SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zoledro-Denk 4 mg/5 ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: zoledronic acid

Each vial with 5 ml concentrate contains 4 mg zoledronic acid (as monohydrate).
Each ml concentrate contains 0.8 mg zoledronic acid (as monohydrate).

Excipient with known effect: Each vial with 5 ml concentrate contains less than 1 mmol (23 mg) sodium.

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion; intravenous use.
Clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- Prevention of skeletal related events (pathological fractures, spinal compression, radiation or surgery to bone, or tumour-induced hypercalcaemia) in adult patients with advanced malignancies involving bone.

- Treatment of adult patients with tumour-induced hypercalcaemia (TIH).

- Treatment of osteoporosis in post-menopausal women and in 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 and in men at increased risk of fracture.

- Treatment of Paget`s disease of the bone in adults.

4.2 Posology and method of administration

Zoledro-Denk 4 mg/5 ml must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated with Zoledro-Denk 4 mg/5 ml should be given the package leaflet and the patient reminder card (available on http://denkpharma.de/en/therapeutic-areas/product-portfolio-of-denk-pharma/#zoledro-denk-4-mg-5-ml).

Posology

Prevention of skeletal related events in patients with advanced malignancies involving bone

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

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

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

Treatment of TIH

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

Treatment of osteoporosis

Adults and elderly
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 4 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 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.

Treatment of Paget’s disease

Adults and elderly
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 4 mg zoledronic acid.

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 4 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).

In patients with osteoporosis and Paget’s disease, adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following zoledronic acid administration (see section 4.4).

Note
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.

The incidence of post-dose symptoms in the treatment of osteoporosis and Paget's disease occurring within the first three days after administration of zoledronic acid can be reduced with the administration of paracetamol or ibuprofen shortly following zoledronic acid administration.

Posology adjustments for special populations

Treatment of TIH and Prevention of skeletal related events in patients with advanced malignancies involving bone

Renal impairment

TIH:
Zoledronic acid treatment in TIH patients who also have severe renal impairment should be considered only after evaluating the risks and benefits of treatment. In the clinical studies, patients with serum creatinine > 400 µmol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µmol/l or < 4.5 mg/dl (see section 4.4).

Prevention of skeletal related events in patients with advanced malignancies involving bone:
When initiating treatment with zoledronic acid in patients with multiple myeloma or metastatic bone lesions from solid tumours, serum creatinine and creatinine clearance (CLcr) should be determined. CLcr is calculated from serum creatinine using the Cockcroft-Gault formula. Zoledronic acid is not recommended for patients presenting with severe renal impairment prior to initiation of therapy, which is defined for this population as CLcr < 30 ml/min. In clinical trials with zoledronic acid, patients with serum creatinine > 265 µmol/l or > 3.0 mg/dl were excluded.

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30-60 ml/min, the following zoledronic acid dose is recommended (see also section 4.4):

Baseline creatinine clearance (ml/min)	Zoledronic acid recommended dose*
> 60	4.0 mg zoledronic acid
50–60	3.5 mg* zoledronic acid
40–49	3.3 mg* zoledronic acid
30–39	3.0 mg* zoledronic acid

*****Doses have been calculated assuming target AUC of 0.66 (mg•hr/l) (CLcr=75 ml/min). The reduced doses for patients with renal impairment are expected to achieve the same AUC as that seen in patients with creatinine clearance of 75 ml/min.

Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated.

In the clinical trials, renal deterioration was defined as follows:
- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 µmol/l), an increase of 0.5 mg/dl or 44 µmol/l;
- For patients with abnormal baseline serum creatinine (> 1.4 mg/dl or > 124 µmol/l), an increase of 1.0 mg/dl or 88 µmol/l.

In the clinical studies, zoledronic acid treatment was resumed only when the creatinine level returned to within 10% of the baseline value (see section 4.4). Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption.

Osteoporosis and Paget's disease

Patients with renal impairment
Zoledronic acid is contraindicated in patients with creatinine clearance < 35 ml/min (see sections 4.3 and 4.4).
No dose adjustment is necessary in patients with creatinine clearance ≥ 35 ml/min.

Patients with hepatic impairment
No dose adjustment is required (see section 5.2).

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

Paediatric population
Zoledronic acid should not be used in children and adolescents below 18 years of age. The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established.
Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration
Intravenous use.

Zoledro-Denk 4 mg/5 ml concentrate for solution for infusion, further diluted with 100 ml (see section 6.6), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced zoledronic acid doses are recommended (see section "Posology" above and section 4.4).

Instructions for preparing reduced doses of Zoledro-Denk 4 mg/5 ml

Withdraw an appropriate volume of the concentrate for solution for infusion (4 mg/5 ml) as needed:
- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

The withdrawn amount of Zoledro-Denk 4 mg/5 ml concentrate must be further diluted in 100 ml of sterile 0.9% w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zoledro-Denk 4 mg/5 ml must not be mixed with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution, and should be administered as a single intravenous solution in a separate infusion line.

Patients must be maintained well hydrated prior to and following administration of zoledronic acid.

4.3 Contraindications

- Hypersensitivity to the active substance, to other 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)
- Breast-feeding (see section 4.6)
- Pregnancy (see section 4.6)

4.4 Special warnings and precautions for use

General
Patients must be assessed prior to administration of zoledronic acid to ensure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.

Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating zoledronic acid therapy. If hypocalcaemia, hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered.

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

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

Adequate calcium and vitamin D intake are recommended in association with zoledronic acid administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following zoledronic acid administration (see section 4.2).
Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum calcium before infusion of zoledronic acid is recommended for patients with Paget's disease.

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

Patients being treated with Zoledro-Denk 4 mg/5 ml should not be treated with any other medicines containing zoledronic acid or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Renal insufficiency
Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with zoledronic acid outweighs the possible risk.

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

Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, advanced age, concomitant diuretic therapy, multiple cycles of zoledronic acid and other bisphosphonates as well as use of other nephrotoxic medicinal products. While the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration in renal function may still occur. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid. 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. Increases in serum creatinine also occur in some patients with chronic

administration of zoledronic acid at recommended doses for prevention of skeletal related events, although less frequently.

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

- Creatinine clearance should be calculated based on actual body weight using the Cockcroft-Gault formula prior to each dose of zoledronic acid.
- Transient increase in serum creatinine may be greater in patients with underlying impaired renal function.
- Monitoring of serum creatinine should be considered in at-risk patients.
- Zoledronic acid should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section 4.5).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of zoledronic acid.
- A single dose should not exceed 4 mg and the duration of infusion should be at least 15 minutes (see section 4.2).

Patients should have their serum creatinine levels assessed prior to each dose of zoledronic acid. Upon initiation of treatment in patients with bone metastases with mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal deterioration during treatment, zoledronic acid should be withheld. Zoledronic acid should only be resumed when serum creatinine returns to within 10% of baseline. Zoledronic acid treatment should be resumed at the same dose as that given prior to treatment interruption.

Patients with TIH and patients with cancer and bone metastases:
In view of the potential impact of zoledronic acid on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine ≥ 400 µmol/l or ≥ 4.5 mg/dl for patients with TIH and ≥ 265 µmol/l or ≥ 3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and only limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance < 30 ml/min), the use of zoledronic acid is not recommended in patients with severe renal impairment.

Patients with osteoporosis or Paget's disease of the bone
The use of zoledronic acid with severe renal impairment (creatinine clearance < 35 ml/min) is contraindicated due to an increased risk of renal failure in this population.

Hepatic insufficiency

Prevention of skeletal related events in patients with advanced malignancies involving bone and treatment of TIH
As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical trials and in the post-marketing setting in patients receiving zoledronic acid.

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

The following risk factors should be considered when evaluating an individual's risk of developing ONJ:

- Potency of the bisphosphonate (higher risk for highly potent compounds), route of administration (higher risk for parenteral administration) and cumulative dose of bisphosphonate.
- Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), smoking.
- Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), radiotherapy to neck and head, corticosteroids.
- History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and poorly fitting dentures.

All patients should be encouraged to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain or swelling, or non-healing of sores or discharge during treatment with zoledronic acid. While on treatment, invasive dental procedures should be performed only after careful consideration and be avoided in close proximity to zoledronic acid administration. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw.

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

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

Additionally, there have been sporadic reports of osteonecrosis of other sites, including the hip and femur, reported predominantly in adult cancer patients treated with zoledronic acid.

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients using zoledronic acid. However, such reports have been infrequent. The time to onset of symptoms varied from one day to several months after starting treatment. Most patients had relief of symptoms after stopping treatment. A subset had recurrence of symptoms when rechallenged with the same medicinal product or another bisphosphonate.

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

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

Hypocalcaemia
Hypocalcaemia has been reported in patients treated with zoledronic acid. Cardiac arrhythmias and neurologic adverse events (including convulsions, hypoaesthesia and tetany) have been reported secondary to cases of severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some instances, the hypocalcaemia may be life-threatening (see section 4.8). Caution is advised when zoledronic acid is administered with medicinal products known to cause hypocalcaemia, as they may have a synergistic effect resulting in severe hypocalcaemia (see section 4.5). Serum calcium should be measured and hypocalcaemia must be corrected before initiating zoledronic acid therapy. Patients should be adequately supplemented with calcium and vitamin D.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid shows no appreciable binding to plasma proteins and does not inhibit human P450 enzymes *in vitro* (see section 5.2), but no formal clinical interaction studies have been performed.

Caution is advised when bisphosphonates are administered with aminoglycosides, calcitonin or loop diuretics since these agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required (see section 4.4).

Caution is indicated when zoledronic acid is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

In multiple myeloma patients, the risk of renal dysfunction may be increased when zoledronic acid is used in combination with thalidomide.

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

Caution is advised when zoledronic acid is administered with anti-angiogenic medicinal products as an increase in the incidence of ONJ has been observed in patients treated concomitantly with these medicinal products.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid must not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.

Breast-feeding
It is not known whether zoledronic acid is excreted into human milk. Zoledronic acid is contraindicated in breast-feeding women (see section 4.3).

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

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness and somnolence, may have influence on the ability to drive or use machines, therefore caution should be exercised with the use of zoledronic acid along with driving and operating of machinery.

4.8 Undesirable effects

The following side effects were observed when zoledronic acid was administered to prevent bone complications in patients with bone metastases or tumour-induced hypercalcaemia:

Summary of the safety profile
Within three days after zoledronic acid administration, an acute phase reaction has commonly been reported, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, rigors and arthritis with subsequent joint swelling; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 1a.

Tabulated list of adverse reactions
The following adverse reactions, listed in table 1a, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with zoledronic acid 4 mg:
Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1a

Blood and lymphatic system disorders	
Common:	Anaemia
Uncommon:	Thrombocytopenia, leukopenia
Rare:	Pancytopenia
Immune system disorders	
Uncommon:	Hypersensitivity reaction
Rare:	Angioneurotic oedema
Psychiatric disorders	
Uncommon:	Anxiety, sleep disturbance
Rare:	Confusion
Nervous system disorders	
Common:	Headache
Uncommon:	Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence
Very rare:	Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)

Eye disorders	
Common:	Conjunctivitis
Uncommon:	Blurred vision, scleritis and orbital inflammation
Rare:	Uveitis
Very rare:	Episcleritis
Cardiac disorders	
Uncommon:	Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse
Rare:	Bradycardia, cardiac arrhythmia (secondary to hypocalcaemia)
Respiratory, thoracic and mediastinal disorders	
Uncommon:	Dyspnoea, cough, bronchoconstriction
Rare:	Interstitial lung disease
Gastrointestinal disorders	
Common:	Nausea, vomiting, decreased appetite
Uncommon:	Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth
Skin and subcutaneous tissue disorders	
Uncommon:	Pruritus, rash (including erythematous and macular rash), increased sweating
Musculoskeletal and connective tissue disorders	
Common:	Bone pain, myalgia, arthralgia, generalised pain
Uncommon:	Muscle spasms, osteonecrosis of the jaw
Very rare:	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction) and other anatomical sites including femur and hip
Renal and urinary disorders	
Common:	Renal impairment
Uncommon:	Acute renal failure, haematuria, proteinuria
Rare:	Acquired Fanconi syndrome
General disorders and administration site conditions	
Common:	Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)
Uncommon:	Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction

Investigations	
Very common:	Hypophosphataemia
Common:	Blood creatinine and blood urea increased, hypocalcaemia
Uncommon:	Hypomagnesaemia, hypokalaemia
Rare:	Hyperkalaemia, hypernatraemia

Description of selected adverse reactions

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

Osteonecrosis of the jaw
Cases of osteonecrosis of the jaw have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid (see section 4.4). Many of these patients were also receiving chemotherapy and corticosteroids and had signs of local infection including osteomyelitis. The majority of the reports refer to cancer patients following tooth extractions or other dental surgeries.

Atrial fibrillation
In one 3-year, randomised, double-blind controlled trial that evaluated the efficacy and safety of zoledronic acid 5 mg once yearly vs. placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidence of atrial fibrillation was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid, including those with zoledronic acid 4 mg every 3-4 weeks in oncology patients. The mechanism behind the increased incidence of atrial fibrillation in this single clinical trial is unknown.

Acute phase reaction
This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea arthralgia and arthritis with subsequent joint swelling. The onset time is $\leq$ 3 days post-zoledronic acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.

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

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with zoledronic acid in the above mentioned indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient evidence to support an association between zoledronic acid therapy, the reported event of hypocalcaemia, and the

secondary development of cardiac arrhythmia. Furthermore, there is evidence of an association between hypocalcaemia and secondary neurological events reported in these cases including; convulsions, hypoaesthesia and tetany (see section 4.4).

The following side effects were observed when zoledronic acid was administered to treat osteoporosis or Paget's disease:

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%), flu-like symptoms (6.7%), arthralgia (4.8%) and headache (5.1%). The incidence of these reactions decreased markedly with subsequent annual doses of zoledronic acid. The majority of these reactions occur within the first three days following 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 as described below.

Tabulated list of adverse reactions

Adverse reactions are ranked under headings of frequency, the most frequent first, using the following convention: Very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1b

Infections and infestations	
Uncommon	Influenza, nasopharyngitis
Blood and lymphatic system disorders	
Uncommon	Anaemia
Immune system disorders	
Not known**	Hypersensitivity reactions including rare cases of bronchospasm, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock
Metabolism and nutrition disorders	
Common	Hypocalcaemia*
Uncommon	Decreased appetite
Rare	Hypophosphataemia
Psychatric disorders	
Uncommon	Insomnia

Nervous system disorders	
Common	Headache, dizziness
Uncommon	Lethargy, paraesthesia, somnolence, tremor, syncope, dysgeusia
Eye disorders	
Common	Ocular hyperaemia
Uncommon	Conjunctivitis, eye pain
Rare	Uveitis, episcleritis, iritis
Not known**	Scleritis and parophthalmia
Ear and labyrinth disorders	
Uncommon	Vertigo
Cardiac disorders	
Common	Atrial fibrillation
Uncommon	Palpitations
Vascular disorders	
Uncommon	Hypertension, flushing
Not known**	Hypotension (some of the patients had underlying risk factors)
Respiratory, thoracic and mediastinal disorders	
Uncommon	Cough, dyspnoea
Gastrointestinal disorders	
Common	Nausea, vomiting, diarrhoea
Uncommon	Dyspepsia, abdominal pain, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis, toothache, gastritis[#]
Skin and subcutaneous tissue disorders	
Uncommon	Rash, hyperhydrosis, pruritus, erythema
Musculoskeletal and connective tissue disorders	
Common	Myalgia, arthralgia, bone pain, back pain, pain in extremity
Uncommon	Neck pain, musculoskeletal stiffness, joint swelling, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, joint stiffness, arthritis, muscular weakness
Rare	Atypical subtrochanteric and diaphyseal femoral fractures† (bisphosphonate class adverse reaction)
Very rare	Osteonecrosis of the external auditory canal (bisphosphonate class adverse reaction)
Not known**	Osteonecrosis of the jaw (see sections 4.4 and 4.8 Class effects)

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

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

Description of selected adverse reactions

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

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

placebo treatment groups over three years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of zoledronic acid-treated patients versus 0.8% of placebo-treated patients.

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

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

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

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

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

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

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.

4.9 Overdose

Clinical experience with acute overdose of zoledronic acid is limited. The administration of doses up to 48 mg of zoledronic acid in error has been reported. Patients who have received doses higher than those recommended (see section 4.2) should be carefully monitored, since renal function impairment (including renal failure) and serum electrolyte (including calcium, phosphorus and magnesium) abnormalities have been observed. In the event of hypocalcaemia, calcium gluconate infusions should be administered as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

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

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

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.

In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone disease. The following properties have been demonstrated in preclinical studies:

- *In vivo:* Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment, making it less conducive to tumour cell growth, anti-angiogenic activity and anti-pain activity.
- *In vitro:* Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

Clinical trial results in the prevention of skeletal related events in patients with advanced malignancies involving bone
The first randomised, double-blind, placebo-controlled study compared zoledronic acid 4 mg to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients. Zoledronic acid 4 mg significantly reduced the proportion of patients experiencing at least one skeletal related event (SRE), delayed the median time to first SRE by > 5 months, and reduced the annual incidence of events per patient - skeletal morbidity rate. Multiple event analysis showed a 36% risk reduction in developing SREs in the zoledronic acid 4 mg group compared with placebo. Patients receiving zoledronic acid 4 mg reported less increase in pain than those receiving placebo, and the difference reached significance at months 3, 9, 21 and 24. Fewer zoledronic acid 4 mg patients suffered pathological fractures. The treatment effects were less pronounced in patients with blastic lesions. Efficacy results are provided in Table 2.

In a second study including solid tumours other than breast or prostate cancer, zoledronic acid 4 mg significantly reduced the proportion of patients with an SRE, delayed the median time to first SRE by >2 months, and reduced the skeletal morbidity rate. Multiple event analysis showed 30.7% risk reduction in developing SREs in the zoledronic acid 4 mg group compared with placebo. Efficacy results are provided in Table 3.

Table 2: Efficacy results (prostate cancer patients receiving hormonal therapy)

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
N	214	208	214	208	214	208
Proportion of patients with SREs (%)	38	49	17	25	26	33
p-value	0.028		0.052		0.119	
Median time to SRE (days)	488	321	NR	NR	NR	640
p-value	0.009		0.020		0.055	
Skeletal morbidity rate	0.77	1.47	0.20	0.45	0.42	0.89
p-value	0.005		0.023		0.060	
Risk reduction of suffering from multiple events** (%)	36	-	NA	NA	NA	NA
p-value	0.002		NA		NA	

* Includes vertebral and non-vertebral fractures

** Accounts for all skeletal events, the total number as well as time to each event during the trial

NR Not Reached

NA Not Applicable

Table 3: Efficacy results (solid tumours other than breast or prostate cancer)

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo	Zoledronic acid 4 mg	Placebo
N	257	250	257	250	257	250
Proportion of patients with SREs (%)	39	48	16	22	29	34
p-value	0.039		0.064		0.173	
Median time to SRE (days)	236	155	NR	NR	424	307
p-value	0.009		0.020		0.079	
Skeletal morbidity rate	1.74	2.71	0.39	0.63	1.24	1.89
p-value	0.012		0.066		0.099	
Risk reduction of suffering from multiple events** (%)	30.7	-	NA	NA	NA	NA
p-value	0.003		NA		NA	

* Includes vertebral and non-vertebral fractures

** Accounts for all skeletal events, the total number as well as time to each event during the trial

NR Not Reached

NA Not Applicable

In a third phase III randomised, double-blind trial, zoledronic acid 4 mg or 90 mg pamidronate every 3 to 4 weeks were compared in patients with multiple myeloma or breast cancer with at least one bone

lesion. The results demonstrated that zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of SREs. The multiple event analysis revealed a significant risk reduction of 16% in patients treated with zoledronic acid 4 mg in comparison with patients receiving pamidronate. Efficacy results are provided in Table 4.

Table 4: Efficacy results (breast cancer and multiple myeloma patients)

	Any SRE (+TIH)		Fractures*		Radiation therapy to bone	
	Zoledronic acid 4 mg	Pam 90 mg	Zoledronic acid 4 mg	Pam 90 mg	Zoledronic acid 4 mg	Pam 90 mg
N	561	555	561	555	561	555
Proportion of patients with SREs (%)	48	52	37	39	19	24
p-value	0.198		0.653		0.037	
Median time to SRE (days)	376	356	NR	714	NR	NR
p-value	0.151		0.672		0.026	
Skeletal morbidity rate	1.04	1.39	0.53	0.60	0.47	0.71
p-value	0.084		0.614		0.015	
Risk reduction of suffering from multiple events** (%)	16	-	NA	NA	NA	NA
p-value	0.030		NA		NA	

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

Zoledronic acid 4 mg was also studied in a double-blind, randomised, placebo-controlled trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of 4 mg zoledronic acid on the skeletal related event (SRE) rate ratio, calculated as the total number of SRE events (excluding hypercalcaemia and adjusted for prior fracture), divided by the total risk period. Patients received either 4 mg zoledronic acid or placebo every four weeks for one year. Patients were evenly distributed between zoledronic acid-treated and placebo groups.

The SRE rate (events/person year) was 0.628 for zoledronic acid and 1.096 for placebo. The proportion of patients with at least one SRE (excluding hypercalcaemia) was 29.8% in the zoledronic acid-treated group versus 49.6% in the placebo group (p=0.003). Median time to onset of the first SRE was not reached in the zoledronic acid-treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid 4 mg reduced the risk of SREs by 41% in a multiple event analysis (risk ratio=0.59, p=0.019) compared with placebo.

In the zoledronic acid-treated group, statistically significant improvement in pain scores (using the Brief Pain Inventory, BPI) was seen at 4 weeks and at every subsequent time point during the study, when compared to placebo. The pain score for zoledronic acid was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score.

Clinical trial results in the treatment of TIH

Clinical studies in tumour-induced hypercalcaemia (TIH) demonstrated that the effect of zoledronic acid is characterised by decreases in serum calcium and urinary calcium excretion. In Phase I dose

finding studies in patients with mild to moderate tumour-induced hypercalcaemia (TIH), effective doses tested were in the range of approximately 1.2–2.5 mg.

To assess the effects of 4 mg zoledronic acid versus pamidronate 90 mg, the results of two pivotal multicentre studies in patients with TIH were combined in a pre-planned analysis. There was faster normalisation of corrected serum calcium at day 4 for zoledronic acid 8 mg and at day 7 for zoledronic acid 4 mg and 8 mg. The following response rates were observed:

Table 5: Proportion of complete responders by day in the combined TIH studies

	Day 4	Day 7	Day 10
Zoledronic acid 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zoledronic acid 8 mg (N=90)	55.6% (p=0.021)*	83.3% (p=0.010)*	86.7% (p=0.015)*
Pamidronate 90 mg (N=99)	33.3%	63.6%	69.7%
*p-values compared to pamidronate			

Median time to normocalcaemia was 4 days. Median time to relapse (re-increase of albumin-corrected serum calcium ≥ 2.9 mmol/l) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg (p-values: 0.001 for 4 mg and 0.007 for 8 mg zoledronic acid). There were no statistically significant differences between the two zoledronic acid doses.

In clinical trials 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg) were retreated with 8 mg zoledronic acid. The response rate in these patients was about 52%. Since those patients were retreated with the 8 mg dose only, there are no data available allowing comparison with the 4 mg dose.

In clinical trials performed in patients with tumour-induced hypercalcaemia (TIH), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

Clinical efficacy in the treatment of post-menopausal osteoporosis (PFT)

The efficacy and safety of zoledronic acid 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-naive. 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 6).

Table 6: 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 7.

Table 7: 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 time points (6, 12, 24 and 36 months). Treatment with zoledronic acid resulted in a 6.7% increase in BMD at the lumbar spine, 6.0% at the total hip, 5.1% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone histology
Bone biopsies were obtained from the iliac crest 1 year after the third annual dose in 152 post-menopausal patients with osteoporosis treated with zoledronic acid (N=82) or placebo (N=70). Histomorphometric analysis showed a 63% reduction in bone turnover. In patients treated with Zoledronic acid, no osteomalacia, marrow fibrosis or woven bone formation was detected.

Tetracycline label was detectable in all but one of 82 biopsies obtained from patients on zoledronic acid. Microcomputed tomography (μCT) analysis demonstrated increased trabecular bone volume and preservation of trabecular bone architecture in patients treated with zoledronic acid compared to placebo.

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

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

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

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

Effect on all clinical fractures
The incidence rates of key clinical fracture variables are presented in Table 8.

Table 8: 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 zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralization defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

Paediatric population

Clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years
The effects of intravenous zoledronic acid in the treatment of paediatric patients (age 1 to 17 years) with severe osteogenesis imperfecta (types I, III and IV) were compared to intravenous pamidronate in one international, multicentre, randomised, open-label study with 74 and 76 patients in each treatment group, respectively. The study treatment period was 12 months preceded by a 4- to 9-week screening period during which vitamin D and elemental calcium supplements were taken for at least 2 weeks. In the clinical programme patients aged 1 to < 3 years received 0.025 mg/kg zoledronic acid (up to a

maximum single dose of 0.35 mg) every 3 months and patients aged 3 to 17 years received 0.05 mg/kg zoledronic acid (up to a maximum single dose of 0.83 mg) every 3 months. An extension study was conducted in order to examine the long-term general and renal safety of once yearly or twice yearly zoledronic acid over the 12-month extension treatment period in children who had completed one year of treatment with either zoledronic acid or pamidronate in the core study.

The primary endpoint of the study was the percent change from baseline in lumbar spine bone mineral density (BMD) after 12 months of treatment. Estimated treatment effects on BMD were similar, but the trial design was not sufficiently robust to establish non-inferior efficacy for zoledronic acid. In particular there was no clear evidence of efficacy on incidence of fracture or on pain. Fracture adverse events of long bones in the lower extremities were reported in approximately 24% (femur) and 14% (tibia) of zoledronic acid-treated patients vs 12% and 5% of pamidronate-treated patients with severe osteogenesis imperfecta, regardless of disease type and causality but overall incidence of fractures was comparable for the zoledronic acid and pamidronate-treated patients: 43% (32/74) vs 41% (31/76). Interpretation of the risk of fracture is confounded by the fact that fractures are common events in patients with severe osteogenesis imperfecta as part of the disease process.

The type of adverse reactions observed in this population was similar to those previously seen in adults with advanced malignancies involving the bone (see section 4.8). The adverse reactions ranked under headings of frequency, are presented in Table 9. The following conventional classification is used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 9: Adverse reactions observed in paediatric patients with severe osteogenesis imperfecta[1]

Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia
Respiratory, thoracic and mediastinal disorders	
Common:	Nasopharyngitis
Gastrointestinal disorders	
Very common:	Vomiting, nausea
Common:	Abdominal pain
Musculoskeletal and connective tissue disorders	
Common:	Pain in extremities, arthralgia, musculoskeletal pain
General disorders and administration site conditions	
Very common:	Pyrexia, fatigue
Common:	Acute phase reaction, pain
Investigations	
Very common:	Hypocalcaemia
Common:	Hypophosphataemia

[1] Adverse events occurring with frequencies < 5% were medically assessed and it was shown that these cases are consistent with the well established safety profile of zoledronic acid (see section 4.8)

In paediatric patients with severe osteogenesis imperfecta, zoledronic acid seems to be associated with more pronounced risks for acute phase reaction, hypocalcaemia and unexplained tachycardia, in comparison to pamidronate, but this difference declined after subsequent infusions.

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

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

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

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

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

5.2 Pharmacokinetic properties

Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients with bone metastases yielded the following pharmacokinetic data, which were found to be dose independent.

After initiating the infusion of zoledronic acid, the plasma concentrations of zoledronic acid rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of zoledronic acid on day 28.

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2\alpha}$ 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 zoledronic acid 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 ± 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, and 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.

The interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as seen with other bisphosphonates.

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid.

The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 cancer patients studied. 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.

In an *in vitro* study, zoledronic acid showed low affinity for the cellular components of human blood, with a mean blood to plasma concentration ratio of 0.59 in a concentration range of 30 ng/ml to 5000 ng/ml. The plasma protein binding is low, with the unbound fraction ranging from 60% at 2 ng/ml to 77% at 2000 ng/ml of zoledronic acid.

Paediatric population
Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid pharmacokinetics in children aged 3 to 17 years are similar to those in adults at a similar mg/kg dose level. Age, body weight, gender and creatinine clearance appear to have no effect on zoledronic acid systemic exposure.

5.3 Preclinical safety data

Acute toxicity
The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/kg in rats. 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
Zoledronic acid was teratogenic in the rat at subcutaneous doses ≥ 0.2 mg/kg. Although no teratogenicity or foetotoxicity was observed in the rabbit, maternal toxicity was found. Dystocia was observed at the lowest dose (0.01 mg/kg bodyweight) tested in the rat.

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium citrate
Water for injections

6.2 Incompatibilities

To avoid potential incompatibilities, Zoledro-Denk 4 mg/5 ml is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

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

6.3 Shelf life

Unopened vial: 3 years

Shelf-life after first opening: The product should be used immediately after first opening.

Shelf-life after dilution:
Chemical and physical in-use stability after dilution of Zoledro-Denk 4 mg/5 ml with 0.9% w/v sodium chloride solution and 5% w/v glucose solution has been demonstrated for 48 hours at room temperature (20 - 24°C) or when stored in a refrigerator at 2-8°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 to 8°C. The refrigerated solution should then be equilibrated to room temperature prior to administration.

6.4 Special precautions for storage

Store below 30 °C.
Do not freeze.

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

6.5 Nature and contents of container

Zoledro-Denk 4 mg/5 ml is available in 5 ml colourless, transparent plastic vials (cycloolefine polymer) with fluoro-polymer coated bromobutyl rubber stopper.

Pack size: 1 vial containing 5 ml concentrate for solution for infusion.

6.6 Special precautions for disposal and other handling

Prior to administration, 5.0 ml concentrate from one vial Zoledro-Denk 4 mg/5 ml or the volume of the concentrate withdrawn as required must be further diluted with 100 ml calcium-free infusion solution (0.9% w/v sodium chloride solution or 5% w/v glucose solution).

Additional information on handling of Zoledro-Denk 4 mg/5ml, including guidance on preparation of reduced doses, is provided in section 4.2.

Aseptic techniques must be followed during the preparation of the infusion.
For single use only.

The medicinal product should be inspected visually prior to use. The solution should only be used if it is clear, practically free from particles and if the container is undamaged.

Healthcare professionals are advised not to dispose of unused Zoledro-Denk 4 mg/5 ml via the domestic sewage system.

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

7. MARKETING AUTHORISATION HOLDER

DENK PHARMA GmbH & Co. KG
Prinzregentenstr. 79
81675 München
Germany

8. MARKETING AUTHORISATION NUMBER IN GERMANY

84802.00.00

9. DATE OF FIRST AUTHORISATION IN GERMANY

07.08.2012

10. DATE OF REVISION OF THE TEXT

08/2019

11. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription