SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Zoledronic acid Ennogen 4 mg/5 ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial with 5 ml concentrate contains 4 mg zoledronic acid, corresponding to 4.264mg Zoledronic acid monohydrate.

One ml concentrate contains 0.8 mg Zoledronic acid (as monohydrate).

Excipient(s) with known effect:

This medicinal product contains less than 1 mmol sodium (23 mg) per vial (5 ml), i.e. essentially “sodium free”.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear and colourless solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Posology

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

Adults and older people

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

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

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

Treatment of TIH

Adults and older people

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

Renal impairment

TIH:
Zoledronic acid Ennogen 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 µ mol/l or > 4.5 mg/dl were excluded. No dose adjustment is necessary in TIH patients with serum creatinine < 400 µ mol/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 Ennogen 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 Ennogen 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 Ennogen, patients with serum creatinine > 265 µ mol/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 Ennogen dose is recommended (see also section 4.4):

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

* 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 Ennogen 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 < 124µ mol/l), an increase of 0.5 mg/dl or 44 µ mol/l;

-For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 µ mol/l), an increase of 1.0 mg/dl or 88 µ mol/l.

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

Paediatric population

The safety and efficacy of zoledronic acid monohydrate in children aged 1 year to 17 years have not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

Method of administration

Intravenous use.

Zoledronic acid Ennogen 4 mg concentrate for solution for infusion, further diluted in 100 ml (see section 6.6), should be given as a single intravenous infusion in no less than 15 minutes.

In patients with mild to moderate renal impairment, reduced Zoledronic acid Ennogen doses are recommended (see section “Posology” above and section 4.4).

Instructions for preparing reduced doses of Zoledronic acid Ennogen Withdraw an

appropriate volume of the concentrate needed, as follows:

- 4.4 ml for 3.5 mg dose
- 4.1 ml for 3.3 mg dose
- 3.8 ml for 3.0 mg dose

For instructions on the dilution of the medicinal product before administration, see section
6.6. The withdrawn amount of concentrate must be further diluted in 100 ml of sterile 0.9%

w/v sodium chloride solution or 5% w/v glucose solution. The dose must be given as a single intravenous infusion over no less than 15 minutes.

Zoledronic acid Ennogen concentrate 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 Ennogen.

8.3 Contraindications

- Hypersensitivity to the active substance, to other bisphosphonates or to any of the excipients listed in section 6.1
- Breast-feeding (see section 4.6)

12.4 Special warnings and precautions for use

General

Patients must be assessed prior to administration of Zoledronic acid Ennogen 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 Ennogen therapy. If hypocalcaemia, hypophosphatemia, 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.

Patients being treated with zoledronic acid monohydrate should not be treated with such products concomitantly or any other bisphosphonate, 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 Ennogen 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 Ennogen has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of Zoledronic acid Ennogen 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 monohydrate 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 monohydrate. Increases in serum creatinine also occur in some patients with chronic administration of Zoledronic acid Ennogen at recommended doses for prevention of skeletal related events, although less frequently.

Patients should have their serum creatinine levels assessed prior to each dose of Zoledronic acid

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

In view of the potential impact of zoledronic acid monohydrate on renal function, the lack of clinical safety data in patients with severe renal impairment (in clinical trials defined as serum creatinine $\geq$ 400 µ mol/l or $\geq$ 4.5 mg/dl for patients with TIH and $\geq$ 265 µ mol/l or $\geq$ 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 Ennogen is not recommended in patients with severe renal impairment.

Hepatic insufficiency
As only limited clinical data are available in patients with severe hepatic insufficiency, no specific recommendations can be given for this patient population.

Osteonecrosis

Osteonecrosis of the jaw
Osteonecrosis of the jaw (ONJ) has been reported uncommonly in clinical trials in patients receiving Zoledronic acid Ennogen. Post-marketing experience and the literature suggest a greater frequency of reports of ONJ based on tumour type (advanced breast cancer, multiple myeloma). A study showed that ONJ was higher in myeloma patients when compared to other cancers (see section 5.1).

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

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

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

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

Musculoskeletal pain
In post-marketing experience, severe and occasionally incapacitating bone, joint, and/or muscle pain have been reported in patients taking Zoledronic acid Ennogen. 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 re challenged with Zoledronic acid Ennogen 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 Ennogen. 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 Ennogen 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 Ennogen therapy. Patients

should be adequately supplemented with calcium and vitamin D.

Sodium

This medicinal product contains less than 1 mmol sodium (23 mg) per vial (5 ml), i.e. essentially "sodium free". However, if a solution of common salt (0.9% w/v sodium chloride solution) is used for the dilution of Zoledronic acid Ennogen prior to administration then the dose of sodium received would be higher.

4.5 Interaction with other medicinal products and other forms of interaction

In clinical studies, Zoledronic acid Ennogen has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions occurring. Zoledronic acid monohydrate 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 Ennogen 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 Ennogen is used in combination with thalidomide.

Caution is advised when Zoledronic acid Ennogen 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 monohydrate in pregnant women. Animal reproduction studies with zoledronic acid monohydrate have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid Ennogen should not be used during pregnancy. Women of child-bearing potential should be advised to avoid becoming pregnant.

Breast-feeding

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

Fertility

Zoledronic acid monohydrate 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 monohydrate 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 Ennogen along with driving and operating of machinery.

16.8 Undesirable effects

Summary of the safety profile

Within three days after Zoledronic acid Ennogen 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 Ennogen in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, atrial fibrillation, anaphylaxis, interstitial lung disease. The frequencies for each of these identified risks are shown in Table 1.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 1, have been accumulated from clinical studies and post-marketing reports following predominantly chronic treatment with 4 mg zoledronic acid monohydrate:

Table 1

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

Blood and lymphatic system disorders
Common: Anaemia

Uncommon: Thrombocytopenia, leukopenia
Rare: Pancytopenia

Immune system disorders
Uncommon: Hypersensitivity reaction
Rare: Angioneurotic oedema

Psychiatric disorders
Uncommon: Anxiety, sleep disturbance
Rare: Confusion

Nervous system disorders
Common: Headache
Uncommon: Dizziness, paraesthesia, dysgeusia, hypoaesthesia, hyperaesthesia, tremor, somnolence Very rare: Convulsions, hypoaesthesia and tetany (secondary to hypocalcaemia)

Eye disorders
Common: Conjunctivitis
Uncommon: Blurred vision, scleritis and orbital 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, diarrhoea
Uncommon: 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
Not Known: Tubulointerstitial nephritis

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 Ennogen has been associated with reports of renal dysfunction. In a pooled analysis of safety data from Zoledronic acid Ennogen registration trials for the prevention of skeletal-related events in patients with advanced malignancies involving bone, the frequency of renal impairment adverse events suspected to be related to Zoledronic acid Ennogen (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 Ennogen 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 monohydrate (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 Ennogen (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 monohydrate 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 monohydrate 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 monohydrate 5 mg and placebo, respectively. The imbalance observed in this trial has not been observed in other trials with zoledronic acid monohydrate, including those with Zoledronic acid Ennogen (zoledronic acid monohydrate) 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 Ennogen 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 (bisphosphonate class adverse reaction).

Hypocalcaemia-related ADRs
Hypocalcaemia is an important identified risk with Zoledronic acid Ennogen in the approved indications. Based on the review of both clinical trial and post-marketing cases, there is sufficient

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

20.9 Overdose

Clinical experience with acute overdose of Zoledronic acid Ennogen is limited. The administration of doses up to 48 mg of zoledronic acid monohydrate 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.

21 PHARMACOLOGICAL PROPERTIES

21.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of bone diseases,

bisphosphonates, ATC code: M05BA08

Mechanism of action
Zoledronic acid monohydrate 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 monohydrate inhibits bone resorption without adversely affecting the formation, mineralisation or mechanical properties of bone.

In addition to being a potent inhibitor of bone resorption, zoledronic acid monohydrate 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 monohydrate 4 mg to placebo for the prevention of skeletal related events (SREs) in prostate cancer patients. Zoledronic acid monohydrate 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 monohydrate 4 mg group compared with placebo. Patients receiving zoledronic acid monohydrate 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 monohydrate 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 monohydrate 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 monohydrate 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 monohydrate 4 mg	Placebo	zoledronic acid mono hydrate 4 mg	Placebo	zoledronic acid monohydrate	Placebo
N	214	208	214	208	214	208
Proportion of patients	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 monohydrate 4 mg	Placebo	zoledronic acid monohydrate 4 mg	Placebo	zoledronic acid monohydrate 4 mg	Placebo
N	257	250	257	250	257	250
Proportion of patients	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	N A	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 monohydrate 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 monohydrate 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 monohydrate 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 monohydrate	Pam 90 mg	zoledronic acid monohydr	Pam 90 mg	zoledronic acid	Pam 90 mg

	4 mg		ate 4 mg		mono hydrate 4 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

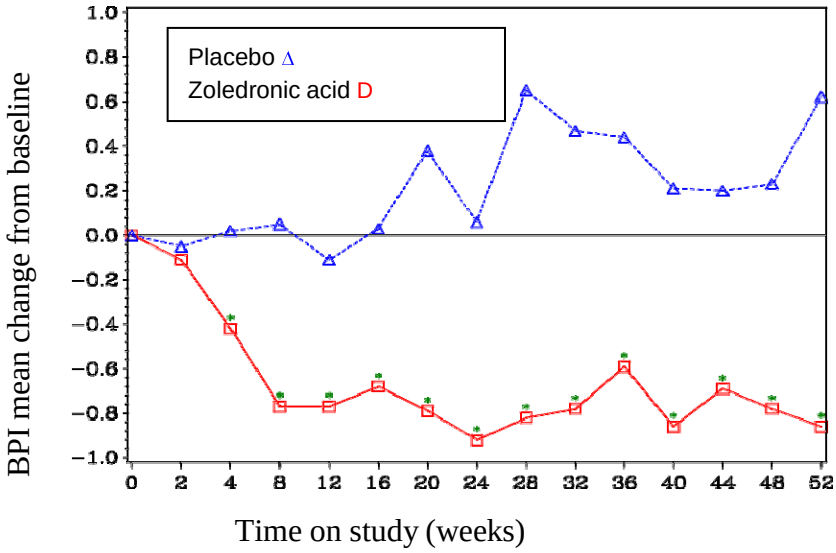
Zoledronic acid monohydrate 4 mg was also studied in a double-blind, randomised, placebo- controlled trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of 4 mg zoledronic acid monohydrate on the skeletal related event (SRE) rate ratio, calculated as the total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

The SRE rate (events/person year) was 0.628 for zoledronic acid monohydrate and 1.096 for placebo. The proportion of patients with at least one SRE (excluding hypercalcaemia) was

29.8% in the zoledronic acid monohydrate -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 monohydrate -treated arm at the end of the study and was significantly prolonged compared to placebo (p=0.007). Zoledronic acid monohydrate 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 monohydrate-treated group, statistically significant improvement in pain scores (using the Brief Pain Inventory, BPI) was seen at 4 weeks and at every subsequent time point during the study, when compared to placebo (Figure 1). The pain score for zoledronic acid monohydrate was consistently below baseline and pain reduction was accompanied by a trend in reduced analgesics score.

Figure 1: Mean changes from baseline in BPI scores. Statistically significant differences are marked (*p<0.05) for between treatment comparisons (4 mg zoledronic acid monohydrate vs placebo)



CZOL446EUS122/SWOG study

The primary objective of this observational study was to estimate the cumulative incidence of osteonecrosis of the jaw (ONJ) at 3 years in cancer patients with bone metastasis receiving zoledronic acid. The osteoclast inhibition therapy, other cancer therapy, and dental care was performed as clinically indicated in order to best represent academic and community-based care. A baseline dental examination was recommended but was not mandatory.

Among the 3491 evaluable patients, 87 cases of ONJ diagnosis were confirmed. The overall estimated cumulative incidence of confirmed ONJ at 3 years was 2.8% (95% CI: 2.3-3.5%). The rates were 0.8% at year 1 and 2.0% at year 2. Rates of 3-year confirmed ONJ were highest in myeloma patients (4.3%) and lowest in breast cancer patients (2.4%). Cases of confirmed ONJ were statistically significantly higher in patients with multiple myeloma (p=0.03) than other cancers combined.

Clinical trial results in the treatment of TIH

Clinical studies in tumour-induced hypercalcaemia (TIH) demonstrated that the effect of zoledronic acid monohydrate 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 monohydrate versus pamidronate 90 mg, the results of two pivotal multicentre studies in patients with TIH were combined in a pre-planned analysis. There was faster normalisation of corrected serum calcium at day 4 for 8 mg zoledronic acid monohydrate and at day 7 for 4 mg and 8 mg zoledronic acid monohydrate. 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 monohydrate 4 mg (N=86)	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*
Zoledronic acid monohydrate 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 monohydrate 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 monohydrate). There were no statistically significant differences between the two zoledronic acid monohydrate doses.

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

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

Paediatric population

Clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years

The effects of intravenous zoledronic acid monohydrate 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 monohydrate (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 monohydrate (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 monohydrate over the 12-month extension treatment period in children who had completed one year of treatment with either zoledronic acid monohydrate 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 monohydrate. 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 monohydrate -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 monohydrate and pamidronate-treated patients: 43% (32/74) vs 41% (31/76). Interpretation of the risk of fracture is confounded by the fact that fractures are common events in patients with severe osteogenesis imperfecta as part of the disease process.

The type of adverse reactions observed in this population were similar to those previously seen in adults with advanced malignancies involving the bone (see section 4.8). The adverse reactions ranked under headings of frequency, are presented in Table 6. The following conventional classification is used: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 6: Adverse reactions observed in paediatric patients with severe osteogenesis imperfecta[1]

Nervous system disorders	
Common:	Headache
Cardiac disorders	
Common:	Tachycardia
Respiratory, thoracic and mediastinal disorders	
Common:	Nasopharyngitis
Gastrointestinal disorders	
Very common: Common:	Vomiting, nausea Abdominal pain
Musculoskeletal and connective tissue disorders	
Common:	Pain in extremities, arthralgia, musculoskeletal pain
General disorders and administration site conditions	
Very common: Common:	Pyrexia, fatigue Acute phase reaction, pain
Investigations	
Very common: Common:	Hypocalcaemia 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 Ennogen (see section 4.8)

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

The European Medicines Agency has waived the obligation to submit the results of studies with zoledronic acid monohydrate in all subsets of the paediatric population in the treatment of tumour-induced hypercalcaemia and prevention of skeletal-related events in patients with advanced malignancies involving bone (see section 4.2 for information on paediatric use).

22.2 Pharmacokinetic properties

Single and multiple 5- and 15-minute infusions of 2, 4, 8 and 16 mg zoledronic acid monohydrate 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 monohydrate, the plasma concentrations of zoledronic acid monohydrate 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 monohydrate on day 28.

Intravenously administered zoledronic acid monohydrate is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½}$ 0.24 and $t_{½}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½}$ 146 hours. There was no accumulation of zoledronic acid monohydrate in plasma after multiple doses given every 28 days. Zoledronic acid monohydrate is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue.

From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 l/h, independent of dose, and unaffected by gender, age, race, and body weight. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid monohydrate 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 monohydrate was high, as seen with other bisphosphonates.

No pharmacokinetic data for zoledronic acid monohydrate are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid monohydrate 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 monohydrate.

The renal clearance of zoledronic acid monohydrate was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 cancer patients studied. Population analysis showed that for a patient with creatinine clearance of 20 ml/min (severe renal impairment), or 50 ml/min (moderate impairment), the corresponding predicted clearance of zoledronic acid monohydrate would be 37% or 72%, respectively, of that of a patient showing creatinine clearance of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal insufficiency (creatinine clearance < 30 ml/min).

In an in vitro study, zoledronic acid monohydrate 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 monohydrate.

Special populations

Paediatric patients

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that zoledronic acid monohydrate 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 monohydrate systemic exposure.

5.3 Preclinical safety data

Acute toxicity

The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/kg in rats.

Subchronic and chronic toxicity

Zoledronic acid monohydrate was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2–3 days in dogs for up to 52 weeks was also well tolerated.

The most frequent finding in repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

The safety margins relative to renal effects were narrow in the long-term repeat-dose parenteral animal studies but the cumulative no adverse event levels (NOAELs) in the single dose (1.6 mg/kg) and multiple dose studies of up to one month (0.06–0.6 mg/kg/day) did not indicate renal effects at doses equivalent to or exceeding the highest intended human therapeutic dose. Longer-term repeat administration at doses bracketing the highest intended human therapeutic dose of zoledronic acid monohydrate produced toxicological effects in other organs, including the gastrointestinal tract, liver, spleen and lungs, and at intravenous injection sites.

Reproduction toxicity

Zoledronic acid monohydrate was teratogenic in the rat at subcutaneous doses $\geq$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 monohydrate was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Sodium citrate

Water for injections

6.2 Incompatibilities

To avoid potential incompatibilities, Zoledronic acid Ennogen 4mg/5ml concentrate for solution for infusion is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

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

6.3 Shelf life

2 years.

After dilution: From a microbiological point of view, the diluted solution for infusion 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. The refrigerated solution should then be equilibrated to room temperature prior to administration.

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted solution for infusion, see section 6.3.

6.5 Nature and contents of container

Vial: 5-ml clear tubular Type 1 glass vial with 20 mm florotech coated butyl rubber stopper and 20 mm Flip off with Aluminium seal.

Unit packs containing 1 or 4 vials.

Multi-packs containing 10 (10 packs of 1) vials.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

Additional information on handling of Zoledronic acid Ennogen, including guidance on preparation of reduced doses, is provided in section 4.2.

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

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

Healthcare professionals are advised not to dispose of unused Zoledronic acid Ennogen 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

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10 DATE OF REVISION OF THE TEXT

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