

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 5 mg solution for infusion in bottles

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each bottle with 100 ml of solution 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 Teva Pharma. This is especially important for the elderly (≥ 65 years) and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with Zoledronic acid Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma. 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 \geq 35 ml/min.

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Elderly (\geq 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 Teva Pharma is administered via a vented infusion line and given slowly at a constant infusion rate. The infusion time must not be less than 15 minutes. For information on the infusion of Zoledronic acid Teva Pharma, see section 6.6.

Patients treated with Zoledronic acid Teva Pharma should be given the package leaflet and the patient reminder card.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Renal function

The use of Zoledronic acid Teva Pharma 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 Teva Pharma 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 Pharma 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 Pharma.
- A single dose of Zoledronic acid Teva Pharma 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 Teva Pharma (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 Teva Pharma (see section 4.8).

Adequate calcium and vitamin D intake are recommended in association with Zoledronic acid Teva Pharma 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 Teva Pharma 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 Teva Pharma is recommended for patients with Paget's disease.

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

Osteonecrosis of the jaw (ONJ)

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

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Zoledronic acid Teva Pharma in patients with concomitant risk factors.

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

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions.

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

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

Osteonecrosis of the external auditory canal

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

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

General

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

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 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 Teva Pharma is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Zoledronic acid Teva Pharma is not recommended in women of childbearing potential.

Pregnancy

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

Fertility

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

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall percentage of patients who experienced adverse reactions were 44.7%, 16.7% and 10.2% after the first, second and third infusion, respectively. Incidence of individual adverse reactions following the first infusion was: pyrexia (17.1%), myalgia (7.8%), influenza-like illness (6.7%), arthralgia (4.8%) and headache (5.1%). 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.

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 ($\geq 1/10$);

common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

<i>Infections and infestations</i>	<i>Uncommon</i>	Influenza, nasopharyngitis
<i>Blood and lymphatic system disorders</i>	<i>Uncommon</i>	Anaemia
<i>Immune system disorders</i>	<i>Not known**</i>	Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
<i>Metabolism and nutrition disorders</i>	<i>Common</i>	Hypocalcaemia*
	<i>Uncommon</i>	Decreased appetite
<i>Psychiatric disorders</i>	<i>Uncommon</i>	Insomnia
<i>Nervous system disorders</i>	<i>Common</i>	Headache, dizziness
	<i>Uncommon</i>	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
<i>Eye disorders</i>	<i>Common</i>	Ocular hyperaemia
	<i>Uncommon</i>	Conjunctivitis, eye pain
	<i>Rare</i>	Uveitis, episcleritis, iritis
	<i>Not known**</i>	Scleritis and parophthalmia
<i>Ear and labyrinth disorders</i>	<i>Uncommon</i>	Vertigo
<i>Cardiac disorders</i>	<i>Common</i>	Atrial fibrillation
	<i>Uncommon</i>	Palpitations
<i>Vascular disorders</i>	<i>Uncommon</i>	Hypertension, flushing
	<i>Not known**</i>	Hypotension (some of the patients had underlying risk factors)
<i>Respiratory, thoracic and mediastinal disorders</i>	<i>Uncommon</i>	Cough, dyspnoea
<i>Gastrointestinal disorders</i>	<i>Common</i>	Nausea, vomiting, diarrhoea
	<i>Uncommon</i>	Dyspepsia, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis [#]
<i>Skin and subcutaneous tissue disorders</i>	<i>Uncommon</i>	Rash, hyperhidrosis, pruritus, erythema
<i>Musculoskeletal and connective tissue disorders</i>	<i>Common</i>	Myalgia, arthralgia, bone pain, back pain, pain in extremity
	<i>Uncommon</i>	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, shoulder pain, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	<i>Rare</i>	Atypical subtrochanteric and diaphyseal femoral fractures [†] (bisphosphonate class adverse reaction)
	<i>Very rare</i>	Osteonecrosis of the external auditory canal [†] (bisphosphonate class adverse reaction)
	<i>Not known**</i>	Osteonecrosis of the jaw (see sections 4.4 and 4.8 Class effects)
<i>Renal and urinary disorders</i>	<i>Uncommon</i>	Blood creatinine increased, pollakiuria,

	<i>Not known**</i>	proteinuria 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	<i>Very common</i>	Pyrexia
	<i>Common</i>	Influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	<i>Uncommon</i>	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	<i>Not known**</i>	Dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea
Investigations	<i>Common</i>	C-reactive protein increased
	<i>Uncommon</i>	Blood calcium decreased

Observed in patients taking concomitant glucocorticosteroids.

* Common in Paget's disease only.

** Based on post-marketing reports. Frequency cannot be estimated from available data.

† Identified in post-marketing experience.

Description of selected adverse reactions

Atrial fibrillation

In the HORIZON – Pivotal Fracture Trial [PFT] (see section 5.1), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving zoledronic acid (1.3%) (51 out of 3,862) compared with patients receiving placebo (0.6%) (22 out of 3,852). The mechanism behind the increased incidence of atrial fibrillation is unknown. In the osteoporosis trials (PFT, HORIZON - Recurrent Fracture Trial [RFT]) the pooled atrial fibrillation incidences were comparable between zoledronic acid (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events the pooled incidences were 1.3% for zoledronic acid and 0.8% for placebo.

Class effects:

Renal impairment

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

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

Hypocalcaemia

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

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

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

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

Local reactions

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

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, including zoledronic acid (see section 4.4). In a large clinical trial in 7,736 patients, osteonecrosis of the jaw has been reported in one patient treated with zoledronic acid and one patient treated with placebo. Cases of ONJ have been reported in the post-marketing setting for Zoledronic acid Teva Pharma.

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	Placebo	Absolute reduction	Relative risk
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	acid (N=3,875) event rate (%)	(N=3,861) event rate (%)	in fracture event rate % (CI)	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 (μ CT) 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 treatment. 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 $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β , with $t_{1/2}$ 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, $39 \pm 16\%$ 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 $75 \pm 33\%$ 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 $AUC_{(0-24hr)}$, 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 Pharma 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

6.2 Incompatibilities

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

6.3 Shelf life

18 months

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 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 solution.

Zoledronic acid Teva Pharma is supplied in packs of 1 bottle and multipacks of 5 (5 x 1) or 10 (10 x 1) bottles.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.
Only clear solution free from particles and discoloration should be used.

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

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/001
EU/1/12/772/002
EU/1/12/772/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 August 2012
Date of latest renewal:

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>.

Medicinal product no longer authorised

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 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 Teva Pharma. This is especially important for the elderly (≥ 65 years) and for patients receiving diuretic therapy.

Adequate calcium and vitamin D intake are recommended in association with Zoledronic acid Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma. 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 Teva Pharma 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 Teva Pharma 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 Teva Pharma 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 \geq 35 ml/min.

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Elderly (\geq 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 Teva Pharma is administered via a vented infusion line and given slowly at a constant infusion rate. The infusion time must not be less than 15 minutes. For information on the infusion of Zoledronic acid Teva Pharma, see section 6.6.

Patients treated with Zoledronic acid Teva Pharma should be given the package leaflet and the patient reminder card.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Renal function

The use of Zoledronic acid Teva Pharma 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 Teva Pharma 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 Pharma 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 Pharma.
- A single dose of Zoledronic acid Teva Pharma 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 Teva Pharma (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 Teva Pharma (see section 4.8).

Adequate calcium and vitamin D intake are recommended in association with Zoledronic acid Teva Pharma 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 Teva Pharma 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 Teva Pharma is recommended for patients with Paget's disease.

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

Osteonecrosis of the jaw (ONJ)

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

The start of treatment or of a new course of treatment should be delayed in patients with unhealed open soft tissue lesions in the mouth. A dental examination with preventive dentistry and an individual benefit-risk assessment is recommended prior to treatment with Zoledronic acid Teva Pharma in

patients with concomitant risk factors.

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

- Potency of the medicinal product that inhibits bone resorption (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bone resorption therapy.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: corticosteroids, chemotherapy, angiogenesis inhibitors, radiotherapy to head and neck.
- Poor oral hygiene, periodontal disease, poorly fitting dentures, history of dental disease, invasive dental procedures, e.g. tooth extractions.

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

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

Osteonecrosis of the external auditory canal

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

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain, often associated with imaging features of stress fractures, weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment.

During bisphosphonate treatment patients should be advised to report any thigh, hip or groin pain and any patient presenting with such symptoms should be evaluated for an incomplete femur fracture.

General

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

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

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 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 Teva Pharma is administered in conjunction with medicinal products that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration) (see section 4.4).

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Zoledronic acid Teva Pharma is not recommended in women of childbearing potential.

Pregnancy

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

Fertility

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

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The overall percentage of patients who experienced adverse reactions were 44.7%, 16.7% and 10.2% after the first, second and third infusion, respectively. Incidence of individual adverse reactions following the first infusion was: pyrexia (17.1%), myalgia (7.8%), influenza-like illness (6.7%), arthralgia (4.8%) and headache (5.1%). 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.

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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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

<i>Infections and infestations</i>	<i>Uncommon</i>	Influenza, nasopharyngitis
<i>Blood and lymphatic system disorders</i>	<i>Uncommon</i>	Anaemia
<i>Immune system disorders</i>	<i>Not known**</i>	Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
<i>Metabolism and nutrition disorders</i>	<i>Common</i>	Hypocalcaemia*
	<i>Uncommon</i>	Decreased appetite
<i>Psychiatric disorders</i>	<i>Uncommon</i>	Insomnia
<i>Nervous system disorders</i>	<i>Common</i>	Headache, dizziness
	<i>Uncommon</i>	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
<i>Eye disorders</i>	<i>Common</i>	Ocular hyperaemia
	<i>Uncommon</i>	Conjunctivitis, eye pain
	<i>Rare</i>	Uveitis, episcleritis, iritis
	<i>Not known**</i>	Scleritis and parophthalmia
<i>Ear and labyrinth disorders</i>	<i>Uncommon</i>	Vertigo
<i>Cardiac disorders</i>	<i>Common</i>	Atrial fibrillation
	<i>Uncommon</i>	Palpitations
<i>Vascular disorders</i>	<i>Uncommon</i>	Hypertension, flushing
	<i>Not known**</i>	Hypotension (some of the patients had underlying risk factors)
<i>Respiratory, thoracic and mediastinal disorders</i>	<i>Uncommon</i>	Cough, dyspnoea
<i>Gastrointestinal disorders</i>	<i>Common</i>	Nausea, vomiting, diarrhoea
	<i>Uncommon</i>	Dyspepsia, abdominal pain upper, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis [#]
<i>Skin and subcutaneous tissue disorders</i>	<i>Uncommon</i>	Rash, hyperhidrosis, pruritus, erythema
<i>Musculoskeletal and connective tissue disorders</i>	<i>Common</i>	Myalgia, arthralgia, bone pain, back pain, pain in extremity
	<i>Uncommon</i>	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, shoulder pain, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
	<i>Rare</i>	Atypical subtrochanteric and diaphyseal femoral fractures [†] (bisphosphonate class adverse reaction)
	<i>Very rare</i>	Osteonecrosis of the external auditory canal [†] (bisphosphonate class adverse reaction)
	<i>Not known**</i>	Osteonecrosis of the jaw (see

		sections 4.4 and 4.8 Class effects)
Renal and urinary disorders	<i>Uncommon</i>	Blood creatinine increased, pollakiuria, proteinuria
	<i>Not known**</i>	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	<i>Very common</i>	Pyrexia
	<i>Common</i>	Influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	<i>Uncommon</i>	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	<i>Not known**</i>	Dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea
Investigations	<i>Common</i>	C-reactive protein increased
	<i>Uncommon</i>	Blood calcium decreased

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

Description of selected adverse reactions

Atrial fibrillation

In the HORIZON – Pivotal Fracture Trial [PFT] (see section 5.1), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving zoledronic acid (1.3%) (51 out of 3,862) compared with patients receiving placebo (0.6%) (22 out of 3,852). The mechanism behind the increased incidence of atrial fibrillation is unknown. In the osteoporosis trials (PFT, HORIZON - Recurrent Fracture Trial [RFT]) the pooled atrial fibrillation incidences were comparable between zoledronic acid (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events the pooled incidences were 1.3% for zoledronic acid and 0.8% for placebo.

Class effects:

Renal impairment

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

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

Hypocalcaemia

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

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

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

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

Local reactions

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

Osteonecrosis of the jaw

Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, including zoledronic acid (see section 4.4). In a large clinical trial in 7,736 patients, osteonecrosis of the jaw has been reported in one patient treated with zoledronic acid and one patient treated with placebo. Cases of ONJ have been reported in the post-marketing setting for Zoledronic acid Teva Pharma.

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 (μ CT) 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 treatment. 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 $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hours. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β , with $t_{1/2}$ 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, $39 \pm 16\%$ 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 $75 \pm 33\%$ 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 $AUC_{(0-24hr)}$, 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 Pharma in patients with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

5.3 Preclinical safety data

Acute toxicity

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

Subchronic and chronic toxicity

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

Longer-term repeat administration at cumulative exposures sufficiently exceeding the maximum intended human exposure produced toxicological effects in other organs, including the gastrointestinal tract and liver, and at the site of intravenous administration. The clinical relevance of these findings is unknown. The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

Reproduction toxicity

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

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium citrate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

18 months

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 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 solution.

Zoledronic acid Teva Pharma is supplied in multipacks of 5 (5 x 1) or 10 (10 x 1) bags .

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

For single use only.

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

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

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

7. MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/003

EU/1/12/772/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 August 2012

Date of latest renewal:

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>.

Medicinal product no longer authorised

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 manufacturers responsible for batch release

Teva Pharmaceutical Works Private Limited Company
Táncsics Mihály út 82
HU-2100 Godollo
Hungary

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

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

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

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

• Risk Management Plan (RMP)

The 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 a result of an important (pharmacovigilance or risk minimisation) milestone being reached.

• Additional risk minimisation measures

The Marketing Authorisation Holder (MAH) shall provide an educational programme targeting all physicians who are expected to prescribe/use Zoledronic acid Teva Pharma for the treatment of osteoporosis prior to the launch in Member States. The MAH must agree the content and format of the educational material, together with a communication plan, with the national competent authorities in

Member States prior to distribution of the educational programme. The educational programme contains the following:

- Physician educational material
- Patient educational material

The physician educational material should contain 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 Pharma
- 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 Pharma slowly over a period of no less than 15 minutes
- Once-yearly dosing regime
- That all patients should be provided with the educational material and be counselled about:
 - 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

The patient educational material should contain the following key messages:

- 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

In addition, the following documents should be included in the patient information pack:

- Package leaflet
- Patient reminder card on osteonecrosis of the jaw

Medicinal product no longer authorised

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

Medicinal product no longer authorised

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

IMMEDIATE CARTON (without blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 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

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/001 multipack with 5 bottles
EU/1/12/772/002 multipack with 10 bottles

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON OF MULTIPACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 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

Multipack: 5 bottles of 100 ml

Multipack: 10 bottles of 100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/001 multipack with 5 bottles
EU/1/12/772/002 multipack with 10 bottles

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.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON OF UNIT PACK (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 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.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/005 1 bottle

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.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 5 mg solution for infusion
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

100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/001 multipack with 5 bottles
EU/1/12/772/002 multipack with 10 bottles
EU/1/12/772/005 1 bottle

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING**BAG****1. NAME OF THE MEDICINAL PRODUCT**

Zoledronic acid Teva Pharma 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/003 multipack with 5 bags
EU/1/12/772/004 multipack with 10 bags

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE****17. UNIQUE IDENTIFIER – 2D BARCODE****18. UNIQUE IDENTIFIER - HUMAN READABLE DATA**

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OVERPOUCH

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/003 multipack with 5 bags
EU/1/12/772/004 multipack with 10 bags

13. BATCH NUMBER

Batch

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with blue box)

1. NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Teva Pharma 5 mg solution for infusion
zoledronic acid

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 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 of 100 ml

Multipack: 10 bags of 100 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/12/772/003 multipack with 5 bags
EU/1/12/772/004 multipack with 10 bags

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.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

Medicinal product no longer authorised

B. PACKAGE LEAFLET

Package leaflet: Information for the user

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

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

Zoledronic acid Teva Pharma 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 corticosteroids used to treat inflammation, 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 Pharma strengthens the bone and therefore makes it less likely to break. Zoledronic acid Teva Pharma 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 Pharma 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 Pharma

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

You must not be given Zoledronic acid Teva Pharma:

- 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, pharmacist or nurse before you are given Zoledronic acid Teva Pharma:

- if you are being treated with any medicine containing zoledronic acid, which is also the active substance of Zoledronic acid Teva Pharma (zoledronic acid is used in adult patients with certain types of cancer to prevent bone complications or to reduce the amount of calcium).
- if you have a kidney problem, or used to have one.
- if you are unable to take daily calcium supplements.
- if you have had some or all of the parathyroid glands in your neck surgically removed.
- if you have had sections of your intestine removed.

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

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

Before receiving Zoledronic acid Teva Pharma treatment, tell your doctor, pharmacist or nurse if

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

Your doctor may ask you to undergo a dental examination before you start treatment with Zoledronic acid Teva Pharma.

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

Monitoring test

Your doctor should do a blood test to check your kidney function (levels of creatinine) before each dose of Zoledronic acid Teva Pharma. 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 Pharma, as directed by your healthcare provider.

Children and adolescents

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

Other medicines and Zoledronic acid Teva Pharma

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

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

Pregnancy and breast-feeding

You must not be given Zoledronic acid Teva Pharma 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 using this medicine.

Driving and using machines

If you feel dizzy while taking Zoledronic acid Teva Pharma, do not drive or use machines until you feel better.

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

Paget’s disease

For the treatment of Paget’s disease, Zoledronic acid Teva Pharma should be prescribed only by physicians with experience in the treatment of Paget’s disease of the bone.

The usual dose is 5 mg, given to you as one initial infusion into a vein by your doctor or nurse. The infusion will take at least 15 minutes. Zoledronic acid Teva Pharma 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 Pharma. 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 Pharma 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 Pharma, as directed by your doctor. This will help prevent dehydration. You may eat normally on the day you are treated with Zoledronic acid Teva Pharma. This is especially important in patients who take diuretics (“water pills”) and in elderly patients (age 65 years or over).

If you missed a dose of Zoledronic acid Teva Pharma

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

Before stopping Zoledronic acid Teva Pharma therapy

If you are considering stopping Zoledronic acid Teva Pharma 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 Pharma.

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 Pharma. 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 Pharma.

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 Pharma for the treatment of postmenopausal osteoporosis. It is currently unclear whether Zoledronic acid Teva Pharma 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 Pharma.

Uncommon (may affect up to 1 in 100 people)

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

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

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

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

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

Kidney disorders (e.g. decreased urine output) may occur. Your doctor should do a blood test to check your kidney function before each dose of Zoledronic acid Teva Pharma. 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 Pharma, as directed by your healthcare provider.

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

Zoledronic acid Teva Pharma may also cause other side effects

Very common: may affect more than 1 in 10 people

Fever.

Common: may affect up to 1 in 10 people

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

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

Uncommon: may affect up to 1 in 100 people

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

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

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

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 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 Pharma

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

Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the carton and bottle 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 8°C and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 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 Pharma 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 Pharma looks like and contents of the pack

Zoledronic acid Teva Pharma is a clear and colourless solution. 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
Netherlands

Manufacturer

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

Pharmachemie B.V.

Swensweg 5
2031 GA Haarlem
The Netherlands

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

België/Belgique/Belgien

Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

България

Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Česká republika

Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Danmark

Teva Denmark A/S
Tlf: +45 44 98 55 11

Deutschland

TEVA GmbH
Tel: +49 731 402 08

Eesti

UAB "Sicor Biotech" Eesti filiaal
Tel: +372 661 0801

Lietuva

UAB "Sicor Biotech"
Tel: +370 5 266 02 03

Luxembourg/Luxemburg

Teva Pharma Belgium N.V./S.A./AG,
Belgique/Belgien
Tél/Tel: +32 3 820 73 73

Magyarország

Teva Gyógyszergyár Zrt
Tel.: +36 1 288 64 00

Malta

Teva Pharmaceuticals Ireland, L-Irlanda
Tel: +353 51 321740

Nederland

Teva Nederland B.V.
Tel: +31 800 0228400

Norge

Teva Norway AS
Tlf: +47 66 77 55 90

Ελλάδα

Teva Ελλάς A.E.
Τηλ: +30 210 72 79 099

España

Teva Pharma S.L.U.
Tél: +34 91 387 32 80

France

Teva Santé
Tél: +33 1 55 91 7800

Hrvatska

Pliva Hrvatska d.o.o
Tel: + 385 1 37 20 000

Ireland

Teva Pharmaceuticals Ireland
Tel: +353 51 321 740

Ísland

ratiopharm Oy, Finnland
Sími: +358 20 180 5900

Italia

Teva Italia S.r.l.
Tel: +39 028917981

Κύπρος

Teva Ελλάς A.E., Ελλάδα
Τηλ: +30 210 72 79 099

Latvija

UAB "Sicor Biotech" filiāle Latvija
Tel: +371 673 23 666

Österreich

ratiopharm Arzenimittel Vertriebs-GmbH
Tel: +43 1 97007-0

Polska

Teva Pharmaceuticals Polska Sp. z o.o.
Tel.: +48 22 345 93 00

Portugal

Teva Pharma - Produtos Farmacêuticos Lda
Tel: +351 214 235 910

România

Teva Pharmaceuticals S.R.L
Tel: +40 21 230 65 24

Slovenija

Pliva Ljubljana d.o.o.
Tel: +386 1 58 90 390

Slovenská republika

Teva Pharmaceuticals Slovakia s.r.o.
Tel: +421 2 5726 7911

Suomi/Finland

ratiopharm Oy
Puh/Tel: +358 20 180 5900

Sverige

Teva Sweden AB
Tel: +46 42 12 11 00

United Kingdom

Teva UK Limited
Tel: +44 1323 501 111

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>.

The following information is intended for healthcare professionals only:

How to prepare and administer Zoledronic acid Teva Pharma

- Zoledronic acid Teva Pharma 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 Pharma 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 Pharma 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 Pharma

- 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.

Medicinal product no longer authorised

Package leaflet: Information for the user

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

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

Zoledronic acid Teva Pharma 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 corticosteroids used to treat inflammation, 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 Pharma strengthens the bone and therefore makes it less likely to break. Zoledronic acid Teva Pharma 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 Pharma 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 Pharma

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

You must not be given Zoledronic acid Teva Pharma:

- 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, pharmacist or nurse before you are given Zoledronic acid Teva Pharma:

- if you are being treated with any medicine containing zoledronic acid, which is also the active substance of Zoledronic acid Teva Pharma (zoledronic acid is used in adult patients with certain types of cancer to prevent bone complications or to reduce the amount of calcium).
- if you have a kidney problem, or used to have one.
- if you are unable to take daily calcium supplements.
- if you have had some or all of the parathyroid glands in your neck surgically removed.
- if you have had sections of your intestine removed.

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

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

Before receiving Zoledronic acid Teva Pharma treatment, tell your doctor, pharmacist or nurse if

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

Your doctor may ask you to undergo a dental examination before you start treatment with Zoledronic acid Teva Pharma.

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

Monitoring test

Your doctor should do a blood test to check your kidney function (levels of creatinine) before each dose of Zoledronic acid Teva Pharma. 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 Pharma, as directed by your healthcare provider.

Children and adolescents

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

Other medicines and Zoledronic acid Teva Pharma

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

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

Pregnancy and breast-feeding

You must not be given Zoledronic acid Teva Pharma 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 using this medicine.

Driving and using machines

If you feel dizzy while taking Zoledronic acid Teva Pharma, do not drive or use machines until you feel better.

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

Paget’s disease

For the treatment of Paget’s disease, Zoledronic acid Teva Pharma should be prescribed only by physicians with experience in the treatment of Paget’s disease of the bone.

The usual dose is 5 mg, given to you as one initial infusion into a vein by your doctor or nurse. The infusion will take at least 15 minutes. Zoledronic acid Teva Pharma 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 Pharma. 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 Pharma 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 Pharma, as directed by your doctor. This will help prevent dehydration. You may eat normally on the day you are treated with Zoledronic acid Teva Pharma, This is especially important in patients who take diuretics (“water pills”) and in elderly patients (age 65 years or over).

If you missed a dose of Zoledronic acid Teva Pharma

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

Before stopping Zoledronic acid Teva Pharma therapy

If you are considering stopping Zoledronic acid Teva Pharma 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 Pharma.

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 Pharma. 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 Pharma.

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 Pharma for the treatment of postmenopausal osteoporosis. It is currently unclear whether Zoledronic acid Teva Pharma 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 Pharma.

Uncommon (may affect up to 1 in 100 people)

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

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

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

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

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

Kidney disorders (e.g. decreased urine output) may occur. Your doctor should do a blood test to check your kidney function before each dose of Zoledronic acid Teva Pharma. 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 Pharma, as directed by your healthcare provider.

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

Zoledronic acid Teva Pharma may also cause other side effects

Very common: may affect more than 1 in 10 people

Fever.

Common: may affect up to 1 in 10 people

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

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

Uncommon: may affect up to 1 in 100 people

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

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

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

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 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 Pharma

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

Keep this medicine out of the sight and reach of children.

- Do not use this medicine after the expiry date which is stated on the carton and bag after EXP. The expiry date refers to the last day of that month.
- Store below 30°C.
- After opening the bag, chemical and physical in-use stability has been demonstrated for 24 hours at 2 to 8°C and 25°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 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 Pharma 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 Pharma looks like and contents of the pack

Zoledronic acid Teva Pharma is a clear and colourless solution. 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.

Marketing Authorisation Holder

Teva B.V.
Swensweg 5
2031GA Haarlem
Netherlands

Manufacturer

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

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

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

België/Belgique/Belgien

Teva Pharma Belgium N.V./S.A./AG
Tel/Tél: +32 3 820 73 73

Lietuva

UAB "Sicor Biotech"
Tel: +370 5 266 02 03

България

Тева Фармасютикълс България ЕООД
Тел: +359 2 489 95 82

Luxembourg/Luxemburg

Teva Pharma Belgium N.V./S.A./AG,
Belgique/Belgien
Tél/Tel: +32 3 820 73 73

Česká republika

Teva Pharmaceuticals CR, s.r.o.
Tel: +420 251 007 111

Magyarország

Teva Gyógyszergyár Zrt
Tel.: +36 1 288 64 00

Danmark

Teva Denmark A/S
Tlf: +45 44 98 55 11

Malta

Teva Pharmaceuticals Ireland, L-Irlanda
Tel: +353 51 321740

Deutschland

TEVA GmbH
Tel: +49 731 402 08

Nederland

Teva Nederland B.V.
Tel: +31 800 0228400

Eesti

UAB "Sicor Biotech" Eesti filiaal

Norge

Teva Norway AS

Tel: +372 661 0801

Tlf: +47 66 77 55 90

Ελλάδα

Teva Ελλάς A.E.

Τηλ: +30 210 72 79 099

Österreich

ratiopharm Arzenimittel Vertriebs-GmbH

Tel: +43 1 97007-0

España

Teva Pharma S.L.U.

Tél: +34 91 387 32 80

Polska

Teva Pharmaceuticals Polska Sp. z o.o.

Tel.: +48 22 345 93 00

France

Teva Santé

Tél: +33 1 55 91 7800

Portugal

Teva Pharma - Produtos Farmacêuticos Lda

Tel: +351 214 235 910

Hrvatska

Pliva Hrvatska d.o.o

Tel: + 385 1 37 20 000

România

Teva Pharmaceuticals S.R.L

Tel: +40 21 230 65 24

Ireland

Teva Pharmaceuticals Ireland

Tel: +353 51 321 740

Slovenija

Pliva Ljubljana d.o.o.

Tel: +386 1 58 90 390

Ísland

ratiopharm Oy, Finnland

Sími: +358 20 180 5900

Slovenská republika

Teva Pharmaceuticals Slovakia s.r.o.

Tel: +421 2 5726 7911

Italia

Teva Italia S.r.l.

Tel: +39 028917981

Suomi/Finland

ratiopharm Oy

Puh/Tel: +358 20 180 5900

Κύπρος

Teva Ελλάς A.E., Ελλάδα

Τηλ: +30 210 72 79 099

Sverige

Teva Sweden AB

Tel: +46 42 12 11 00

Latvija

UAB "Sicor Biotech" filiāle Latvijā

Tel: +371 673 23 666

United Kingdom

Teva UK Limited

Tel: +44 1323 501 111

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Other sources of information

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