ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 4 mg/5 ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 5 ml concentrate contains 4 mg zoledronic acid (as monohydrate).

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

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

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

Zoledronic acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated with zoledronic acid 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 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 ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment

TIH:

Zoledronic acid 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 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 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, 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, the following zoledronic acid dose is 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 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, 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 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.

Zoledronic Acid Hospira concentrate for 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 4.4).

Instructions for preparing reduced doses of Zoledronic Acid Hospira

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

For instructions on the dilution of the medicinal product before administration, see section 6.6. The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution for injection (see section 4.4) or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zoledronic Acid Hospira 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 Hospira.

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 zoledronic acid 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 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.

Other products containing zoledronic acid as active substance are available for osteoporosis indications and treatment of Paget´s disease of the bone. Patients being treated with Zoledronic Acid Hospira should not be treated with such products 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 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 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 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 should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. 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 µmol/l or $\geq$ 4.5 mg/dl for patients with TIH and $\geq$ 265 µmol/l or $\geq$ 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 zoledronic acid 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 Zoledronic Acid. 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 zoledronic acid. 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 Zoledronic Acid Hospira.

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 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.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with zoledronic acid. 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 Zoledronic acid 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 zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially “sodium-free”.

This medicinal product may be diluted with sodium-containing solutions (see section 4.2) and this should be considered in relation to the total sodium from all sources that will be administered to the patient.

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, 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 zoledronic acid 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 zoledronic acid is used in combination with thalidomide.

Caution is advised when Zoledronic Acid Hospira 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. Zoledronic acid 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. Zoledronic acid 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 zoledronic acid along with driving and operating of machinery.

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, 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 zoledronic acid 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 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).

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

Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from trials for the use of zoledronic acid 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 of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid (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 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-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).

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with zoledronic acid 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 zoledronic acid 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 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: Medicinal products 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 medicinal products, 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 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)

	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 3: 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 4.

Table 4: 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	

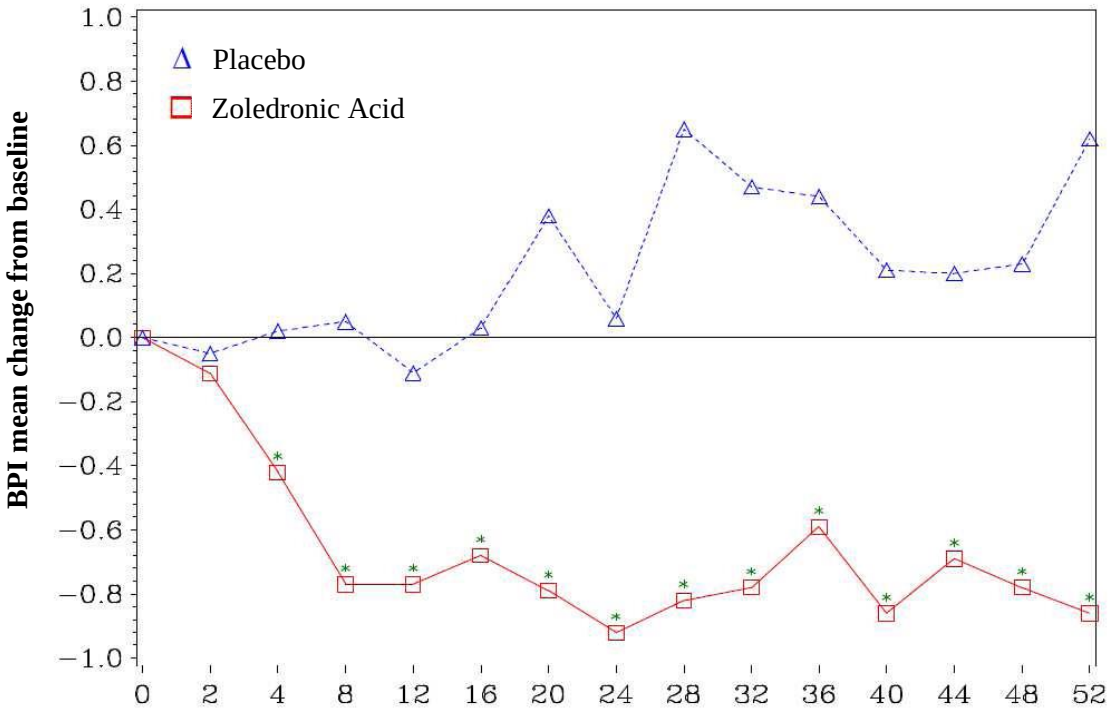
* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial
NR Not Reached
NA Not Applicable

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 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 ≥ 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 6. 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 6: 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 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 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 $\geq$ 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

To avoid potential incompatibilities, Zoledronic Acid Hospira is to be diluted with 0.9% w/v sodium chloride solution for injection 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.

6.3 Shelf life

3 years

After dilution: From a microbiological point of view, the diluted 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 of the diluted solution for infusion, see section 6.3.

6.5 Nature and contents of container

6 ml, type I clear glass vial or 5 ml plastic vial, stoppered with a fluoropolymer-coated halo-butyl closure and sealed with an aluminium seal and flip-off top.

Pack size

Zoledronic Acid Hospira is supplied as packs containing 1 vial.

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 for injection or 5% w/v glucose solution).

Additional information on handling of Zoledronic Acid Hospira, 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 Hospira 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

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/001
EU/1/12/800/002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2012
Date of latest renewal: 24 August 2017

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.

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 4 mg/100 ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One bag with 100 ml contains 4 mg zoledronic acid (as monohydrate).

One ml of the solution contains 0.04 mg zoledronic acid (as monohydrate).

Excipient with known effect

Zoledronic Acid Hospira 4 mg/100 ml contains 360 mg sodium per dosage unit.

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

Zoledronic acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated with zoledronic acid 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 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 ≥ 12.0 mg/dl or 3.0 mmol/l) is a single dose of 4 mg zoledronic acid.

Renal impairment

TIH:

Zoledronic acid 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 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 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, 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 Zoledronic Acid Hospira doses are recommended (see also section 4.4).

Baseline creatinine clearance (ml/min)	**Zoledronic Acid Hospira 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 Hospira 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, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic Acid Hospira 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.

Zoledronic Acid Hospira 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 Zoledronic Acid Hospira 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 Zoledronic Acid Hospira solution indicated from the bag prior to administration.

Table 1: Preparation of reduced doses of Zoledronic Acid Hospira 4 mg/100 ml solution for infusion

Baseline creatinine clearance (ml/min)	**Remove the following amount of Zoledronic Acid Hospira 4 mg/100 ml solution for infusion (ml)**	**Adjusted dose (mg zoledronic acid)**
50-60	12.0	3.5
40-49	18.0	3.3
30-39	25.0	3.0

Zoledronic Acid Hospira 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 Zoledronic Acid Hospira.

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 zoledronic acid 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 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.

Other products containing zoledronic acid as active substance are available for osteoporosis indications and treatment of Paget´s disease of the bone. Patients being treated with Zoledronic Acid Hospira should not be treated with 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 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 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 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 should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. 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 µmol/l or $\geq$ 4.5 mg/dl for patients with TIH and $\geq$ 265 µmol/l or $\geq$ 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 zoledronic acid 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 zoledronic acid. 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 zoledronic acid.

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 Zoledronic Acid Hospira.

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 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.

Hypocalcaemia

Hypocalcaemia has been reported in patients treated with zoledronic acid. 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 zoledronic acid 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 zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

Excipients

This medicinal product contains 360 mg sodium per dosage unit, equivalent to18% of the WHO maximum recommended daily intake (RDI) of 2 g sodium for an adult.

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, 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 zoledronic acid 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 zoledronic acid is used in combination with thalidomide.

Caution is advised when Zoledronic Acid Hospira 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. Zoledronic acid 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. Zoledronic acid 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 zoledronic acid along with driving and operating of machinery.

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, 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 zoledronic acid 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

Zoledronic acid has been associated with reports of renal dysfunction. In a pooled analysis of safety data from trials for the use of zoledronic acid 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 of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid (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 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-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).

Hypocalcaemia-related ADRs

Hypocalcaemia is an important identified risk with zoledronic acid 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 zoledronic acid 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 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: Medicinal products 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 medicinal products, 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	

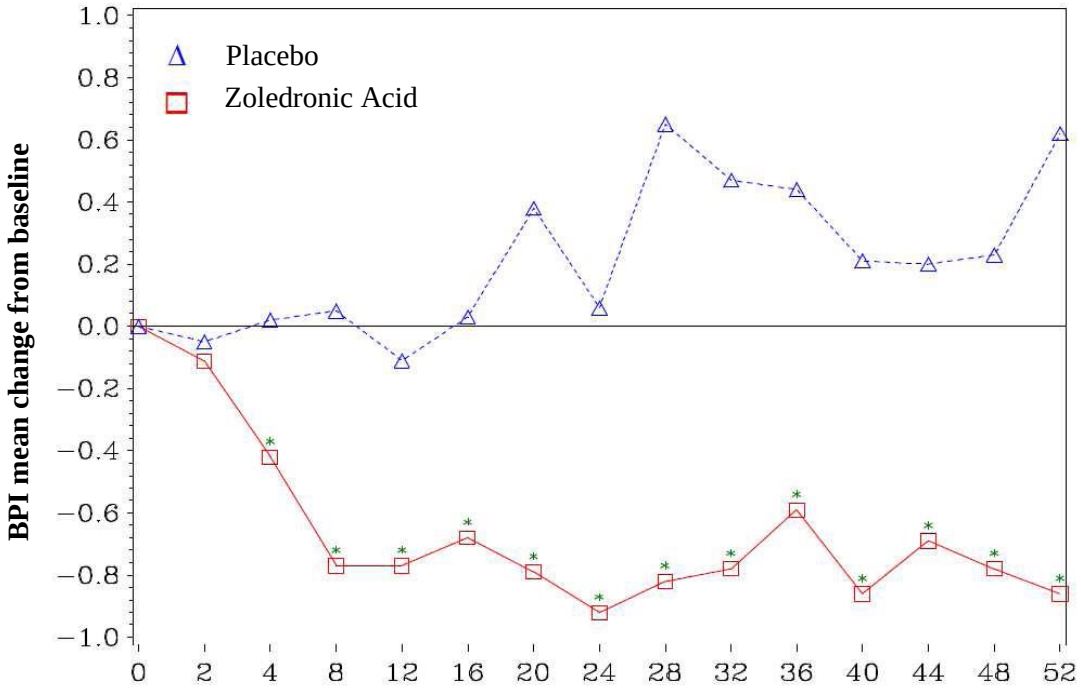
* Includes vertebral and non-vertebral fractures
** Accounts for all skeletal events, the total number as well as time to each event during the trial
NR Not Reached
NA Not Applicable

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 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 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 $\geq$ 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
Sodium chloride
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 bag: 2 years.

After first opening: From a microbiological point of view, the product 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 polypropylene bags with a polypropylene twist-off port fitted with a cap, with a polyester/polypropylene overwrap

Pack size

Zoledronic Acid Hospira is supplied as packs containing 1 bag.

6.6 Special precautions for disposal and other handling

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 Hospira 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

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2012
Date of latest renewal: 24 August 2017

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.

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 5 mg/100 ml solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bag with 100 ml of solution contains 5 mg zoledronic acid (as monohydrate).

Each ml of the solution contains 0.05 mg zoledronic acid anhydrous (as 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

Treatment of Paget's disease of the bone in adults.

4.2 Posology and method of administration

Posology

Patients must be appropriately hydrated prior to administration of Zoledronic Acid Hospira. This is especially important for the elderly (≥65 years) and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with Zoledronic Acid Hospira administration.

For the treatment of Paget's disease, zoledronic acid should be prescribed only by physicians with experience in the treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5 mg zoledronic acid. In patients with Paget’s disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Zoledronic Acid Hospira administration (see section 4.4).

Re-treatment of Paget's disease: After initial treatment with zoledronic acid in Paget's disease, an extended remission period is observed in responding patients. Re-treatment consists of an additional intravenous infusion of 5 mg zoledronic acid after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget’s disease are available (see section 5.1).

Special populations

Patients with renal impairment

Zoledronic acid is contraindicated in patients with creatinine clearance < 35 ml/min (see sections 4.3 and 4.4).

No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Elderly (≥ 65 years)

No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Paediatric population

Zoledronic acid Hospira should not be used in children and adolescents below 18 years of age. There are no data available for children under 5 years of age. Currently available data for children aged 5 to 17 years are described in section 5.1.

Method of administration

Intravenous use.

Zoledronic Acid Hospira (5 mg in 100 ml ready-to-infuse solution) is administered via a vented infusion line and given slowly at a constant infusion rate. The infusion time must not be less than 15 minutes. For information on the infusion of Zoledronic Acid Hospira, see section 6.6.

Patients treated with Zoledronic Acid Hospira should be given the package leaflet and the patient reminder card.

4.3 Contraindications

- Hypersensitivity to the active substance, to any bisphosphonates or to any of the excipients listed in section 6.1.
- Patients with hypocalcaemia (see section 4.4).
- Severe renal impairment with creatinine clearance < 35 ml/min (see section 4.4).
- Pregnancy and breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Renal function

The use of Zoledronic Acid Hospira in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

Renal impairment has been observed following the administration of zoledronic acid (see section 4.8), especially in patients with pre-existing renal dysfunction or other risks including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section 4.5), or dehydration occurring after zoledronic acid administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

The following precautions should be taken into account to minimise the risk of renal adverse reactions:

- Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Gault formula before each Zoledronic Acid Hospira dose.

- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.

- Monitoring of serum creatinine should be considered in at-risk patients.

- Zoledronic acid should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section 4.5).

- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of zoledronic acid.

- A single dose of zoledronic acid should not exceed 5 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Hypocalcaemia

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with zoledronic acid (see section 4.3). Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.

Elevated bone turnover is a characteristic of Paget's disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of zoledronic acid (see section 4.8).

Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following zoledronic acid administration (see section 4.2).

Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum calcium before infusion of zoledronic acid is recommended for patients with Paget´s disease.

Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including zoledronic acid (see section 4.8).

Osteonecrosis of the jaw (ONJ)

ONJ has been reported in the post-marketing setting in patients receiving zoledronic acid for osteoporosis (see section 4.8).

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. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Zoledronic Acid Hospira in patients with concomitant risk factors.

The following should be considered when evaluating a patient’s risk of developing ONJ:

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.

- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions.

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, non-healing of sores or discharge during treatment with zoledronic acid. While on treatment, invasive dental procedures should be performed with caution and avoided in close proximity to zoledronic acid treatment.

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 the external auditory canal

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.

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.

Acute phase reactions

Acute phase reactions (APRs) or post-dose symptoms such as fever, myalgia, flu-like symptoms, arthralgia and headache have been observed, the majority of which occurred within three days following Zoledronic Acid Hospira administration.

APRs may sometimes be serious or prolonged in duration. The incidence of post-dose symptoms can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic Acid Hospira administration. It is also advisable to postpone treatment if the patient is clinically unstable due to an acute medical condition and an APR could be problematic (see section 4.8).

General

Other products containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with Zoledronic Acid Hospira should not be treated with such products or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dosage unit. Patients on low sodium diets can be informed that this medicinal product is essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other medicinal products have been performed. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see section 5.2). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound medicinal products are therefore unlikely.

Zoledronic acid is eliminated by renal excretion. Caution is indicated when zoledronic acid is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidney may increase.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Zoledronic acid is not recommended in women of childbearing potential.

Pregnancy

Zoledronic Acid Hospira is contraindicated during pregnancy (see section 4.3). There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations (see section 5.3). The potential risk for humans is unknown.

Breast-feeding

Zoledronic Acid Hospira is contraindicated during breast-feeding (see section 4.3). It is unknown whether zoledronic acid is excreted into human milk.

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 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, may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall percentage of patients who experienced adverse reactions were 44.7%, 16.7% and 10.2% after the first, second and third infusion, respectively. Incidence of individual adverse reactions

following the first infusion was: pyrexia (17.1%), myalgia (7.8%), influenza-like illness (6.7%), arthralgia (4.8%) and headache (5.1%),see “acute phase reactions” below.

Tabulated list of adverse reactions

Adverse reactions in Table 1 are listed according to MedDRA system organ class and frequency category. Frequency categories are defined 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). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1

Infections and infestations	*Uncommon*	Influenza, nasopharyngitis
Blood and lymphatic system disorders	*Uncommon*	Anaemia
Immune system disorders	*Not known***	Hypersensitivity reactions including rare cases of bronchospasm, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common*	Hypocalcaemia*
	Uncommon	Decreased appetite
	Rare	Hypophosphataemia
Psychiatric disorders	*Uncommon*	Insomnia
Nervous system disorders	*Common*	Headache, dizziness
	Uncommon	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	*Common*	Ocular hyperaemia
	Uncommon	Conjunctivitis, eye pain
	Rare	Uveitis, episcleritis, iritis
	*Not known***	Scleritis and parophthalmia
Ear and labyrinth disorders	*Uncommon*	Vertigo
Cardiac disorders	*Common*	Atrial fibrillation
	Uncommon	Palpitations
Vascular disorders	*Uncommon*	Hypertension, flushing
	*Not known***	Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic and mediastinal disorders	*Uncommon*	Cough, dyspnoea
Gastrointestinal disorders	*Common*	Nausea, vomiting, diarrhoea
	Uncommon	Dyspepsia, abdominal pain upper, abdominal pain, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]

Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhidrosis, pruritus, erythema
Musculoskeletal and connective tissue disorders	*Common*	Myalgia, arthralgia, bone pain, back pain, pain in extremity
	Uncommon	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	Rare	Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction)
	Very rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
	*Not known***	Osteonecrosis of the jaw (see sections 4.4 and 4.8 Class effects)
Renal and urinary disorders	*Uncommon*	Blood creatinine increased, pollakiuria, proteinuria
	*Not known***	Renal impairment. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period (see sections 4.4 and 4.8 Class effects)
General disorders and administration site conditions	*Very common*	Pyrexia
	Common	Influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	Uncommon	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	*Not known***	Dehydration secondary to acute phase reactions (post-dose symptoms such as pyrexia, vomiting and diarrhoea)
Investigations	*Common*	C-reactive protein increased
	Uncommon	Blood calcium decreased

[#] Observed in patients taking concomitant glucocorticosteroids.
* Common in Paget's disease only.
** Based on post-marketing reports. Frequency cannot be estimated from available data.
† Identified in post-marketing experience.

Description of selected adverse reactions

Atrial fibrillation

In the HORIZON - Pivotal Fracture Trial [PFT] (see section 5.1), 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 and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving zoledronic acid (1.3%) (51 out of 3,862) compared with patients receiving placebo (0.6%) (22 out of 3,852). The mechanism behind the increased incidence of atrial fibrillation is unknown. In the osteoporosis trials (PFT, HORIZON - Recurrent Fracture Trial [RFT]) the pooled atrial fibrillation incidences were comparable between zoledronic acid (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events the pooled incidences were 1.3% for zoledronic acid and 0.8% for placebo.

Class effects

Renal impairment

Zoledronic acid has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal dysfunction or additional risk factors (e.g., advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, severe dehydration), with the majority of them receiving a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In clinical trials in osteoporosis, the change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the zoledronic acid and placebo treatment groups over three years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of zoledronic acid-treated patients versus 0.8% of placebo-treated patients.

Hypocalcaemia

In clinical trials in osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87 mmol/l) following zoledronic acid administration. No symptomatic cases of hypocalcaemia were observed.

In the Paget's disease trials, symptomatic hypocalcaemia was observed in approximately 1% of patients, in all of whom it resolved.

Based on laboratory assessment, transient asymptomatic calcium levels below the normal reference range (less than 2.10 mmol/l) occurred in 2.3% of zoledronic acid-treated patients in a large clinical trial compared to 21% of zoledronic acid-treated patients in the Paget's disease trials. The frequency of hypocalcaemia was much lower following subsequent infusions.

All patients received adequate supplementation with vitamin D and calcium in the post-menopausal osteoporosis trial, the prevention of clinical fractures after hip fracture trial, and the Paget's disease trials (see also section 4.2). In the trial for the prevention of clinical fractures following a recent hip fracture, vitamin D levels were not routinely measured but the majority of patients received a loading dose of vitamin D prior to zoledronic acid administration (see section 4.2).

Local reactions

In a large clinical trial, local reactions at the infusion site, such as redness, swelling and/or pain, were reported (0.7%) following the administration of zoledronic acid.

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, including zoledronic acid (see section 4.4). In a large clinical trial in 7,736 patients, osteonecrosis of the jaw has been reported in one patient treated with zoledronic acid and one patient treated with placebo. Cases of ONJ have been reported in the post-marketing setting for zoledronic acid.

Acute phase reactions

The overall percentage of patients who reported acute phase reactions or post-dose symptoms (including serious cases) after zoledronic acid administration is as follows (frequencies derived from the study in treatment of post-menopausal osteoporosis): fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occurred within the first 3 days following zoledronic acid administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased with subsequent annual doses of zoledronic acid. The percentage of patients who experienced adverse reactions was lower in a smaller study (19.5%, 10.4%, 10.7% after the first, second and third infusion, respectively), where prophylaxis against adverse reactions was used (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 is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an intravenous infusion of calcium gluconate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

Pharmacodynamic effects

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone.

The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase. The long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Zoledronic acid treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the pre-menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

Clinical efficacy in the treatment of Paget's disease of the bone

Zoledronic acid was studied in male and female patients aged above 30 years with primarily mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6–3.0 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg zoledronic acid versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month comparative trials. After 6 months, zoledronic acid showed 96% (169/176) and 89% (156/176) response and serum alkaline phosphatase (SAP) normalisation rates compared to 74% (127/171) and 58% (99/171) for risedronate (all $p<0.001$).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for zoledronic acid and risedronate.

Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended follow-up period. Of the 153 zoledronic acid-treated patients and 115 risedronate-treated patients who entered an extended observation study, after a mean duration of follow-up of 3.8 years from time of dosing, the proportion of patients ending the Extended Observation Period due to the need for re-treatment (clinical judgment) was higher for risedronate (48 patients, or 41.7%) compared with zoledronic acid (11 patients, or 7.2%). The mean time of ending the Extended Observation Period due to the need for Paget’s re-treatment from the initial dose was longer for zoledronic acid (7.7 years) than for risedronate (5.1 years).

Six patients who achieved therapeutic response 6 months after treatment with zoledronic acid and later experienced disease relapse during the extended follow-up period were re-treated with zoledronic acid after a mean time of 6.5 years from initial treatment to re-treatment. Five of the 6 patients had SAP within the normal range at month 6 (Last Observation Carried Forward, LOCF).

Bone histology was evaluated in 7 patients with Paget's disease 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

Paediatric population

A randomised, double-blind, placebo-controlled study was conducted in paediatric patients aged 5 to 17 years treated with glucocorticoids who had decreased bone mineral density (lumbar spine BMD Z-score of -0.5 or less) and a low impact/fragility fracture. The patient population randomised in this study (ITT population) included patients with several sub-types of rheumatic conditions, inflammatory bowel disease, or Duchenne muscular dystrophy. The study was planned to include 92 patients, however only 34 patients were enrolled and randomised to receive either a twice-yearly 0.05 mg/kg (max. 5 mg) intravenous zoledronic acid infusion or placebo for one year. All patients were required to receive background therapy of vitamin D and calcium.

Zoledronic acid infusion resulted in an increase in the lumbar spine BMD Z-score least square (LS) mean difference of 0.41 at month 12 relative to baseline compared to placebo (95% CI: 0.02, 0.81; 18 and 16 patients, respectively). No effect on lumbar spine BMD Z-score was evident after 6 months of treatment. At month 12, a statistically significant ($p<0.05$) reduction in three bone turnover markers (P1NP, BSAP, NTX) was observed in the zoledronic acid group as compared to the placebo group. No statistically significant differences in total body bone mineral content were observed between patients treated with zoledronic acid versus placebo at 6 or 12 months. There is no clear evidence establishing a link between BMD changes and fracture prevention in children with growing skeletons.

No new vertebral fractures were observed in the zoledronic acid group as compared to two new fractures in the placebo group.

The most commonly reported adverse reactions after infusion of zoledronic acid were arthralgia (28%), pyrexia (22%), vomiting (22%), headache (22%), nausea (17%), myalgia (17%), pain (17%), diarrhoea (11%) and hypocalcaemia (11%).

More patients reported serious adverse events in the zoledronic acid group than in the placebo group (5 [27.8%] patients versus 1 [6.3%] patient).

In the 12-month open-label extension of the above-mentioned core study, no new clinical fractures were observed. However 2 patients, one in each of the core study treatment groups (zoledronic acid group: 1/9, 11.1% and placebo group: 1/14, 7.1%), had new morphometric vertebral fractures. There were no new safety findings.

Long-term safety data in this population cannot be established from these studies.

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 Paget's disease of the 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 yielded the following pharmacokinetic data, which were found to be dose independent.

Distribution

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, 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 levels.

Elimination

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 the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β, with $t_{½}$ values above) presumably represent rapid uptake into bone and excretion via the kidneys.

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. This uptake into bone is common for all bisphosphonates and is presumably a consequence of the structural analogy to pyrophosphate. As with other bisphosphonates, the retention time of zoledronic acid in bones is very long. 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 or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. 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.

Pharmacokinetic/pharmacodynamic relationships

No interaction studies with other medicinal products have been performed with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the

cytochrome P450 enzyme systems. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound medicinal products are unlikely.

Special populations (see section 4.2)

Renal impairment

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 patients studied. Small observed increases in $AUC_{(0\text{-}24hr)}$, by about 30% to 40% in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of medicinal product with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild (Cl_{cr} = 50–80 ml/min) and moderate renal impairment down to a creatinine clearance of 35 ml/min are not necessary. The use of zoledronic acid in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

5.3 Preclinical safety data

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats. In the single-dose dog infusion studies, 1.0 mg/kg (6 fold the recommended human therapeutic exposure based on AUC) administered over 15 minutes was well tolerated with no renal effects.

Subchronic and chronic toxicity

In the intravenous infusion studies, renal tolerability of zoledronic acid was established in rats when given 0.6 mg/kg as 15-minute infusions at 3-day intervals, six times in total (for a cumulative dose that corresponded to AUC levels about 6 times the human therapeutic exposure) while five 15-minute infusions of 0.25 mg/kg administered at 2-3-week intervals (a cumulative dose that corresponded to 7 times the human therapeutic exposure) were well tolerated in dogs. In the intravenous bolus studies, the doses that were well tolerated decreased with increasing study duration: 0.2 and 0.02 mg/kg daily was well tolerated for 4 weeks in rats and dogs, respectively but only 0.01 mg/kg and 0.005 mg/kg in rats and dogs, respectively, when given for 52 weeks.

Longer-term repeat administration at cumulative exposures sufficiently exceeding the maximum intended human exposure produced toxicological effects in other organs, including the gastrointestinal tract and liver, and at the site of intravenous administration. The clinical relevance of these findings is unknown. The most frequent finding in the 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.

Reproduction toxicity

Teratology studies were performed in two species, both via subcutaneous administration. Teratogenicity was observed in rats at doses $\geq$ 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels.

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. Zoledronic Acid Hospira must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

Unopened bag: 2 years

After opening: 24 hours at 2°C - 8°C

From a microbiological point of view, the product 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.

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 polypropylene bags with a polypropylene twist-off port fitted with a cap, with a polyester/polypropylene overwrap

Pack size

Zoledronic Acid Hospira is supplied as packs containing one bag.

6.6 Special precautions for disposal and other handling

For single use only.

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

If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

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

7 MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17

1050 Bruxelles
Belgium

8 MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorization: 19 November 2012
Date of latest renewal: 24 August 2017

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

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Pfizer Service Company BVBA
Hoge Wei 10
1930 Zaventem
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder.(MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency,
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that a patient reminder card regarding osteonecrosis of the jaw is implemented.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 VIAL AS UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 4 mg/5 ml concentrate for solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial contains 4 mg of zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

It also contains mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
4 mg/5 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use only.
Dilute before use
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Stable for 24 hours at 2ºC – 8ºC after dilution

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/001
EU/1/12/800/002

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zoledronic Acid Hospira 4 mg/5 ml sterile concentrate
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

Dilute before use

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 BAG AS UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 4 mg/100 ml solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 4 mg of zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

It also contains mannitol, sodium citrate, water for injections and sodium chloride.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
4 mg/100 ml *(to appear in roundel)*
1 intravenous bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use only.
For single use only

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/003

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BAG LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zoledronic Acid Hospira 4 mg/100 ml *(to appear in roundel)* solution for infusion
zoledronic acid
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

(included in section 1 text)

6. OTHER

Pfizer Europe MA EEIG

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON FOR 1 BAG AS UNIT PACK

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic Acid Hospira 5 mg/100 ml solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bag of 100 ml contains 5 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

1 intravenous bag

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For intravenous use only.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening: 24 hours at 2ºC – 8ºC.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/800/004

13. BATCH NUMBER

BN

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BAG LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Zoledronic Acid Hospira 5 mg/100 ml *(to appear in roundel)* solution for infusion
zoledronic acid
Intravenous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

BN

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

(included in section 1 text)

6. OTHER

Pfizer Europe MA EEIG

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zoledronic Acid Hospira 4 mg/5 ml concentrate for solution for infusion
zoledronic acid

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Zoledronic Acid Hospira is and what it is used for

The active substance in Zoledronic Acid Hospira is zoledronic acid, which belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change. It is used:
- **To prevent bone complications,** e.g. fractures, in adult patients with bone metastases (spread of cancer from primary site to the bone).
- **To reduce the amount of calcium** in the blood in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

2 What you need to know before you are given Zoledronic Acid Hospira

Follow carefully all instructions given to you by your doctor.

Your doctor will carry out blood tests before you start treatment with Zoledronic Acid Hospira and will check your response to treatment at regular intervals.

You should not be given Zoledronic Acid Hospira:
- if you are breast-feeding.
- if you are allergic to zoledronic acid, another bisphosphonate (the group of substances to which zoledronic acid belongs), or any of the other ingredients of Zoledronic Acid Hospira (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Zoledronic Acid Hospira:
- if you have or have had a **kidney problem.**
- if you have or have had **pain, swelling or numbness** of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Your doctor may recommend a dental examination before you start treatment with Zoledronic Acid Hospira

if you are having **dental treatment** or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic Acid Hospira and inform your doctor about your dental treatment.

While being treated with Zoledronic Acid Hospira, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw.

Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing osteonecrosis of the jaw.

Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin, burning sensation, have been reported in patients treated with zoledronic acid. Irregular heart beat (cardiac arrhythmia), seizures, spasm and twitching (tetany) have been reported as secondary to severe hypocalcaemia. In some instances the hypocalcaemia may be life-threatening. If any of these apply to you, tell your doctor straight away. If you have pre-existing hypocalcaemia, it must be corrected before initiating the first dose of Zoledronic Acid Hospira. You will be given adequate calcium and vitamin D supplements.

Patients aged 65 years and over
Zoledronic Acid Hospira can be given to people aged 65 years and over. There is no evidence to suggest that any extra precautions are needed.

Children and adolescents
Zoledronic Acid Hospira is not recommended for use in adolescents and children below the age of 18 years.

Other medicines and Zoledronic Acid Hospira
Tell your doctor if you are taking, have recently taken or might take any other medicines. It is especially important that you tell your doctor if you are also taking:
- Aminoglycosides (medicines used to treat severe infections), calcitonin (a type of medicine used to treat post-menopausal osteoporosis and hypercalcaemia), loop diuretics (a type of medicine to treat high blood pressure or oedema) or other calcium-lowering medicines, since the combination of these
- with bisphosphonates may cause the calcium level in the blood to become too low.
- Thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.
- Any other medicines that also contains zoledronic acid and is used to treat osteoporosis and other non-cancer diseases of the bone, or any other bisphosphonate, since the combined effects of these medicines taken together with Zoledronic Acid Hospira are unknown.
- Anti-angiogenic medicines (used to treat cancer), since the combination of these with Zoledronic Acid Hospira has been associated with an increased risk of osteonecrosis of the jaw (ONJ).

Pregnancy and breast-feeding
You should not be given Zoledronic Acid Hospira if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You must not be given Zoledronic Acid Hospira if you are breast-feeding.

Ask your doctor for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
There have been very rare cases of drowsiness and sleepiness with the use of Zoledronic Acid Hospira. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

Zoledronic Acid Hospira contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially "sodium-free".

3 How Zoledronic Acid Hospira is used

- Zoledronic Acid Hospira must only be given by healthcare professionals trained in administering bisphosphonates intravenously, i.e. through a vein (also referred to as 'IV' administration).
- Your doctor will recommend that you drink enough water before each treatment to help prevent dehydration.
- Carefully follow all the other instructions given to you by your doctor, pharmacist or nurse.

How much Zoledronic Acid Hospira is given
- The usual single dose given is 4 mg.
- If you have a kidney problem, your doctor will give you a lower dose depending on the severity of your kidney problem.

How often Zoledronic Acid Hospira is given
- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledronic Acid Hospira every three to four weeks.
- If you are being treated to reduce the amount of calcium in your blood, you will normally only be given one infusion of Zoledronic Acid Hospira.

How Zoledronic Acid Hospira is given
- Zoledronic Acid Hospira is given as a drip (infusion) into a vein which should take at least 15 minutes and should be administered as a single intravenous solution in a separate infusion line.

Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day.

If you are given more Zoledronic Acid Hospira than you should be
If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. abnormal levels of calcium, phosphorus and magnesium) and/or changes in kidney function, including severe kidney impairment. If your level of calcium falls too low, you may have to be given supplemental calcium by infusion.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common ones are usually mild and will probably disappear after a short time.

Tell your doctor about any of the following serious side effects straight away:

Common (may affect up to 1 in 10 people):
- Severe kidney impairment (will normally be determined by your doctor with certain specific blood tests).
- Low level of calcium in the blood.

Uncommon (may affect up to 1 in 100 people):
- Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth or jaw discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you

experience such symptoms while being treated with Zoledronic Acid Hospira or after stopping treatment.
- Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for postmenopausal osteoporosis. It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received zoledronic acid.
- Severe allergic reaction: shortness of breath, swelling mainly of the face and throat.

Rare (may affect up to 1 in 1,000 people):
- As a consequence of low calcium values: irregular heart beat (cardiac arrhythmia; secondary to hypocalcaemia).
- A kidney function disorder called Fanconi syndrome (will normally be determined by your doctor with certain urine tests).

Very rare (may affect up to 1 in 10,000 people):
- As a consequence of low calcium values: seizures, numbness and tetany (secondary to hypocalcaemia).
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- Osteonecrosis has also very rarely been seen occurring with other bones than the jaw, especially the hip or thigh. Tell your doctor immediately if you experience symptoms such as new onset or worsening of aches, pain or stiffness while being treated with Zoledronic Acid Hospira or after stopping treatment.

Tell your doctor about any of the following side effects as soon as possible:

Very common (may affect more than 1 in 10 people):- Low level of phosphate in the blood.

Common (may affect up to 1 in 10 people):
- Headache and a flu-like syndrome consisting of fever, fatigue, weakness, drowsiness, chills and bone, joint and/or muscle ache. In most cases no specific treatment is required and the symptoms disappear after a short time (couple of hours or days).
- Gastrointestinal reactions such as nausea and vomiting as well as loss of appetite.
- Conjunctivitis.
- Low level of red blood cells (anaemia).

Uncommon (may affect up to 1 in 100 people):
- Hypersensitivity reactions.
- Low blood pressure.
- Chest pain.
- Skin reactions (redness and swelling) at the infusion site, rash, itching.
- High blood pressure, shortness of breath, dizziness, anxiety, sleep disturbances, taste disturbances, trembling, tingling or numbness of the hands or feet, diarrhoea, constipation, abdominal pain, dry mouth.
- Low counts of white blood cells and blood platelets.
- Low level of magnesium and potassium in the blood. Your doctor will monitor this and take any necessary measures.
- Weight increase.
- Increased sweating.
- Sleepiness.
- Blurred vision, tearing of the eye, eye sensitivity to light.
- Sudden coldness with fainting, limpness or collapse.
- Difficulty in breathing with wheezing or coughing.

– Urticaria.

Rare (may affect up to 1 in 1,000 people):
– Slow heart beat.
– Confusion.
– Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.
– Interstitial lung disease (inflammation of the tissue around the air sacks of the lungs)
– Flu-like symptoms including arthritis and joint swelling.
– Painful redness and/or swelling of the eye.

Very rare (may affect up to 1 in 10,000 people):
– Fainting due to low blood pressure.
– Severe bone, joint and/or muscle pain, occasionally incapacitating.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Zoledronic Acid Hospira

Your doctor, pharmacist or nurse knows how to store Zoledronic Acid Hospira properly (see section 6).

6 Contents of the pack and other information

What Zoledronic Acid Hospira contains
– The active substance of Zoledronic Acid Hospira is zoledronic acid. One vial contains 4 mg zoledronic acid (as monohydrate).
– The other ingredients are mannitol, sodium citrate, water for injections.

What Zoledronic Acid Hospira looks like and contents of the pack
Zoledronic Acid Hospira is supplied as a liquid concentrate (referred to as a ‘concentrate for solution for infusion’ or ‘sterile concentrate’) in a vial. One vial contains 4 mg of zoledronic acid.

Each pack contains one vial with concentrate.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
Pfizer Service Company BVBA
Hoge Wei 10
1930 Zaventem
Belgium

For any further information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Pfizer Oy

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Pfizer AB
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This leaflet was last revised in

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

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

How to prepare and administer Zoledronic Acid Hospira

- To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the Zoledronic Acid Hospira concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic Acid Hospira is required, first withdraw the appropriate volume as indicated below and then dilute it further with 100 ml of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride solution for injection or 5% w/v glucose solution.

Do not mix Zoledronic Acid Hospira concentrate with calcium-containing or other divalent cation-containing solutions such as lactated Ringer's solution.

Instructions for preparing reduced doses of Zoledronic Acid Hospira:
Withdraw the appropriate volume of the liquid concentrate, as follows:
- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

- For single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used. Aseptic techniques must be followed during the preparation of the infusion.

- From a microbiological point of view, the diluted 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.

- The solution containing zoledronic acid is given as a single 15-minute intravenous infusion in a separate infusion line. The hydration status of patients must be assessed prior to and following administration of zoledronic acid to ensure that they are adequately hydrated.

- Studies with several types of infusion lines made from polyvinylchloride, polyethylene and polypropylene showed no incompatibility with zoledronic acid.

- Since no data are available on the compatibility of Zoledronic Acid Hospira with other intravenously administered substances, Zoledronic Acid Hospira must not be mixed with other medicinal products/substances and should always be given through a separate infusion line.

How to store Zoledronic Acid Hospira

- Keep Zoledronic Acid Hospira out of the reach and sight of children.
- Do not use Zoledronic Acid Hospira after the expiry date stated on the pack.
- The unopened vial does not require any specific storage conditions.
- The diluted Zoledronic Acid Hospira infusion solution should be used immediately in order to avoid microbial contamination.

Package leaflet: Information for the user

Zoledronic Acid Hospira 4 mg/100 ml solution for infusion
zoledronic acid

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Zoledronic Acid Hospira is and what it is used for

The active substance in Zoledronic Acid Hospira is zoledronic acid, which belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change. It is used:
- **To prevent bone complications,** e.g. fractures, in adult patients with bone metastases (spread of cancer from primary site to the bone).
- **To reduce the amount of calcium** in the blood in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

2 What you need to know before you are given Zoledronic Acid Hospira

Follow carefully all instructions given to you by your doctor.

Your doctor will carry out blood tests before you start treatment with Zoledronic Acid Hospira and will check your response to treatment at regular intervals.

You should not be given Zoledronic Acid Hospira:
- if you are breast-feeding.
- if you are allergic to zoledronic acid, another bisphosphonate (the group of substances to which zoledronic acid belongs), or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor before you are given Zoledronic Acid Hospira:
- if you have or have had a kidney problem.
- if you have or have had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth. Your doctor may recommend a dental examination before you start treatment with Zoledronic Acid Hospira.

- if you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic Acid Hospira and inform your doctor about your dental treatment.

While being treated with Zoledronic Acid Hospira, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups.

Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of a condition called osteonecrosis of the jaw.

Patients who are undergoing chemotherapy and/or radiotherapy, who are taking steroids, who are undergoing dental surgery, who do not receive routine dental care, who have gum disease, who are smokers, or who were previously treated with a bisphosphonate (used to treat or prevent bone disorders) may have a higher risk of developing osteonecrosis of the jaw.

Reduced levels of calcium in the blood (hypocalcaemia), sometimes leading to muscle cramps, dry skin, burning sensation, have been reported in patients treated with zoledronic acid. Irregular heart beat (cardiac arrhythmia), seizures, spasm and twitching (tetany) have been reported as secondary to severe hypocalcaemia. In some instances the hypocalcaemia may be life-threatening. If any of these apply to you, tell your doctor straight away. If you have pre-existing hypocalcaemia, it must be corrected before initiating the first dose of Zoledronic acid. You will be given adequate calcium and vitamin D supplements.

Patients aged 65 years and over
Zoledronic Acid Hospira can be given to people aged 65 years and over. There is no evidence to suggest that any extra precautions are needed.

Children and adolescents
Zoledronic Acid Hospira is not recommended for use in adolescents and children below the age of 18 years.

Other medicines and Zoledronic Acid Hospira
Tell your doctor if you are taking, have recently taken or might take any other medicines, It is especially important that you tell your doctor if you are also taking:
- Aminoglycosides (medicines used to treat severe infections), calcitonin (a type of medicine used to treat post-menopausal osteoporosis and hypercalcaemia), loop diuretics (a type of medicine to treat high blood pressure or oedema) or other calcium-lowering medicines, since the combination of these with bisphosphonates may cause the calcium level in the blood to become too low.
- Thalidomide (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.
- Any other medicines that also contains zoledronic acid and is used to treat osteoporosis and other non-cancer diseases of the bone, or any other bisphosphonate, since the combined effects of these medicines taken together with Zoledronic Acid Hospira are unknown.
- Anti-angiogenic medicines (used to treat cancer), since the combination of these with Zoledronic Acid Hospira has been associated with an increased risk of osteonecrosis of the jaw (ONJ).

Pregnancy and breast-feeding
You should not be given Zoledronic Acid Hospira if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You must not be given Zoledronic Acid Hospira if you are breast-feeding.

Ask your doctor for advice before taking any medicine while you are pregnant or breast-feeding.

Driving and using machines
There have been very rare cases of drowsiness and sleepiness with the use of Zoledronic Acid Hospira. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

Zoledronic Acid Hospira contains sodium

This medicine contains 360 mg sodium (main component of cooking/table salt) in each dosage unit. This is equivalent to 18% of the recommended maximum daily dietary intake of sodium for an adult.

3 How Zoledronic Acid Hospira is used

- Zoledronic Acid Hospira must only be given by healthcare professionals trained in administering bisphosphonates intravenously, i.e. through a vein.
- Your doctor will recommend that you drink enough water before each treatment to help prevent dehydration.
- Carefully follow all the other instructions given to you by your doctor, pharmacist or nurse.

How much Zoledronic Acid Hospira is given
- The usual single dose given is 4 mg.
- If you have a kidney problem, your doctor will give you a lower dose depending on the severity of your kidney problem.

How often Zoledronic Acid Hospira is given
- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledronic Acid Hospira every three to four weeks.
- If you are being treated to reduce the amount of calcium in your blood, you will normally only be given one infusion of Zoledronic Acid Hospira.

How Zoledronic Acid Hospira is given
- Zoledronic Acid Hospira is given as a drip (infusion) into a vein which should take at least 15 minutes and should be administered as a single intravenous solution in a separate infusion line.

Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day.

If you are given more Zoledronic Acid Hospira than you should be
If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. abnormal levels of calcium, phosphorus and magnesium) and/or changes in kidney function, including severe kidney impairment. If your level of calcium falls too low, you may have to be given supplemental calcium by infusion.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The most common ones are usually mild and will probably disappear after a short time.

Tell your doctor about any of the following serious side effects straight away:

Common (may affect up to 1 in 10 people):
- Severe kidney impairment (will normally be determined by your doctor with certain specific blood tests).
- Low level of calcium in the blood.

Uncommon (may affect up to 1 in 100 people):
- Pain in the mouth, teeth and/or jaw, swelling or non-healing sores inside the mouth or jaw discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms while being treated with Zoledronic Acid Hospira or after stopping treatment.
- Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for postmenopausal osteoporosis. It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received zoledronic acid.
- Severe allergic reaction: shortness of breath, swelling mainly of the face and throat.

Rare (may affect up to 1 in 1,000 people):
- As a consequence of low calcium values: irregular heart beat (cardiac arrhythmia; secondary to hypocalcaemia).
- A kidney function disorder called Fanconi syndrome (will normally be determined by your doctor with certain urine tests).

Very rare (may affect up to 1 in 10,000 people):
- As a consequence of low calcium values: seizures, numbness and tetany (secondary to hypocalcaemia).
- Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.
- Osteonecrosis has also very rarely been seen occurring with other bones than the jaw, especially the hip or thigh. Tell your doctor immediately if you experience symptoms such as new onset or worsening of aches, pain or stiffness while being treated with Zoledronic Acid Hospira or after stopping treatment.

Tell your doctor about any of the following side effects as soon as possible:

Very common (may affect more than 1 in 10 people):
- Low level of phosphate in the blood.

Common (may affect up to 1 in 10 people):
- Headache and a flu-like syndrome consisting of fever, fatigue, weakness, drowsiness, chills and bone, joint and/or muscle ache. In most cases no specific treatment is required and the symptoms disappear after a short time (couple of hours or days).
- Gastrointestinal reactions such as nausea and vomiting as well as loss of appetite.
- Conjunctivitis.
- Low level of red blood cells (anaemia).

Uncommon (may affect up to 1 in 100 people):
- Hypersensitivity reactions.
- Low blood pressure.
- Chest pain.
- Skin reactions (redness and swelling) at the infusion site, rash, itching.
- High blood pressure, shortness of breath, dizziness, anxiety, sleep disturbances, taste disturbances, trembling, tingling or numbness of the hands or feet, diarrhoea, constipation, abdominal pain, dry mouth.
- Low counts of white blood cells and blood platelets.
- Low level of magnesium and potassium in the blood. Your doctor will monitor this and take any necessary measures.
  Weight increase.
  Increased sweating.
- Sleepiness.
- Blurred vision, tearing of the eye, eye sensitivity to light.

- Sudden coldness with fainting, limpness or collapse.
- Difficulty in breathing with wheezing or coughing.
- Urticaria.

Rare (may affect up to 1 in 1,000 people):
- Slow heart beat.
- Confusion.
- Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.
- Interstitial lung disease (inflammation of the tissue around the air sacks of the lungs)
- Flu-like symptoms including arthritis and joint swelling.
- Painful redness and/or swelling of the eye.

Very rare (may affect up to 1 in 10,000 people):
- Fainting due to low blood pressure.
- Severe bone, joint and/or muscle pain, occasionally incapacitating.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Zoledronic Acid Hospira

Your doctor, pharmacist or nurse knows how to store Zoledronic Acid Hospira properly (see section 6).

6 Contents of the pack and other information

What Zoledronic Acid Hospira contains
- The active substance of Zoledronic Acid Hospira 4 mg/100 ml solution for infusion is zoledronic acid. Each bag with 100 ml of solution contains 4 mg zoledronic acid (as monohydrate).
  One ml solution contains 0.04 mg zoledronic acid (as monohydrate).
- The other ingredients are mannitol, sodium citrate, sodium chloride and water for injections. (see section 2, Zoledronic Acid Hospira 4mg/100ml solution for infusion contains sodium).

What Zoledronic Acid Hospira looks like and contents of the pack
Zoledronic Acid Hospira is a clear and colourless solution. It comes in 100 ml plastic bags as a ready-to-use solution for infusion. Each pack contains one bag which contains 4 mg of zoledronic acid.

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This leaflet was last revised in

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

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

How to prepare and administer Zoledronic Acid Hospira

- Zoledronic Acid Hospira 4 mg/100 ml solution for infusion contains 4 mg zoledronic acid in 100 ml of infusion solution for immediate use in patients with normal renal function.

- For single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used. Aseptic techniques must be followed during the preparation of the infusion.

- From a microbiological point of view, the product 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.

- The solution containing zoledronic acid must not be further diluted or mixed with other infusion solutions. It is given as a single 15-minute intravenous infusion in a separate infusion line. The hydration status of patients must be assessed prior to and following administration of zoledronic acid to assure that they are adequately hydrated.

- Zoledronic Acid Hospira 4 mg/100 ml solution for infusion can be used immediately without further preparation for patients with normal renal function. In patients with mild to moderate renal impairment, reduced doses should be prepared as instructed below.

To prepare reduced doses for patients with baseline CLcr ≤ 60 ml/min, refer to Table 1 below. Remove the volume of Zoledronic Acid Hospira solution indicated from the bag prior to administration.

Table 1: Preparation of reduced doses of Zoledronic Acid Hospira 4 mg/100 ml solution for infusion

Baseline creatinine clearance (ml/min)	**Remove the following amount of Zoledronic Acid Hospira 4 mg/100 ml solution for infusion (ml)**	**Adjusted dose (mg zoledronic acid) ***
50-60	12.0	3.5
40-49	18.0	3.3
30-39	25.0	3.0

***** 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.

- Studies with several types of infusion lines made from polyvinylchloride, polyethylene and polypropylene showed no incompatibility with zoledronic acid.

- Since no data are available on the compatibility of Zoledronic Acid Hospira with other intravenously administered substances, Zoledronic Acid Hospira must not be mixed with other medicinal products/substances and should always be given through a separate infusion line.

How to store Zoledronic Acid Hospira

- Keep Zoledronic Acid Hospira out of the reach and sight of children.
- Do not use Zoledronic Acid Hospira after the expiry date stated on the pack.
- The bag does not require any specific storage conditions.

- After opening the bag, the product should be used immediately in order to avoid microbial contamination.

Package leaflet: Information for the user

Zoledronic Acid Hospira 5 mg/100 ml solution for infusion
zoledronic acid

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1 What Zoledronic Acid Hospira is and what it is used for

Zoledronic Acid Hospira contains the active substance zoledronic acid. It belongs to a group of medicines called bisphosphonates and is used to treat Paget's disease of the bone in adults.

It is normal that old bone is removed and is replaced with new bone material. This process is called remodelling. In Paget's disease, bone remodelling is too rapid and new bone is formed in a disordered fashion, which makes it weaker than normal. If the disease is not treated, bones may become deformed and painful, and may break. Zoledronic Acid Hospira works by returning the bone remodelling process to normal, securing formation of normal bone, thus restoring strength to the bone.

2 What you need to know before you are given Zoledronic Acid Hospira

Follow all instructions given to you by your doctor, pharmacist or nurse carefully before you are given Zoledronic Acid Hospira.

You must not be given Zoledronic Acid Hospira:
- if you are allergic to zoledronic acid, other bisphosphonates or any of the other ingredients of this medicine (listed in section 6).
- if you have hypocalcaemia (this means that the levels of calcium in your blood are too low).
- if you have severe kidney problems.
- if you are pregnant.
- if you are breast-feeding.

Warnings and precautions

Talk to your doctor before you are given Zoledronic Acid Hospira:
- if you are being treated with any medicine containing zoledronic acid, which is also the active substance of Zoledronic Acid Hospira (zoledronic acid is used in adult patients with certain types of cancer to prevent bone complications or to reduce the amount of calcium).
- if you have a kidney problem, or used to have one.
- if you are unable to take daily calcium supplements.

- if you have had some or all of the parathyroid glands in your neck surgically removed.
- if you have had sections of your intestine removed.

A side effect called osteonecrosis of the jaw (ONJ) (bone damage in the jaw) has been reported in the post-marketing setting in patients receiving zoledronic acid for osteoporosis. ONJ can also occur after stopping treatment.

It is important to try and prevent ONJ developing as it is a painful condition that can be difficult to treat. In order to reduce the risk of developing osteonecrosis of the jaw, there are some precautions you should take.

Before receiving Zoledronic Acid Hospira treatment, tell your doctor, pharmacist or nurse if

- you have any problems with your mouth or teeth such as poor dental health, gum disease, or a planned tooth extraction;
- you do not receive routine dental care or have not had a dental check-up for a long time;
- you are a smoker (as this may increase the risk of dental problems);
- you have previously been treated with a bisphosphonate (used to treat or prevent bone disorders);
- you are taking medicines called corticosteroids (such as prednisolone or dexamethasone)
- you have cancer.

Your doctor may ask you to undergo a dental examination before you start treatment with Zoledronic Acid Hospira.

While being treated with Zoledronic Acid Hospira, you should maintain good oral hygiene (including regular teeth brushing) and receive routine dental check-ups. If you wear dentures you should make sure these fit properly. If you are under dental treatment or are due to undergo dental surgery (e.g. tooth extractions), inform your doctor about your dental treatment and tell your dentist that you are being treated with Zoledronic Acid Hospira. Contact your doctor and dentist immediately if you experience any problems with your mouth or teeth such as loose teeth, pain or swelling, or non-healing of sores or discharge, as these could be signs of osteonecrosis of the jaw.

Monitoring test

Your doctor should do a blood test to check your kidney function (levels of creatinine) before each dose of Zoledronic Acid Hospira. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Zoledronic Acid Hospira, as directed by your healthcare provider.

Children and adolescents

Zoledronic Acid Hospira is not recommended for anyone under 18 years of age.

Other medicines and Zoledronic Acid Hospira

Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

It is important for your doctor to know all the medicines you are taking, especially if you are taking any medicines known to be harmful to your kidneys (e.g. aminoglycosides) or diuretics (“waterpills”) that may cause dehydration.

Pregnancy and breast-feeding

You must not be given Zoledronic Acid Hospira if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby.

Ask your doctor, pharmacist or nurse for advice before taking this medicine.

Driving and using machines

If you feel dizzy while taking Zoledronic Acid Hospira, do not drive or use machines until you feel better.

Zoledronic Acid Hospira contains sodium

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially "sodium-free".

3 How Zoledronic Acid Hospira is given

Follow carefully all instructions given to you by your doctor or nurse. Check with your doctor or nurse if you are not sure.

For the treatment of Paget's disease, Zoledronic Acid Hospira should be prescribed only by physicians with experience in the treatment of Paget's disease of the bone.

The usual dose is 5 mg, given to you as one initial infusion into a vein by your doctor or nurse. The infusion will take at least 15 minutes. Zoledronic Acid Hospira may work for longer than one year, and your doctor will let you know if you need to be treated again.

Your doctor may advise you to take calcium and vitamin D supplements (e.g. tablets) for at least the first ten days after being given Zoledronic Acid Hospira. It is important that you follow this advice carefully so that the level of calcium in your blood does not become too low in the period after the infusion. Your doctor will inform you regarding the symptoms associated with hypocalcaemia.

Zoledronic Acid Hospira with food and drink

Make sure you drink enough fluids (at least one or two glasses) before and after the treatment with Zoledronic Acid Hospira, as directed by your doctor. This will help to prevent dehydration. You may eat normally on the day you are treated with Zoledronic Acid Hospira. This is especially important in patients who take diuretics ("water pills") and in elderly patients (age 65 years or over).

If you missed a dose of Zoledronic Acid Hospira

Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Before stopping Zoledronic Acid Hospira therapy

If you are considering stopping Zoledronic Acid Hospira treatment, please go to your next appointment and discuss this with your doctor. Your doctor will advise you and decide how long you should be treated with Zoledronic Acid Hospira.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4 Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects related to the first infusion are very common (occurring in more than 30% of patients) but are less common following subsequent infusions. The majority of the side effects, such as fever and

chills, pain in the muscles or joints, and headache, occur within the first three days following the dose of Zoledronic Acid Hospira. The symptoms are usually mild to moderate and go away within three days. Your doctor can recommend a mild pain reliever such as ibuprofen or paracetamol to reduce these side effects. The chance of experiencing these side effects decreases with subsequent doses of Zoledronic Acid Hospira.

Some side effects could be serious

Common (may affect up to 1 in 10 people)

Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for the treatment of postmenopausal osteoporosis. It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received Zoledronic Acid Hospira.

Uncommon (may affect up to 1 in 100 people)

Swelling, redness, pain and itching to the eyes or eye sensitivity to light.

Very rare (may affect up to 1 in 10,000 people)

Talk to your doctor if you have ear pain, discharge from the ear, and/or an ear infection. These could be signs of bone damage in the ear.

Not known (frequency cannot be estimated from the available data)

Pain in the mouth and/or jaw, swelling or non-healing sores in the mouth or jaw, discharge, numbness or a feeling of heaviness in the jaw, or loosening of a tooth; these could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms while being treated with Zoledronic Acid Hospira or after stopping treatment.

Kidney disorders (e.g. decreased urine output) may occur. Your doctor should do a blood test to check your kidney function before each dose of Zoledronic Acid Hospira. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Zoledronic Acid Hospira, as directed by your healthcare provider.

If you experience any of the above side effects, you should contact your doctor immediately.

Zoledronic Acid Hospira may also cause other side effects

Very common (may affect more than 1 in 10 people)

Fever

Common (may affect up to 1 in 10 people)

Headache, dizziness, sickness, vomiting, diarrhoea, pain in the muscles, pain in the bones and/or joints, pain in the back, arms or legs, flu-like symptoms (e.g. tiredness, chills, joint and muscle pain), chills, feeling of tiredness and lack of interest, weakness, pain, feeling unwell, swelling and/or pain at the infusion site.

In patients with Paget's disease, symptoms due to low blood calcium, such as muscle spasms, or numbness, or a tingling sensation especially in the area around the mouth have been reported.

Uncommon (may affect up to 1 in 100 people)

Flu, upper respiratory tract infections, decreased red cell count, loss of appetite, sleeplessness, sleepiness which may include reduced alertness and awareness, tingling sensation or numbness, extreme tiredness, trembling, temporary loss of consciousness, eye infection or irritation or inflammation with pain and redness, spinning sensation, increased blood pressure, flushing, cough, shortness of breath, upset stomach, abdominal pain, constipation, dry mouth, heartburn, skin rash, excessive sweating, itching, skin reddening, neck pain, stiffness in muscles, bones and/or joints, joint swelling, muscle spasms, shoulder pain, pain in your chest muscles and rib cage, joint inflammation, muscular weakness, abnormal kidney test results, abnormal frequent urination, swelling of hands, ankles or feet, thirst, toothache, taste disturbances.

Rare (may affect up to 1 in 1,000 people)

Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone. Low levels of phosphate in the blood.

Not known (frequency cannot be estimated from the available data)
Severe allergic reactions including dizziness and difficulty breathing, swelling mainly of the face and throat, decreased blood pressure, dehydration secondary to acute phase reactions (post-dose symptoms such as fever, vomiting and diarrhoea).

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5 How to store Zoledronic Acid Hospira

Your doctor, pharmacist or nurse knows how to store Zoledronic Acid Hospira properly.

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and bag after EXP.
- The unopened bag does not require any special storage conditions.
- After opening the bag, the product should be used immediately in order to avoid microbial contamination. 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. Allow the refrigerated solution to reach room temperature before administration.

6 Contents of the pack and other information

What Zoledronic Acid Hospira 5 mg/100 ml solution for infusion contains

- The active substance is zoledronic acid. Each bag with 100 ml of solution contains 5 mg zoledronic acid anhydrous (as monohydrate).
  One ml solution contains 0.05 mg zoledronic acid (as monohydrate).
- The other ingredients are mannitol, sodium citrate and water for injections.

What Zoledronic Acid Hospira looks like and contents of the pack

Zoledronic Acid Hospira is a clear and colourless solution. It comes in 100 ml plastic bags as a ready-to-use solution for infusion. Each pack contains one bag.

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

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

How to prepare and administer Zoledronic Acid Hospira

- Zoledronic Acid Hospira is ready for use.

For single use only. Any unused solution should be discarded. Only clear solution free from particles and discoloration should be used. Zoledronic Acid Hospira must not be mixed or given intravenously with any other medicinal product and must be given through a separate vented infusion line at a constant infusion rate. The infusion time must not be less than 15 minutes. Zoledronic Acid Hospira must not be allowed to come into contact with any calcium-containing solutions. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during preparation of the infusion. The infusion must be conducted according to standard medical practice.

How to store Zoledronic Acid Hospira

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the carton and bag after EXP.
- The unopened bag does not require any special storage conditions.
- After opening the bag, the product should be used immediately in order to avoid microbial contamination. 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 2ºC – 8ºC. Allow the refrigerated solution to reach room temperature before administration.