic acid 4 mg concentrate for ml solution for infusion. further diluted in 100 ml (see section 6.6), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced zoledronic acid doses are recommended (see section “Posology” above and section 6.3).

Instructions for preparing reduced doses of Zoledronic Acid MCM PHARMA

Withdraw an appropriate volume of the concentrate needed, as follows:

- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

The withdrawn amount of concentrate must be further 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 over no less than 15 minutes.

Zoledronic Acid MCM PHARMA zoledronic acid concentrate 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 separate infusion line.

Patients must be maintained well hydrated prior to and following administration of Zoledronic Acid MCM PHARMA

4.3 Contraindications

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

4.4 Special warnings and precautions for useGeneral

Patients must be assessed prior to administration of Zoledronic Acid MCM PHARMA 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 Zoledronic Acid MCM PHARMA 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.

Patients being treated with Zoledronic acid MCM PHARMA should not be treated with any other medicines containing zoledronic acid 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 Zoledronic Acid MCM PHARMA 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.

Zoledronic acid 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 Zoledronic Acid MCM PHARMA and other bisphosphonates as well as use of other nephrotoxic drugs. 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 zoledronic acid. Increases in serum creatinine also occur in some patients with chronic administration of zoledronic acid 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 zoledronic acid. 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, Zoledronic Acid MCM PHARMA should be withheld. Zoledronic Acid MCM PHARMA should only be resumed when serum creatinine returns to within 10% of baseline (see section 4.2).

Zoledronic acid 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 $\geq 400 \mu\text{mol/l}$ or $\geq 4.5 \text{ mg/dl}$ for patients with TIH and $\geq 265 \mu\text{mol/l}$ or $\geq 3.0 \text{ mg/dl}$ 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 $< 30 \text{ ml/min}$), the use of Zoledronic Acid MCM PHARMA 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 of the jaw

Osteonecrosis of the jaw (ONJ) has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as Zoledronic Acid MCM PHARMA. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal pain

In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking zoledronic acid. 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 the zoledronic acid 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.

This medicinal product contains less than 1 mmol sodium (23mg) per vial, i.e. essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, zoledronic acid 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, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required.

Caution is indicated when Zoledronic Acid MCM PHARMA 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 is used in combination with thalidomide.

Reports of ONJ have been received in patients treated with Zometa and concomitant anti-angiogenic 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. Zoledronic Acid MCM PHARMA should not be used during pregnancy.

Breast-feeding

It is not known whether zoledronic acid is excreted into human milk. Zoledronic Acid MCM PHARMA 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 mobilisation, 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 affect the ability to drive or use machines, though no studies on this effect with zoledronic acid have been performed.

4.8 Undesirable effects

Summary of the safety profile

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

The following are the important identified risks with zoledronic acid in the approved indications:

Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. The frequencies for each of these identified risks are shown in Table 1.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid:

Table 1

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).

<i>Blood and lymphatic system disorders</i>		
	Common:	Anaemia
	Uncommon:	Thrombocytopenia, leucopenia
	Rare:	Pancytopenia
<i>Immune system disorders</i>		
	Uncommon:	Hypersensitivity reactions
	Rare:	Angioneurotic oedema
<i>Psychiatric disorders</i>		
	Uncommon:	Anxiety, sleep disturbance
	Rare:	Confusion
<i>Nervous system disorders</i>		
	Common:	Headache
	Uncommon:	Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence
<i>Eye disorders</i>		
	Common:	Conjunctivitis
	Uncommon:	Blurred vision, scleritis and orbital inflammation
	Very rare:	Uveitis, episcleritis
<i>Cardiac disorders</i>		
	Common:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
	Uncommon:	Bradycardia
<i>Respiratory, thoracic and mediastinal disorders</i>		
	Uncommon:	Dyspnoea, cough, bronchoconstriction
<i>Gastrointestinal disorders</i>		
	Common:	Nausea, vomiting, anorexia
	Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
<i>Skin and subcutaneous tissue disorders</i>		
	Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
<i>Musculoskeletal and connective tissue disorders</i>		
	Common:	Bone pain, myalgia, arthralgia generalized pain
	Uncommon:	Muscle cramps, osteonecrosis of the jaw*

<i>Renal and urinary disorders</i>		
	Common:	Renal impairment
	Uncommon:	Acute renal failure, haematuria, proteinuria
<i>General disorders and administration site conditions</i>		
	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
<i>Investigations</i>		
	Very common:	Hypophosphataemia
	Common:	Blood creatinine and blood urea increased, Hypocalcaemia
	Uncommon:	Hypomagnesaemia, hypokalaemia
	Rare:	Hyperkalaemia, hypernatraemia
* Based on clinical trials with adjudication of possible cases of osteonecrosis of the jaw. Since these reports are subject to confounding factors, it is not possible to reliably establish a causal relationship to exposure to the medicinal product.		

Description of selected adverse reactions

Renal function impairment

Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from 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 zoledronic acid (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 zoledronic acid 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 (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged (see section 4.4).

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 zoledronic acid (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 and arthralgia. The onset time is ≤ 3 days post-zoledronic acid 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 (bisphosphonate class adverse reaction).

4.9 Overdose

Clinical experience with acute overdose of zoledronic acid 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, bisphosphonate, ATC code: M05 BA 08

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 antitumour 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 patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 2.

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 3.

Table 2: Efficacy results (prostate cancer patients receiving hormonal therapy)

	<u>Any SRE (+TIH)</u>		<u>Fractures*</u>		<u>Radiation therapy to bone</u>	
	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 3: Efficacy results (solid tumours other than breast or prostate cancer)

	<u>Any SRE (+TIH)</u>		<u>Fractures*</u>		<u>Radiation therapy to bone</u>	
	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 4.

Table 4: Efficacy results (breast cancer and multiple myeloma patients)

	<u>Any SRE (+TIH)</u>		<u>Fractures*</u>		<u>Radiation therapy to bone</u>	
	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		0.652		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	

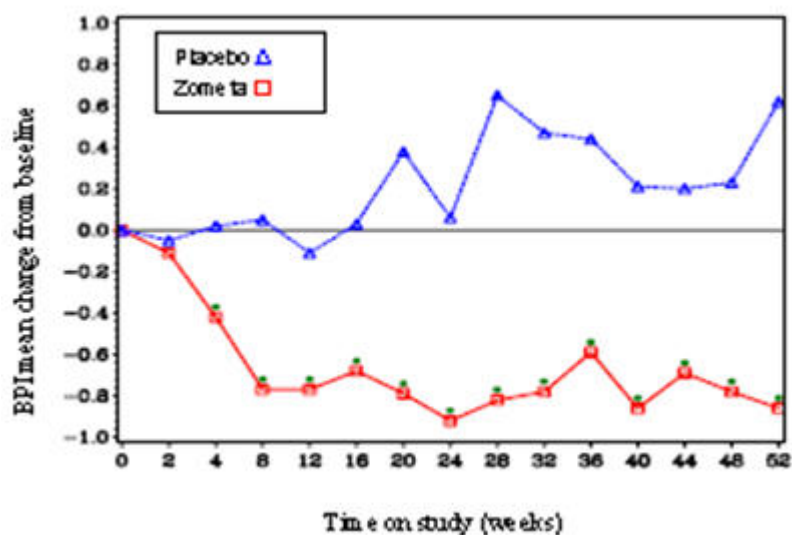
- * Includes vertebral and non-vertebral fractures
 ** Accounts for all skeletal events, the total number as well as time to each event during the trial
 NR Not Reached
 NA Not Applicable

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 4mg 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)



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 90 mg pamidronate, 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 5: 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 \geq 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 (4 mg, 8 mg zoledronic acid or 90 mg pamidronate) were retreated with zoledronic acid 8 mg. 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 populationClinical 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 6. The following conventional classification is used: very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1,000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1,000$), very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 6: Adverse reactions observed in paediatric patients with severe osteogenesis imperfecta¹

<i>Nervous system disorders</i>	Common:	Headache
<i>Cardiac disorders</i>	Common:	Tachycardia
<i>Respiratory, thoracic and mediastinal disorders</i>	Common:	Nasopharyngitis
<i>Gastrointestinal disorders</i>	Very common Common:	Vomiting, nausea Abdominal pain
<i>Musculoskeletal and connective tissue disorders</i>	Common:	Pain in extremities, arthralgia, musculoskeletal pain
<i>General disorders and administration site conditions</i>	Very common: Common:	Pyrexia, fatigue Acute phase reaction, pain
<i>Investigations</i>	Very common: Common:	Hypocalcaemia 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 zoledronic acid (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 the reference medicinal product containing 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 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 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 $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of drug in plasma after multiple doses of the drug given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, $39 \pm 16\%$ 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 $75 \pm 33\%$ of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 cancer patients studied. Population analysis showed that for a patient with creatinine clearance of 20 ml/min (severe renal impairment), or 50 ml/min (moderate impairment), the corresponding predicted clearance of zoledronic acid would be 37% or 72%, respectively, of that of a patient showing creatinine clearance of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

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

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 (E421)
Sodium citrate (E331)
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6.

6.3 Shelf life

Unopened bottle: 3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C- 8°C when diluted with 100ml of physiological saline or 5% w/v glucose.

After dilution: 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

Zoledronic Acid MCM PHARMA 4 mg/5 ml concentrate for solution for infusion is supplied as packs containing 1, 4 or 10 vials. Not all pack sizes may be marketed.

Vial: 5-ml plastic vial made of clear, colourless cycloolefine copolymer with fluoropolymer-coated bromobutyl rubber stopper and aluminium cap with plastic flip-off component.

6.6 Special precautions for disposal and other handling

Prior to administration, 5.0 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).

This medicinal product 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 separate infusion line. Additional information on handling of Zoledronic Acid MCM PHARMA, including guidance on preparation of reduced doses, 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 Zoledronic Acid MCM PHARMA 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

MCM Pharma GmbH
Kleine Johannisstraße 10
200457 Hamburg
Germany

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 16th November 2012

10 DATE OF REVISION OF THE TEXT

October 2014