

Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product

Zolos 5mg – Zoledronic acid 5mg in 100ml Solution for Infusion

2. Qualitative and quantitative composition

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

Each ml of the solution contains 0.05 mg zoledronic acid anhydrous, corresponding to 0.0533 mg zoledronic acid monohydrate.

Excipients with known effect: Sodium. Each bag contains <1 mmol sodium.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Solution for infusion.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of osteoporosis

- in post-menopausal women
- in adult men

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

Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy

- in post-menopausal women
- in adult men

at increased risk of fracture.

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

4.2 Posology and method of administration

Posology

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

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

Osteoporosis

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

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

In patients with a recent low-trauma hip fracture, it is recommended to give the zoledronic acid infusion two or more weeks after hip fracture repair (see section 5.1). In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first zoledronic acid infusion.

Paget's disease

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

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

Special populations

Patients with renal impairment

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

No dose adjustment is necessary in patients with creatinine clearance $\geq$ 35ml/min.

Patients with hepatic impairment

No dose adjustment is required (see section 5.2).

Elderly ($\geq$ 65 years)

Currently available data for children aged 5 to 17 years are described in section 5.1.

Method of administration

Intravenous use.

Zoledronic acid (5mg in 100ml ready-to-infuse solution) is administered an infusion line and given at a constant infusion rate. The infusion time must not be less than 15 minutes.

For information on the infusion of zoledronic acid, see section 6.6.

Patients treated with zoledronic acid 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 in patients with severe renal impairment (creatinine clearance < 35ml/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 considered to minimise the risk of renal adverse reactions:

- Patients, especially elderly patients, and those receiving diuretic therapy, should be appropriately hydrated prior to administration of zoledronic acid
- A single dose of zoledronic acid should not exceed 5mg and the duration of infusion should be at least 15minutes (see section 4.2).

Hypocalcaemia

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

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

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

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

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

Osteonecrosis of the jaw (ONJ)

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

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

- 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

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

Acute phase reactions

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

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

General

Other products containing zoledronic acid as an active substance are available for oncology indications. Patients being treated with Zoledronic acid 5mg solution for infusion should not be treated with such products or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies with other medicinal products have been performed.

Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see section 5.2). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound medicinal products are therefore unlikely.

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

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

4.6 Fertility, pregnancy, and lactation

Women of childbearing potential

Zoledronic acid is not recommended in women of childbearing potential.

Pregnancy

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

Breast-feeding

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

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

System Organ Class	Frequency	Undesirable effects
Infections and infestations	Uncommon	Influenza, nasopharyngitis
Blood and lymphatic system disorders	Uncommon	Anaemia
Immune system disorders	Not known**	Hypersensitivity reactions including rare cases of bronchospasm, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	Common	Hypocalcaemia*
	Uncommon	Decreased appetite
	Rare	Hypophosphatemia
Psychiatric disorders	Uncommon	Insomnia
Nervous system disorders	Common	Headache, dizziness
	Uncommon	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	Common	Ocular hyperaemia
	Uncommon	Conjunctivitis, eye pain
	Rare	Uveitis, episcleritis, iritis
	Not known**	Scleritis and par ophthalmia
Ear and labyrinth disorders	Uncommon	Vertigo
Cardiac disorders	Common	Atrial fibrillation
	Uncommon	Palpitations
Vascular disorders	Uncommon	Hypertension, flushing
	Not known**	Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic, and mediastinal disorders	Uncommon	Dyspnoea, cough
Gastrointestinal disorders	Common	Nausea, vomiting, diarrhoea
	Uncommon	Dyspepsia, abdominal pain upper, abdominal pain, gastro-oesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis#
Skin and subcutaneous tissue disorders	Uncommon	Rash, hyperhidrosis, pruritus, erythema
Musculoskeletal and connective tissue disorders	Common	Myalgia, arthralgia, bone pain, back pain, pain in extremity
	Uncommon	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, mus

Renal and urinary disorders	Uncommon	Blood creatinine increased, pollakiuria, proteinuria
	Not known**	Renal impairment. Rare cases of renal failure requiring dialysis and rare cases with a fatal outcome have been reported in patients with pre-existing renal dysfunction or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period (see sections 4.4 and 4.8 Class effects)
General disorders and administration site conditions	Very common	Pyrexia
	Common	Influenza-like illness, chills, fatigue, asthenia, pain, malaise, infusion site reaction
	Uncommon	Peripheral oedema, thirst, acute phase reaction, non-cardiac chest pain
	Not known**	Dehydration secondary to acute phase reactions (post-dose symptoms such as pyrexia, vomiting and diarrhoea)
Investigations	Common	C-reactive protein increased
	Uncommon	Blood calcium decreased

Observed in patients taking concomitant glucocorticoids.

* 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 [R

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), the majority of whom received a 4mg dose every 3-4weeks, 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 2.10mmol/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 ONJ have been reported in the post-marketing setting for zoledronic acid.

Acute phase reactions

The overall percentage of patients who reported acute phase reactions or post-dose symptoms (including serious cases) after zoledronic acid administration is as follows (frequencies derived from the study in treatment of post-menopausal osteoporosis): fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occurred within the first 3 days following zoledronic acid administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased with subsequent annual doses of zoledronic acid. The percentage of patients who experienced adverse reactions was lower in a smaller study (19.5%, 10.4%, 10.7% after the first, second and third infusion, respectively), where prophylaxis against adverse reactions was used (see section 4.4).

Reporting of suspected adverse reactions: Healthcare professionals are asked to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System (PvERS) <https://pv.pharmacyboardkenya.org>

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.

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 1,500mg elemental calcium and 400 to 1,200IU 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. Summary of results provided in table below.

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.	

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 all 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 the table below.

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)

Bone turnover markers

Bone specific alkaline phosphatase (BSAP), serum N-terminal pro-peptide 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 5mg annual dose of zoledronic acid significantly reduced BSAP by 30% relative to baseline at 12months which was sustained at 28% below baseline levels at 36months. P1NP was significantly reduced by 61% below baseline levels at 12months and was sustained at 52% below baseline levels at 36months. B-CTX was significantly reduced by 61% below baseline levels at 12months and was sustained at 55% below baseline levels at 36months. During this entire 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 17.9days and 11.3days respectively compared to placebo and significantly reduced the mean days of limited activity and the days of bed rest due to fractures by 2.9days and 0.5days respectively compared to placebo (all $p < 0.01$).

Clinical efficacy in the treatment of osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT)

The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2,127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study medication. Approximately 42% of patients had a femoral neck BMD T-score below -2.5 and approximately 45% of the patients had a femoral neck BMD T-score above -2.5. Zoledronic acid was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. Vitamin D levels were not routinely measured but a loading dose of vitamin

Effect on all clinical fractures

The incidence rates of key clinical fracture variables are presented in table below.

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)

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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 > 7.5mg/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 5mg single infusion or to oral risedronate 5mg daily for one year. All participants received 1,000mg elemental calcium plus 400 to 1,000IU 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.

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 zoledronate 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 5mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

Paediatric population

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

Zoledronic acid infusion resulted in an increase in the lumbar spine BMD Z-score least square (LS) mean difference of 0.41 at month 12 relative to baseline compared to placebo (95% CI: 0.02, 0.81; 18 and 16 patients, respectively). No effect on lumbar spine B

No statistically significant differences in total body bone mineral content were observed between patients treated with zoledronic acid versus placebo at 6 or 12 months. There is no clear evidence establishing a link between BMD changes and fracture prevention in children with growing skeletons.

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

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

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

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

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

5.2 Pharmacokinetic properties

Single and multiple 5 and 15-minute infusions of 2, 4, 8 and 16mg 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 $t_{1/2\alpha}$

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 medicinal products are unlikely.

Special populations (see section 4.2)

Renal impairment

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing $75 \pm 33\%$ 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 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 10mg/kg body weight in mice and 0.6mg/kg in rats. In the single-dose dog infusion studies, 1.0mg/kg (6-fold the recommended human therapeutic exposure based on AUC) administered over 15 minutes was well tolerated with no renal effects.

Sub chronic and chronic toxicity

In the intravenous infusion studies, renal tolerability of zoledronic acid was established in rats when given 0.6mg/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 0.25mg/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 0.02mg/kg daily was well tolerated for 4 weeks in rats and dogs, respectively but only 0.01mg/kg and 0.005mg/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 (0.01mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1mg/kg due to decreased serum calcium levels.

Mutagenicity and carcinogenic potential

6. Pharmaceutical particulars

6.1 List of excipients

Mannitol,
Sodium citrate
Water for Injections.

6.2 Incompatibilities

This medicinal product must not be allowed to come into contact with any calcium-containing solutions.

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

6.3 Shelf life

Unopened shelf life: 2 years.

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

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C - 8°C.

6.4 Special precautions for storage

Do not store above 30°C.

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Bag sizes: 100ml.

The bags are composed of polyolefin/polyamide co-extruded plastic.

The bags are overwrapped with a protective tri-laminate pouch.

6.6 Special precautions for disposal and other handling

8. Marketing authorisation number

H2025/CTD11091/24610

9. Date of first authorisation/renewal of the authorisation

1st September 2025

10. Date of revision of the text

26th August 2026