ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Actavis 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 concentrate for solution for infusion.

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

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

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

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

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

Renal impairment
TIH:
Zoledronic acid Actavis 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 micromol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 micromol/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 Actavis 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 Actavis 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 micromol/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 Actavis dose is recommended (see also section 4.4):

Baseline Creatinine Clearance (ml/min)	**Zoledronic acid Actavis 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 Actavis 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 micromol/l), an increase of 0.5 mg/dl or 44 micromol/l;
- For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 micromol/l), an increase of 1.0 mg/dl or 88 micromol/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 Actavis 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 Actavis 4 mg/5 ml 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 Actavis
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 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 or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zoledronic acid Actavis 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 Actavis.

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 Actavis 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 Actavis 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 substances are available for osteoporosis indications and treatment of Paget´s disease of the bone. Patients being treated with Zoledronic acid Actavis 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 Actavis 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, used as indicated in sections 4.1 and 4.2, 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 Actavis. 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 Actavis should be withheld. Zoledronic acid Actavis should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid Actavis treatment should be resumed at the same dose as that given prior to treatment interruption.

In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 micromol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 micromol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of Zoledronic acid Actavis 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 Actavis. 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.

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients that were given zoledronic acid as indicated in sections 4.1 and 4.2. 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.

Excipient(s)
Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, zoledronic acid, used as indicated in sections 4.1 and 4.2, 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 Actavis 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 Actavis is used in combination with thalidomide.

Caution is advised when Zoledronic acid Actavis 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 Actavis 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 Actavis 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 Actavis along with driving and operating of machinery.

4.8 Undesirable effects

Summary of the safety profile
Within three days after zoledronic acid administration, used as indicated in sections 4.1 and 4.2, 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
	Rare:	inflammation
		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, used as indicated in sections 4.1 and 4.2, has been associated with reports of renal dysfunction. In a pooled analysis of safety data from zoledronic acid registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to zoledronic acid (adverse reactions) was as follows: multiple myeloma (3.2%), prostate cancer (3.1%), breast cancer (4.3%), lung and other solid tumours (3.2%). Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).

Osteonecrosis of the jaw

Cases of osteonecrosis 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 (used as indicated in sections 4.1 and 4.2), and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

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

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with 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: Drugs for treatment of bone diseases, bisphosphonates, ATC code: M05BA08

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

The selective action of bisphosphonates on bone is based on their high affinity for mineralised bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity is still unclear. In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:
- *In vivo:* Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment, making it less conducive to tumour cell growth, anti-angiogenic activity and anti-pain activity.
- *In vitro:* Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

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

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

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
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, 4 mg zoledronic acid 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 4 mg zoledronic acid 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 4 mg zoledronic acid 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	

	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
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

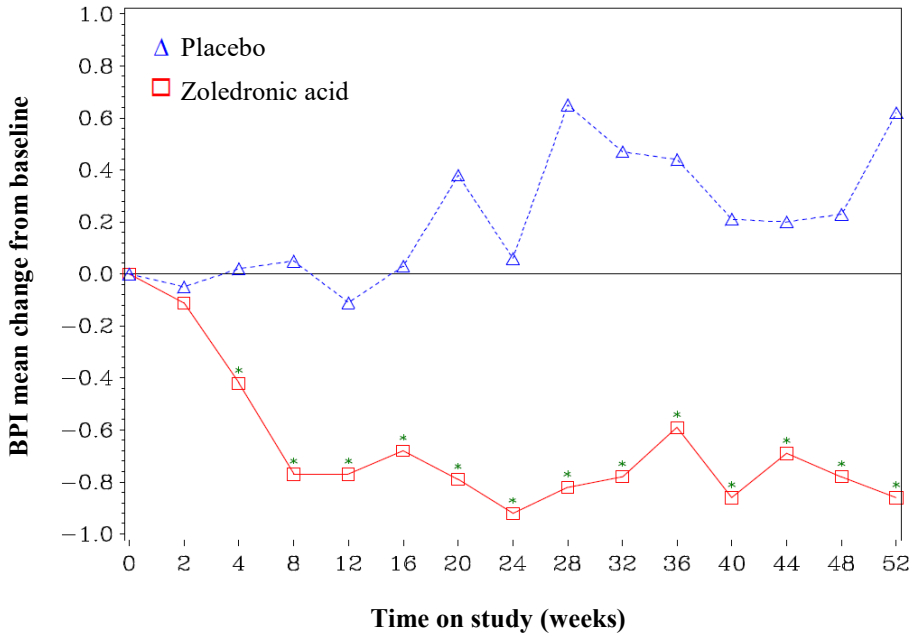
NA Not Applicable

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 as indicated in sections 4.1 and 4.2 (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 ≥ 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 Actavis 4 mg/5 ml concentrate for solution for infusion is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

This medicinal product must not be mixed with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution, and should be administered as a single intravenous solution in a separate infusion line.

6.3 Shelf life

3 years.

After dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C and at 25°C after dilution in 100 ml 0.9% w/v sodium chloride solution or 100 ml 5% w/v glucose.

From a microbiological point of view, the solution for infusion should be used immediately after dilution. 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.
If refrigerated, the solution must be allowed to reach room temperature before administration.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of Zoledronic acid Actavis after dilution, see section 6.3.

6.5 Nature and contents of container

5 ml concentrate in a plastic vial made of clear, colourless oleofinic polymer closed with fluoropolymer-coated bromobutyl rubber stopper and aluminium cap with plastic flip-off component.

Pack sizes: 1, 4 or 10 vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Prior to administration, 5 ml concentrate from one vial or the volume of the concentrate withdrawn as required must be further diluted with 100 ml of calcium-free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution).

Additional information on handling of Zoledronic acid Actavis, 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 Actavis 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

Actavis Group PTC ehf.
Reykjavíkurvegur 76-78
220 Hafnarfjörður
Iceland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/759/001
EU/1/12/759/002
EU/1/12/759/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 April 2012
Date of latest renewal: 09 Desember 2016

10. DATE OF REVISION OF THE TEXT

MM/YYYY

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

Actavis Italy S.p.A
Via Pasteur, 10
20014 Nerviano (MI)
Italy

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 marketing authorisation holder shall submit PSURs for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and 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.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

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

CARTONS FOR VIALS

1. NAME OF THE MEDICINAL PRODUCT

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

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

3. LIST OF EXCIPIENTS

Contains mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion

1 x 5 ml vial
4 x 5 ml vials
10 x 5 ml vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.
Intravenous use after dilution.

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

Shelf life after dilution: See leaflet.

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

Actavis Group PTC ehf.
220 Hafnarfjörður
Iceland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/759/001 1vial
EU/1/12/759/002 4 vials
EU/1/12/759/003 10 vials

13. BATCH NUMBER

Lot

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.>

<Not applicable.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

< PC {number}
SN {number}
NN {number} >

<Not applicable.>

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

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

Zoledronic acid Actavis 4 mg/5 ml sterile concentrate
zoledronic acid
IV

2. METHOD OF ADMINISTRATION

Dilute before use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

4 mg/5 ml

6. OTHER

[Actavis logo]

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zoledronic acid Actavis 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 Actavis is and what it is used for

The active substance in Zoledronic acid Actavis 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 Actavis

Follow carefully all instructions given to you by your doctor.

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

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

Warnings and precautions
Talk to your doctor before you are given Zoledronic acid Actavis:
- 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 Actavis.
- if you are having **dental treatment** or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic acid Actavis and inform your doctor about your dental treatment.

While being treated with Zoledronic acid Actavis, 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 Actavis. You will be given adequate calcium and vitamin D supplements.

Patients aged 65 years and over
Zoledronic acid Actavis 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 Actavis is not recommended for use in adolescents and children below the age of 18 years.

Other medicines and Zoledronic acid Actavis
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.
- Other medicines that contain zoledronic acid which are 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 Actavis are unknown.
- Anti-angiogenic medicines (used to treat cancer), since the combination of these with zoledronic acid has been associated with an increased risk of osteonecrosis of the jaw (ONJ).

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

You must not be given Zoledronic acid Actavis 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. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

Zoledronic acid Actavis contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How Zoledronic acid Actavis is used

- Zoledronic acid Actavis 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 Actavis 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 Actavis 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 Actavis 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 Actavis.

How Zoledronic acid Actavis is given
- Zoledronic acid Actavis 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 Actavis 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 Actavis 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 Actavis 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 Actavis

Your doctor, pharmacist or nurse knows how to store Zoledronic acid Actavis properly.

6. Contents of the pack and other information

What Zoledronic acid Actavis contains
- The active substance is zoledronic acid. One vial contains 4 mg zoledronic acid (as monohydrate).
- The other ingredients are: mannitol, sodium citrate and water for injections.

What Zoledronic acid Actavis looks like and contents of the pack
Zoledronic acid Actavis is supplied as a clear and colourless concentrate for solution for infusion (sterile concentrate) in a plastic vial. One vial contains 5 ml of solution.
Zoledronic acid Actavis is supplied as packs containing 1, 4 or 10 vials. Not all pack sizes may be marketed.

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Manufacturer
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This leaflet was last revised in {month YYYY}.

Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

How to prepare and administer Zoledronic acid Actavis

- To prepare an infusion solution containing 4 mg Zoledronic acid Actavis, further dilute the Zoledronic acid Actavis concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic acid Actavis 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 or 5% w/v glucose solution.

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

  Instructions for preparing reduced doses of Zoledronic acid Actavis:
  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.

- Shelf life after dilution: Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C - 8°C and at 25°C after dilution in 100 ml 0.9% w/v sodium chloride solution or 100 ml 5% w/v glucose. From a microbiological point of view, the solution for infusion should be used immediately after dilution. 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. If refrigerated, the solution must be allowed to reach room temperature before 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 Actavis to ensure that they are adequately hydrated.

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

How to store Zoledronic acid Actavis

- Keep Zoledronic acid Actavis out of the sight and reach of children.
- Do not use Zoledronic acid Actavis after the expiry date stated on the vial and carton after EXP.
- This medicinal product does not require any specific storage conditions.
- For storage conditions of Zoledronic acid Actavis after dilution, see “Shelf life after dilution” above.