ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion in bottles

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle contains 5 mg zoledronic acid (as monohydrate).

Each ml of the solution contains 0.05 mg zoledronic acid (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 osteoporosis
- in post-menopausal women
- in adult men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
- in post-menopausal women
- in adult men

at increased risk of fracture.

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. This is especially important for the elderly and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration.

Osteoporosis
For the treatment of post-menopausal osteoporosis, osteoporosis in men and the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5 mg zoledronic acid administered once a year.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of zoledronic acid on an individual patient basis, particularly after 5 or more years of use.

In patients with a recent low-trauma hip fracture, it is recommended to give the zoledronic acid infusion at least two weeks after hip fracture repair (see section 5.1). In patients with a recent low-trauma hip fracture, a

loading dose of 50 000 to 125 000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first zoledronic acid infusion.

Paget's disease
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 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).

Older people (≥ 65 years)
No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Paediatric population
The safety and efficacy of zoledronic acid in children and adolescents below 18 years of age have not been established. No data are available.

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

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 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 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)

Osteonecrosis of the jaw has been reported in patients treated with zoledronic acid. Many of the reported cases have been associated with dental procedures such as tooth extraction. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, anti-angiogenic medicinal products, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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.

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

The incidence of post-dose symptoms occuring within the first three days after administration of Zoledronic acid Teva Generics can be reduced with the administration of paracetamol or ibuprofen shortly following Zoledronic acid Teva Generics administration

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml, i.e. 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 drugs 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

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

Women of childbearing potential
Zoledronic acid is not recommended in women of childbearing potential.

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

Zoledronic acid Teva Generics has no or negligible influence on the ability to drive and use machines. Adverse reactions, such as dizziness, may affect the ability to drive or use machines, though no studies on this effect with zoledronic acid have been performed.

4.8 Undesirable effects

Summary of the safety profile

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: fever (17.1%), myalgia (7.8%), flu-like symptoms (6.7%), arthralgia (4.8%) and headache (5.1%). The incidence of these reactions decreased markedly with subsequent annual doses of zoledronic acid. The majority of these reactions occur within the first three days following zoledronic acid administration. The majority of these reactions were mild to moderate and resolved within three days of the event onset. 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.

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.

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 bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common*	Hypocalcaemia*
	Uncommon	Anorexia, decreased appetite
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 orbital inflammation
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, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhydrosis, 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, shoulder pain, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	Rare	Atypical subtrochanteric and diaphyseal femoral fractures† (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*	Fever
	Common	Flu-like symptoms, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	Uncommon	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	*Not known***	Dehydration secondary to post-dose symptoms such as fever, 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
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
Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported, predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic medicinal products, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). It is prudent to avoid dental surgery as recovery may be prolonged (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. Both cases resolved.

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).

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: Drugs 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 post-menopausal osteoporosis (PFT)
The efficacy and safety of zoledronic acid 5 mg once a year for 3 consecutive years were demonstrated in post-menopausal women (7,736 women aged 65-89 years) with either: a femoral neck bone mineral density (BMD) with a T-score ≤ –1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score ≤ –2.5 with or without evidence of existing vertebral fracture(s). 85% of patients were bisphosphonate-naïve. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1,000 to 1,500 mg elemental calcium and 400 to 1,200 IU of vitamin D supplements daily.

Effect on morphometric vertebral fractures
Zoledronic acid significantly decreased the incidence of one or more new vertebral fractures over three years and as early as the one year timepoint (see Table 2).

Table 2 Summary of vertebral fracture efficacy at 12, 24 and 36 months

Outcome	Zoledronic acid (%)	Placebo (%)	Absolute reduction in fracture incidence % (CI)	Relative reduction in fracture incidence % (CI)
At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)**
At least one new vertebral fracture (0–2 year)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)**
At least one new vertebral fracture (0–3 year)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)**
** p <0.0001				

Zoledronic acid-treated patients aged 75 years and older exhibited a 60% reduction in the risk of vertebral fractures compared to placebo patients (p<0.0001).

Effect on hip fractures
Zoledronic acid demonstrated a consistent effect over 3 years, resulting in a 41% reduction in the risk of hip fractures (95% CI, 17% to 58%). The hip fracture event rate was 1.44% for zoledronic acid-treated patients compared to 2.49% for placebo-treated patients. The risk reduction was 51% in bisphosphonate-naïve patients and 42% in patients allowed to take concomitant osteoporosis therapy.

Effect on all clinical fractures
All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 3.

Table 3 Between treatment comparisons of the incidence of key clinical fracture variables over 3 years

Outcome	Zoledronic acid (N=3,875) event rate (%)	Placebo (N=3,861) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.4	12.8	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture (2)	0.5	2.6	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture (1)	8.0	10.7	2.7 (1.4, 4.0)	25 (13, 36)*
*p-value <0.001, **p-value <0.0001 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

Effect on bone mineral density (BMD)
Zoledronic acid significantly increased BMD at the lumbar spine, hip, and distal radius relative to treatment with placebo at all timepoints (6, 12, 24 and 36 months). Treatment with zoledronic acid resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, 5.1% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone histology
Bone biopsies were obtained from the iliac crest 1 year after the third annual dose in 152 post-menopausal patients with osteoporosis treated with zoledronic acid (N=82) or placebo (N=70). Histomorphometric analysis showed a 63% reduction in bone turnover. In patients treated with zoledronic acid, no osteomalacia, marrow fibrosis or woven bone formation was detected. Tetracycline label was detectable in all but one of 82 biopsies obtained from patients on zoledronic acid. Microcomputed tomography (μCT) analysis demonstrated increased trabecular bone volume and preservation of trabecular bone architecture in patients treated with zoledronic acid compared to placebo.

Bone turnover markers
Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (b-CTx) were evaluated in subsets ranging from 517 to 1,246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of zoledronic acid significantly reduced BSAP by 30% relative to baseline at 12 months which was sustained at 28% below baseline levels at 36 months. P1NP was significantly reduced by 61% below baseline levels at 12 months and was sustained at 52% below baseline levels at 36 months. B-CTx was significantly reduced by 61% below baseline levels at 12 months and was sustained at 55% below baseline levels at 36 months. During this entire time period bone turnover markers were within the pre-menopausal range at the end of each year. Repeat dosing did not lead to further reduction of bone turnover markers.

Effect on height
In the three-year osteoporosis study standing height was measured annually using a stadiometer. The zoledronic acid group revealed approximately 2.5 mm less height loss compared to placebo (95% CI: 1.6 mm, 3.5 mm) [p<0.0001].

Days of disability
Zoledronic acid significantly reduced the mean days of limited activity and the days of bed rest due to back pain by 17.9 days and 11.3 days respectively compared to placebo and significantly reduced the mean days of limited activity and the days of bed rest due to fractures by 2.9 days and 0.5 days respectively compared to placebo (all p<0.01).

Clinical efficacy in the treatment of osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT)
The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2,127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study medication. Approximately 42% of patients had a femoral neck BMD T-score below -2.5 and approximately 45% of the patients had a femoral neck BMD T-score above -2.5. zoledronic acid was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or via the intramuscular route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1,000 to 1,500 mg of elemental calcium plus 800 to 1,200 IU of vitamin D supplementation per day. Ninety-five percent of the patients received their infusion two or more weeks after the hip fracture repair and the median timing of infusion was approximately six weeks after the hip fracture repair. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on all clinical fractures
The incidence rates of key clinical fracture variables are presented in Table 4.

Table 4 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Zoledronic acid (N = 1,065) event rate (%)	Placebo (N = 1,062) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.6	13.9	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture (2)	1.7	3.8	2.1 (0.5, 3.7)	46 (8, 68)*
Non-vertebral fracture (1)	7.6	10.7	3.1 (0.3, 5.9)	27 (2, 45)*
*p-value <0.05, **p-value <0.01 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

The study was not designed to measure significant differences in hip fracture, but a trend was seen towards reduction in new hip fractures.

All cause mortality was 10% (101 patients) in the zoledronic acid-treated group compared to 13% (141 patients) in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality (p=0.01).

The incidence of delayed hip fracture healing was comparable between zoledronic acid (34 [3.2%]) and placebo (29 [2.7%]).

Effect on bone mineral density (BMD)
In the HORIZON-RFT study zoledronic acid treatment significantly increased BMD at the total hip and femoral neck relative to treatment with placebo at all timepoints. Treatment with zoledronic acid resulted in an increase in BMD of 5.4% at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo.

Clinical efficacy in men
In the HORIZON-RFT study 508 men were randomised into the study and 185 patients had BMD assessed at 24 months. At 24 months a similar significant increase of 3.6% in total hip BMD was observed for patients treated with zoledronic acid as compared to the effects observed in post-menopausal women in the HORIZON-PFT study. The study was not powered to show a reduction in clinical fractures in men; the incidence of clinical fractures was 7.5% in men treated with zoledronic acid versus 8.7% for placebo.

In another study in men (study CZOL446M2308) an annual infusion of zoledronic acid was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline.

Clinical efficacy in osteoporosis associated with long-term systemic glucocorticoid therapy
The efficacy and safety of zoledronic acid in the treatment and prevention of osteoporosis associated with long-term systemic glucocorticoid therapy were assessed in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women aged 18-85 years (mean age for men 56.4 years; for women 53.5 years) treated with > 7.5 mg/day oral prednisone (or equivalent). Patients were stratified with respect to duration of glucocorticoid use prior to randomisation (≤ 3 months versus > 3 months). The duration of the trial was one year. Patients were randomised to either zoledronic acid 5 mg single infusion or to oral risedronate 5 mg daily for one year. All participants received 1,000 mg elemental calcium plus 400 to 1,000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively. The majority of patients continued to receive glucocorticoids for the one year duration of the trial.

Effect on bone mineral density (BMD)
The increases in BMD were significantly greater in the zoledronic acid-treated group at the lumbar spine and femoral neck at 12 months compared to risedronate (all p<0.03). In the subpopulation of patients receiving glucocorticoids for more than 3 months prior to randomisation, zoledronic acid increased lumbar spine BMD by 4.06% versus 2.71% for risedronate (mean difference: 1.36%; p<0.001). In the subpopulation of patients that had received glucocorticoids for 3 months or less prior to randomisation, zoledronic acid increased lumbar spine BMD by 2.60% versus 0.64% for risedronate (mean difference: 1.96%; p<0.001). The study was not powered to show a reduction in clinical fractures compared to risedronate. The incidence of fractures was 8 for zoledronic acid-treated patients versus 7 for risedronate-treated patients (p=0.8055).

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.

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, osteoporosis in post-menopausal women at an increased risk of fracture, osteoporosis in men at increased risk of fracture and prevention of clinical fractures after a hip fracture in men and women (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 drugs 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 drug 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 ≥ 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

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml vial, i.e. essentially "sodium free".

6.2 Incompatibilities

This medicinal product must not be allowed to come into contact with any calcium-containing solutions. The medicinal product must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

18 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C and 25ºC.

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 to 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

Cyclic Olefin Polymer (COP) plastic bottle, fitted with a chlorobutyl/butyl rubber stopper and aluminium cap fitted with violet plastic flip off disc.
Each bottle contains 100 ml of solution
Zoledronic acid Teva Generics is supplied in packs of 1, 5 or 10 bottles. The pack sizes of 5 and 10 bottles are only available in multipacks.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/001
EU/1/14/912/002
EU/1/14/912/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2014

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 Teva Generics 5 mg solution for infusion in bags

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Each ml of the solution contains 0.05 mg zoledronic acid (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 osteoporosis
- in post-menopausal women
- in adult men

at increased risk of fracture, including those with a recent low-trauma hip fracture.

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy
- in post-menopausal women
- in adult men

at increased risk of fracture.

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. This is especially important for the elderly and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration.

Osteoporosis
For the treatment of post-menopausal osteoporosis, osteoporosis in men and the treatment of osteoporosis associated with long-term systemic glucocorticoid therapy, the recommended dose is a single intravenous infusion of 5 mg zoledronic acid administered once a year.

The optimal duration of bisphosphonate treatment for osteoporosis has not been established. The need for continued treatment should be re-evaluated periodically based on the benefits and potential risks of zoledronic acid on an individual patient basis, particularly after 5 or more years of use.

In patients with a recent low-trauma hip fracture, it is recommended to give the zoledronic acid infusion at least two weeks after hip fracture repair (see section 5.1). In patients with a recent low-trauma hip fracture, a

loading dose of 50 000 to 125 000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first zoledronic acid infusion.

Paget's disease
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 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).

Older people (≥ 65 years)
No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Paediatric population
The safety and efficacy of zoledronic acid in children and adolescents below 18 years of age have not been established. No data are available.

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

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 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 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 Teva Generics 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 Teva Generics.
- A single dose of Zoledronic acid Teva Generics 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)

Osteonecrosis of the jaw has been reported in patients treated with zoledronic acid. Many of the reported cases have been associated with dental procedures such as tooth extraction. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, anti-angiogenic medicinal products, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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.

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

The incidence of post-dose symptoms occuring within the first three days after administration of zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following zoledronic acid administration.

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml; i.e. 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 drugs 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

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

Women of childbearing potential
Zoledronic acid is not recommended in women of childbearing potential.

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

Zoledronic acid Teva Generics has no or negligible influence on the abililty to drive and use machines. Adverse reactions, such as dizziness, may affect the ability to drive or use machines, though no studies on this effect with zoledronic acid have been performed.

4.8 Undesirable effects

Summary of the safety profile

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: fever (17.1%), myalgia (7.8%), flu-like symptoms (6.7%), arthralgia (4.8%) and headache (5.1%). The incidence of these reactions decreased markedly with subsequent annual doses of zoledronic acid. The majority of these reactions occur within the first three days following zoledronic acid administration. The majority of these reactions were mild to moderate and resolved within three days of the event onset. 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.

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.

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 bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	*Common*	Hypocalcaemia*
	Uncommon	Anorexia, decreased appetite
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 orbital inflammation
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, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	*Uncommon*	Rash, hyperhydrosis, 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, shoulder pain, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	Rare	Atypical subtrochanteric and diaphyseal fermoral fractures† (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*	Fever
	Common	Flu-like symptoms, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	Uncommon	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	*Not known***	Dehydration secondary to post-dose symptoms such as fever, 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

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

Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported, predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, anti-angiogenic medicinal products, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). It is prudent to avoid dental surgery as recovery may be prolonged (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. Both cases resolved.

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).

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: Drugs 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 post-menopausal osteoporosis (PFT)
The efficacy and safety of zoledronic acid 5 mg once a year for 3 consecutive years were demonstrated in post-menopausal women (7,736 women aged 65–89 years) with either: a femoral neck bone mineral density (BMD) with a T-score ≤ –1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score ≤ –2.5 with or without evidence of existing vertebral fracture(s). 85% of patients were bisphosphonate-naïve. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1,000 to 1,500 mg elemental calcium and 400 to 1,200 IU of vitamin D supplements daily.

Effect on morphometric vertebral fractures
Zoledronic acid significantly decreased the incidence of one or more new vertebral fractures over three years and as early as the one year timepoint (see Table 2).

Table 2 Summary of vertebral fracture efficacy at 12, 24 and 36 months

Outcome	Zoledronic acid (%)	Placebo (%)	Absolute reduction in fracture incidence % (CI)	Relative reduction in fracture incidence % (CI)

At least one new vertebral fracture (0–1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)**
At least one new vertebral fracture (0–2 year)	2.2	7.7	5.5 (4.4, 6.6)	71 (62, 78)**
At least one new vertebral fracture (0–3 year)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)**
** p <0.0001				

Zoledronic acid-treated patients aged 75 years and older exhibited a 60% reduction in the risk of vertebral fractures compared to placebo patients (p<0.0001).

Effect on hip fractures
Zoledronic acid demonstrated a consistent effect over 3 years, resulting in a 41% reduction in the risk of hip fractures (95% CI, 17% to 58%). The hip fracture event rate was 1.44% for zoledronic acid-treated patients compared to 2.49% for placebo-treated patients. The risk reduction was 51% in bisphosphonate-naïve patients and 42% in patients allowed to take concomitant osteoporosis therapy.

Effect on all clinical fractures
All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 3.

Table 3 Between treatment comparisons of the incidence of key clinical fracture variables over 3 years

Outcome	Zoledronic acid (N=3,875) event rate (%)	Placebo (N=3,861) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.4	12.8	4.4 (3.0, 5.8)	33 (23, 42)**
Clinical vertebral fracture (2)	0.5	2.6	2.1 (1.5, 2.7)	77 (63, 86)**
Non-vertebral fracture (1)	8.0	10.7	2.7 (1.4, 4.0)	25 (13, 36)*
*p-value <0.001, **p-value <0.0001 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

Effect on bone mineral density (BMD)
Zoledronic acid significantly increased BMD at the lumbar spine, hip, and distal radius relative to treatment with placebo at all timepoints (6, 12, 24 and 36 months). Treatment with zoledronic acid resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, 5.1% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone histology
Bone biopsies were obtained from the iliac crest 1 year after the third annual dose in 152 post-menopausal patients with osteoporosis treated with zoledronic acid (N=82) or placebo (N=70). Histomorphometric analysis showed a 63% reduction in bone turnover. In patients treated with zoledronic acid, no osteomalacia, marrow fibrosis or woven bone formation was detected. Tetracycline label was detectable in all but one of 82 biopsies obtained from patients on zoledronic acid. Microcomputed tomography (μCT) analysis demonstrated increased trabecular bone volume and preservation of trabecular bone architecture in patients treated with zoledronic acid compared to placebo.

Bone turnover markers
Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (b-CTx) were evaluated in subsets ranging from 517 to 1,246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of zoledronic acid significantly reduced BSAP by 30% relative to baseline at 12 months which was sustained at 28% below baseline levels at

36 months. P1NP was significantly reduced by 61% below baseline levels at 12 months and was sustained at 52% below baseline levels at 36 months. B-CTx was significantly reduced by 61% below baseline levels at 12 months and was sustained at 55% below baseline levels at 36 months. During this entire time period bone turnover markers were within the pre-menopausal range at the end of each year. Repeat dosing did not lead to further reduction of bone turnover markers.

Effect on height
In the three-year osteoporosis study standing height was measured annually using a stadiometer. The zoledronic acid group revealed approximately 2.5 mm less height loss compared to placebo (95% CI: 1.6 mm, 3.5 mm) [p<0.0001].

Days of disability
Zoledronic acid significantly reduced the mean days of limited activity and the days of bed rest due to back pain by 17.9 days and 11.3 days respectively compared to placebo and significantly reduced the mean days of limited activity and the days of bed rest due to fractures by 2.9 days and 0.5 days respectively compared to placebo (all p<0.01).

Clinical efficacy in the treatment of osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT)
The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2,127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study medication. Approximately 42% of patients had a femoral neck BMD T-score below -2.5 and approximately 45% of the patients had a femoral neck BMD T-score above -2.5. zoledronic acid was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or via the intramuscular route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1,000 to 1,500 mg of elemental calcium plus 800 to 1,200 IU of vitamin D supplementation per day. Ninety-five percent of the patients received their infusion two or more weeks after the hip fracture repair and the median timing of infusion was approximately six weeks after the hip fracture repair. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on all clinical fractures
The incidence rates of key clinical fracture variables are presented in Table 4.

Table 4 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Zoledronic acid (N = 1,065) event rate (%)	Placebo (N = 1,062) event rate (%)	Absolute reduction in fracture event rate % (CI)	Relative risk reduction in fracture incidence % (CI)
Any clinical fracture (1)	8.6	13.9	5.3 (2.3, 8.3)	35 (16, 50)**
Clinical vertebral fracture (2)	1.7	3.8	2.1 (0.5, 3.7)	46 (8, 68)*
Non-vertebral fracture (1)	7.6	10.7	3.1 (0.3, 5.9)	27 (2, 45)*
*p-value <0.05, **p-value <0.01 (1) Excluding finger, toe and facial fractures (2) Including clinical thoracic and clinical lumbar vertebral fractures				

The study was not designed to measure significant differences in hip fracture, but a trend was seen towards reduction in new hip fractures.

All cause mortality was 10% (101 patients) in the zoledronic acid-treated group compared to 13% (141 patients) in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality (p=0.01).

The incidence of delayed hip fracture healing was comparable between zoledronic acid (34 [3.2%]) and placebo (29 [2.7%]).

Effect on bone mineral density (BMD)
In the HORIZON-RFT study zoledronic acid treatment significantly increased BMD at the total hip and femoral neck relative to treatment with placebo at all timepoints. Treatment with zoledronic acid resulted in an increase in BMD of 5.4% at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo.

Clinical efficacy in men
In the HORIZON-RFT study 508 men were randomised into the study and 185 patients had BMD assessed at 24 months. At 24 months a similar significant increase of 3.6% in total hip BMD was observed for patients treated with zoledronic acid as compared to the effects observed in post-menopausal women in the HORIZON-PFT study. The study was not powered to show a reduction in clinical fractures in men; the incidence of clinical fractures was 7.5% in men treated with zoledronic acid versus 8.7% for placebo.

In another study in men (study CZOL446M2308) an annual infusion of zoledronic acid was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline.

Clinical efficacy in osteoporosis associated with long-term systemic glucocorticoid therapy
The efficacy and safety of zoledronic acid in the treatment and prevention of osteoporosis associated with long-term systemic glucocorticoid therapy were assessed in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women aged 18-85 years (mean age for men 56.4 years; for women 53.5 years) treated with > 7.5 mg/day oral prednisone (or equivalent). Patients were stratified with respect to duration of glucocorticoid use prior to randomisation (≤ 3 months versus > 3 months). The duration of the trial was one year. Patients were randomised to either zoledronic acid 5 mg single infusion or to oral risedronate 5 mg daily for one year. All participants received 1,000 mg elemental calcium plus 400 to 1,000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively. The majority of patients continued to receive glucocorticoids for the one year duration of the trial.

Effect on bone mineral density (BMD)
The increases in BMD were significantly greater in the zoledronic acid-treated group at the lumbar spine and femoral neck at 12 months compared to risedronate (all $p<0.03$). In the subpopulation of patients receiving glucocorticoids for more than 3 months prior to randomisation, zoledronic acid increased lumbar spine BMD by 4.06% versus 2.71% for risedronate (mean difference: 1.36% ; $p<0.001$). In the subpopulation of patients that had received glucocorticoids for 3 months or less prior to randomisation, zoledronic acid increased lumbar spine BMD by 2.60% versus 0.64% for risedronate (mean difference: 1.96% ; $p<0.001$). The study was not powered to show a reduction in clinical fractures compared to risedronate. The incidence of fractures was 8 for zoledronic acid-treated patients versus 7 for risedronate-treated patients ($p=0.8055$).

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.

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, osteoporosis in post-menopausal women at an increased risk of fracture, osteoporosis in men at increased risk of fracture and prevention of clinical fractures after a hip fracture in men and women (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 drugs 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 drug 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 Teva Generics 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 ≥ 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

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 ml vial, i.e. essentially “sodium free”.

6.2 Incompatibilities

This medicinal product must not be allowed to come into contact with any calcium-containing solutions. The medicinal product must not be mixed or given intravenously with any other medicinal products.

6.3 Shelf life

18 months

Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C and 25ºC.
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 to 8°C.

6.4 Special precautions for storage

Store below 30°C. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

multilayer polyolefin/styrene-ethylene-butylene (SEB) bag with SFC polypropylene infusion port closed with rubber stopper and snap cap.
Each bag contains 100 ml of solution.
Zoledronic acid Teva Generics is supplied in multipacks containing 5 or 10 bags.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/004
EU/1/14/912/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/04/2014

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. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pharmachemie B.V.
Swensweg 5
2031 GA Haarlem
The Netherlands

TEVA Gyógyszergyár Zrt.
Táncsics Mihály út 82.,
Gödöllő 2100
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

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**

At the time of granting the marketing authorisation, the submission of periodic safety update reports is not required for this medicinal product. However, the marketing authorisation holder shall submit periodic safety update reports for this medicinal product if the product is included 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 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 submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The Marketing Authorisation Holder (MAH) shall ensure that the educational programme implemented for the authorised indications of treatment of osteoporosis in post-menopausal women and in men at increased risk of fracture, including those with a recent low-trauma hip fracture, and treatment of osteoporosis associated with long-term systemic glucocorticoid therapy in post-menopausal women and in men at increased risk of fracture is updated. The educational programme contains the following:

- Physician educational material
- Patient information pack

The physician educational material should contain the following key elements:

- The Summary of Product Characteristics
- Reminder card with the following key messages:
    - Need to calculate creatinine clearance based on actual body weight using the Cockcroft-Gault formula before each treatment with Zoledronic acid Teva Generics
    - Contraindication in patients with creatinine clearance < 35 ml/min
    - Contraindication in pregnancy and in breast-feeding women due to potential teratogenicity
    - Need to ensure appropriate hydration of the patient especially those at an advanced age and those receiving diuretic therapy
    - Need to infuse Zoledronic acid Teva Generics slowly over a period of no less than 15 minutes
    - Once-yearly dosing regime
    - Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration
    - Need for appropriate physical activity, non-smoking and healthy diet
- Patient information pack

The patient information pack should be provided and contain the following key messages:

- Package leaflet
- Contraindication in patients with severe kidney problems
- Contraindication in pregnancy and in breast-feeding women
- Need for adequate calcium and vitamin D supplementation, appropriate physical activity, non-smoking and healthy diet
- Key signs and symptoms of serious adverse events
- When to seek attention from the health care provider

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion in bottles
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each bottle contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 bottle of 100 ml
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/001
EU/1/14/912/002
EU/1/14/912/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON FOR MULTIPACKS (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion in bottles
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

multipack: 5 bottles x 100 ml
multipack: 10 bottles x 100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/001
EU/1/14/912/002
EU/1/14/912/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion in bottles
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 bottle of 100 ml.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/001
EU/1/14/912/002
EU/1/14/912/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bottle contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After opening: 24 hours at 2°C - 8°C

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/001
EU/1/14/912/002
EU/1/14/912/003

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BAG

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/004
EU/1/14/912/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING

OVERPOUCH (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion
1 bag of 100 ml
Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/004
EU/1/14/912/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Generics 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One bag contains 5 mg zoledronic acid (as monohydrate).
Each ml of the solution contains 0.05 mg zoledronic acid (as monohydrate).

3. LIST OF EXCIPIENTS

Excipients: Mannitol, sodium citrate and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for infusion

multipack: 5 bags x 100 ml
multipack: 10 bags x 100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

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 2°C - 8°C

9. SPECIAL STORAGE CONDITIONS

Store below 30°C.

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

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/912/004
EU/1/14/912/005

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Zoledronic acid Teva Generics 5 mg solution for infusion in bottles
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 Teva Generics is and what it is used for
2. What you need to know before you are given Zoledronic acid Teva Generics
3. How Zoledronic acid Teva Generics is given
4. Possible side effects
5. How to store Zoledronic acid Teva Generics
6. Contents of the pack and other information

1. What Zoledronic acid Teva Generics is and what it is used for

Zoledronic acid Teva Generics contains the active substance zoledronic acid. It belongs to a group of medicines called bisphosphonates and is used to treat post-menopausal women and adult men with osteoporosis or osteoporosis caused by treatment with steroids, and Paget's disease of the bone in adults.

Osteoporosis
Osteoporosis is a disease that involves the thinning and weakening of the bones and is common in women after the menopause, but can also occur in men. At the menopause, a woman's ovaries stop producing the female hormone oestrogen, which helps keep bones healthy. Following the menopause bone loss occurs, bones become weaker and break more easily. Osteoporosis could also occur in men and women because of the long term use of steroids, which can affect the strength of bones. Many patients with osteoporosis have no symptoms but they are still at risk of breaking bones because osteoporosis has made their bones weaker. Decreased circulating levels of sex hormones, mainly oestrogens converted from androgens, also play a role in the more gradual bone loss observed in men. In both women and men, Zoledronic acid Teva Generics strengthens the bone and therefore makes it less likely to break. Zoledronic acid Teva Generics is also used in patients who have recently broken their hip in a minor trauma such as a fall and therefore are at risk of subsequent bone breaks.

Paget's disease of the bone
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 Teva Generics 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 Teva Generics

Follow all instructions given to you by your doctor, pharmacist or nurse carefully before you are given Zoledronic acid Teva Generics.

You must not be given Zoledronic acid Teva Generics:

- 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 Teva Generics:
- if you are being treated with any other bisphosphonate medicine, since the combined effects of these medicines taken together with Zoledronic acid Teva Generics are unknown. This includes e.g. Zometa or Aclasta (medicines that also contain zoledronic acid and are used to treat the same disease or osteoporosis and other non-cancer diseases of the bone).
- 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.

Before you receive treatment with Zoledronic acid Teva Generics, tell your doctor if you have (or have had) pain, swelling or numbness in your gums, jaw or both, if your jaw feels heavy, or if you have lost a tooth. Before you receive dental treatment or undergo dental surgery, tell your dentist you are receiving treatment with Zoledronic acid Teva Generics.

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

Children and adolescents
Zoledronic acid Teva Generics is not recommended for anyone under 18 years of age. The use of Zoledronic acid Teva Generics in children and adolescents has not been studied.

Other medicines and Zoledronic acid Teva Generics
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

It is especially 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 Teva Generics 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
Zoledronic acid Teva Generics has no or negligible influence on the ability to drive and use machines. If you feel dizzy while taking Zoledronic acid Teva Generics, do not drive or use machines until you feel better.

Zoledronic acid Teva Generics contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 ml, i.e. essentially “sodium-free.”

3. How Zoledronic acid Teva Generics 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.

Osteoporosis
The usual dose is 5 mg given as one infusion per year into a vein by your doctor or nurse. The infusion will take at least 15 minutes.

In case you recently broke your hip, it is recommended that Zoledronic acid Teva Generics is administered two or more weeks after your hip repair surgery.

It is important to take calcium and vitamin D supplements (for example tablets) as directed by your doctor.

For osteoporosis, Zoledronic acid Teva Generics works for one year. Your doctor will let you know when to return for your next dose.

Paget's disease
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 Teva Generics 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 Teva Generics. 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 Teva Generics with food and drink
Make sure you drink enough fluids (at least one or two glasses) before and after the treatment with Zoledronic acid Teva Generics, as directed by your doctor. This will help prevent dehydration. You may eat normally on the day you are treated with Zoledronic acid Teva Generics. This is especially important in patients who take diuretics ("water pills") and in elderly patients.

If you missed a dose of Zoledronic acid Teva Generics
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Before stopping Zoledronic acid Teva Generics therapy
If you are considering stopping Zoledronic acid Teva Generics 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 Teva Generics.

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 Teva Generics. 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 Teva Generics.

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 Teva Generics for the treatment of postmenopausal osteoporosis. It is currently unclear whether Zoledronic acid Teva Generics causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received Zoledronic acid Teva Generics.
Swelling and/or pain at the infusion site may occur.

Uncommon (may affect up to 1 in 100 people)
Skin reactions such as redness.
Swelling, redness, pain and itching to the eyes or eye sensitivity to light.

Not known (frequency cannot be estimated from the available data)
Pain in the mouth, teeth and jaw, swelling or sores inside the mouth, 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 dentist immediately if you experience such symptoms.

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 Teva Generics. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Zoledronic acid Teva Generics, as directed by your healthcare provider.

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

Zoledronic acid Teva Generics 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.

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.

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 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 Teva Generics

Your doctor, pharmacist or nurse knows how to store Zoledronic acid Teva Generics 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 bottle and carton label after EXP. The expiry date refers to the last day of that month.
- The unopened bottle does not require any special storage conditions.
- After opening the bottle, chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8ºC and 25ºC. 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 to 8°C. Allow the refrigerated solution to reach room temperature before administration.
- Do not use this medicine if you notice any discolouration or particles in the solution.
- Do not throw away any medicines via wastewater (or household waste). Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zoledronic acid Teva Generics contains
- The active substance is zoledronic acid. One bottle contains 5 mg zoledronic acid (as monohydrate). Each ml of solution contains 0.05 mg zoledronic acid (as monohydrate).
- The other ingredients are mannitol, sodium citrate and water for injections.

What Zoledronic acid Teva Generics looks like and contents of the pack
Zoledronic acid Teva Generics is a clear and colourless solution for infusion. It comes in a clear plastic bottle. Each bottle contains 100 ml of solution. It is supplied in packs sizes of 1, 5 and 10. The pack sizes of 5 and 10 are only available as multipacks comprising of 5 or 10 packs, each containing 1 bottle.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

Teva B.V.
Swensweg 5, 2031GA Haarlem
The Netherlands

Manufacturer

Teva Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
2100 Gödöllő
Hungary

Pharmachemie B.V.
Swensweg 5
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This leaflet was last revised in {MM/YYYY}

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

INFORMATION FOR THE HEALTHCARE PROESSIONAL

The following information is intended for healthcare professionals only:

How to prepare and administer Zoledronic acid Teva Generics

- Zoledronic acid Teva Generics 5 mg solution for infusion 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 Teva Generics 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 Teva Generics 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 Teva Generics

- 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 bottle after EXP.
- The unopened bottle does not require any special storage conditions.
- After opening the bottle, 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.

Package leaflet: Information for the user

Zoledronic acid Teva Generics 5 mg solution for infusion in bags
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 Teva Generics is and what it is used for
2. What you need to know before you are given Zoledronic acid Teva Generics
3. How Zoledronic acid Teva Generics is given
4. Possible side effects
5. How to store Zoledronic acid Teva Generics
6. Contents of the pack and other information

1. What Zoledronic acid Teva Generics is and what it is used for

Zoledronic acid Teva Generics contains the active substance zoledronic acid. It belongs to a group of medicines called bisphosphonates and is used to treat post-menopausal women and adult men with osteoporosis or osteoporosis caused by treatment with steroids, and Paget's disease of the bone in adults.

Osteoporosis
Osteoporosis is a disease that involves the thinning and weakening of the bones and is common in women after the menopause, but can also occur in men. At the menopause, a woman's ovaries stop producing the female hormone oestrogen, which helps keep bones healthy. Following the menopause bone loss occurs, bones become weaker and break more easily. Osteoporosis could also occur in men and women because of the long term use of steroids, which can affect the strength of bones. Many patients with osteoporosis have no symptoms but they are still at risk of breaking bones because osteoporosis has made their bones weaker. Decreased circulating levels of sex hormones, mainly oestrogens converted from androgens, also play a role in the more gradual bone loss observed in men. In both women and men, Zoledronic acid Teva Generics strengthens the bone and therefore makes it less likely to break. Zoledronic acid Teva Generics is also used in patients who have recently broken their hip in a minor trauma such as a fall and therefore are at risk of subsequent bone breaks.

Paget's disease of the bone
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 Teva Generics 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 Teva Generics

Follow all instructions given to you by your doctor, pharmacist or nurse carefully before you are given Zoledronic acid Teva Generics.

You must not be given Zoledronic acid Teva Generics:

- 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 Teva Generics:
- if you are being treated with any other bisphosphonate medicine, since the combined effects of these medicines taken together with Zoledronic acid Teva Generics are unknown. This includes e.g. Zometa or Aclasta (medicines that also contain zoledronic acid and are used to treat the same disease or osteoporosis and other non-cancer diseases of the bone).
- 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.

Before you receive treatment with Zoledronic acid Teva Generics, tell your doctor if you have (or have had) pain, swelling or numbness in your gums, jaw or both, if your jaw feels heavy, or if you have lost a tooth. Before you receive dental treatment or undergo dental surgery, tell your dentist you are receiving treatment with Zoledronic acid Teva Generics.

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

Children and adolescents
Zoledronic acid Teva Generics is not recommended for anyone under 18 years of age. The use of Zoledronic acid Teva Generics in children and adolescents has not been studied.

Other medicines and Zoledronic acid Teva Generics
Tell your doctor, pharmacist or nurse if you are taking, have recently taken or might take any other medicines.

It is especially 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 Teva Generics 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 any medicine.

Driving and using machines
Zoledronic acid Teva Generics has no or negligible influence on the ability to drive and use machines. If you feel dizzy while taking Zoledronic acid Teva Generics, do not drive or use machines until you feel better.

Zoledronic acid Teva Generics contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per 100 ml; i.e. essentially “sodium-free.”

3. How Zoledronic acid Teva Generics 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.

Osteoporosis
The usual dose is 5 mg given as one infusion per year into a vein by your doctor or nurse. The infusion will take at least 15 minutes.

In case you recently broke your hip, it is recommended that Zoledronic acid Teva Generics is administered two or more weeks after your hip repair surgery.

It is important to take calcium and vitamin D supplements (for example tablets) as directed by your doctor.

For osteoporosis, Zoledronic acid Teva Generics works for one year. Your doctor will let you know when to return for your next dose.

Paget's disease
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 Teva Generics 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 Teva Generics. 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 Teva Generics with food and drink
Make sure you drink enough fluids (at least one or two glasses) before and after the treatment with Zoledronic acid Teva Generics, as directed by your doctor. This will help to prevent dehydration. You may eat normally on the day you are treated with Zoledronic acid Teva Generics. This is especially important in patients who take diuretics ("water pills") and in elderly patients.

If you missed a dose of Zoledronic acid Teva Generics
Contact your doctor or hospital as soon as possible to re-schedule your appointment.

Before stopping Zoledronic acid Teva Generics therapy
If you are considering stopping Zoledronic acid Teva Generics 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 Teva Generics.

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 Teva Generics. 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 Teva Generics.

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 Teva Generics for the treatment of postmenopausal osteoporosis. It is currently unclear whether Zoledronic acid Teva Generics causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received Zoledronic acid Teva Generics.
Swelling and/or pain at the infusion site may occur.

Uncommon (may affect up to 1 in 100 people)
Skin reactions such as redness.
Swelling, redness, pain and itching to the eyes or eye sensitivity to light.

Not known (frequency cannot be estimated from the available data)
Pain in the mouth, teeth and jaw, swelling or sores inside the mouth, 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 dentist immediately if you experience such symptoms.

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 Teva Generics. It is important for you to drink at least 2 glasses of fluid (such as water), within a few hours before receiving Zoledronic acid Teva Generics, as directed by your healthcare provider.

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

Zoledronic acid Teva Generics 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.

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.

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 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 Teva Generics

Your doctor, pharmacist or nurse knows how to store Zoledronic acid Teva Generics 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 bag and carton after EXP. The expiry date refers to the last day of that month.
- Store below 30°C.
- After opening the bottle, chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8ºC and 25ºC. 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 to 8°C. Allow the refrigerated solution to reach room temperature before administration.
- Do not use this medicine if you notice any discolouration or particles in the solution.
- Do not throw away any medicines via wastewater (or household waste). Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

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

What Zoledronic acid Teva Generics looks like and contents of the pack
Zoledronic acid Teva Generics is a clear and colourless solution for infusion. It comes in a polyolefin/styrene-ethylene-butylene (SEB) foil bag with a foil over pouch. Each bag contains 100 ml of solution. It is supplied in multipacks containing 5 or 10 bags.

Not all pack size may be marketed.

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

INFORMATION FOR THE HEALTHCARE PROFESSIONAL

The following information is intended for healthcare professionals only:

How to prepare and administer Zoledronic acid Teva Generics in bags

- Zoledronic acid Teva Generics 5 mg solution for infusion in bags 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 Teva Generics 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 Teva Generics 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 Teva Generics

- Keep this medicine out of the sight and reach of children.
- Do not use Zoledronic acid Teva Generics after the expiry date which is stated on the bag.
- Store below 30°C.
- Chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8ºC and 25ºC. 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 to 8°C.