TECHNICAL SHEET

1. NAME OF THE MEDICINAL

Zoledronic acid Normon 4 mg/100 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One bag contains 4 mg zoledronic acid, equivalent to 4.26 mg zoledronic acid monohydrate.This medicine contains 1.7-2.6 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Transparent and colorless solution.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

ÿ Prevention of skeletal-related events (pathological fractures, spinal cord compression, radiation or bone surgery, or tumor-induced hypercalcemia) in adult patients with advanced malignancies involving bone.

ÿ Treatment of adult patients with tumor-induced hypercalcemia (TIH).

4.2. Dosage and method of administration

Zoledronic Acid Normon should only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates. Patients treated withZoledronic Acid Normon should be provided with the package leaflet and patient reminder card.

Posology

Prevention of skeletal-related events in patients with advanced neoplasms involving bone.

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

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

The decision to treat patients with bone metastases for the prevention of skeletal-related events should take into account that the onset of treatment effect appears at 2-3 months.

Treatment of HIT

Adults and elderly patients

The recommended dose in hypercalcemia (albumin-corrected serum calcium concentration ÿ12.0 mg/dL or 3.0 mmol/L) is a single dose of 4 mg zoledronic acid.

Kidney failure

HIT:

In patients with HIT who also have severe renal impairment, treatment with zoledronic acid should be considered only after assessment of the risks and benefits of treatment. In clinical trials, patients with serum creatinine > 400 ÿmol/L or
> 4.5 mg/dL were excluded. No dose adjustment is required in patients with HIT with a serum creatinine < 400 ÿmol/Lor < 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 use in patients with severe renalimpairment, defined for this population as CLcr < 30 mL/min, prior to initiation of treatment. In clinical trials with zoledronic acid, patients with serum creatinine > 265 ÿmol/L or > 3.0 mg/dL were excluded.

For patients with normal renal function (defined as CLcr > 60 ml/min), zoledronic acid 4 mg/100 ml solution for infusioncan be administered directly without any additional preparation. In patients with bone metastases who had mild to moderate renal impairment, defined for this population as CLcr 30–60 ml/min, reduced doses of zoledronic acid are recommended prior to initiation of treatment (see also section 4.4).

Baseline creatinine clearance (ml/min)	**Recommended dosage of Zoledronic AcidNormon**
> 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 a target AUC of 0.66 (mg•hr/l) (CLcr = 75 ml/min). In patients with renalimpairment, reduced doses are expected to achieve the same AUC as that observed in patients with creatinine clearance of 75 ml/min.

Once treatment is initiated, serum creatinine should be measured before each dose of zoledronic acid and treatment should bediscontinued if renal function has deteriorated. In clinical trials, renal impairment was defined as follows:

- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 ÿmol/l), an increase of 0.5 mg/dl or 44 ÿmol/l;
- For patients with abnormal baseline creatinine (>1.4 mg/dl or >124 ÿmol/l), an increase of 1.0 mg/dl or 88 ÿmol/l.

In clinical trials, treatment with zoledronic acid was only restarted when the creatinine level returned to within 10% of baseline (see section 4.4). Treatment with zoledronic acid should be resumed at the same dose as before treatment discontinuation.

Pediatric population
The safety and efficacy of zoledronic acid in children aged 1 to 17 years have not been established. Currentlyavailable data are described in section 5.1, however no recommendation on a posology can be made.

Method of administration

Intravenous route.

This medicine should be administered as a single intravenous infusion over at least 15 minutes.

In patients with normal renal function, defined as CLcr > 60 ml/min, zoledronic acid 4 mg/100 ml solution for infusion should not bediluted.
In patients with mild to moderate renal impairment, reduced doses of zoledronic acid are recommended (see section "Posology"above and section 4.4).

To prepare reduced doses for patients with a baseline CLcr ÿ 60 ml/min, refer to Table 1 below. Withdraw the indicated volume ofZoledronic Acid Normon solution from the bag prior to administration.

Table 1: Preparation of reduced doses of Zoledronic Acid Normon 4 mg/100 ml solution for infusion

Baseline creatinine clearance (ml/min)	**Extract the following amount of Acid Zoledronic acid Normon solution for infusion (ml)**	**Adjusted dose (mg of zoledronic acid in 100 ml)**
50-60	12.0	3.5
40-49	18.0	3.3
30-39	25.0	3.0

Zoledronic Acid Normon must not be mixed with other infusion solutions and should be administered as a single intravenous solution in a separate infusion line.

Patients should stay well hydrated before and after administration of the medication.

4.3. Contraindications

- ÿ Hypersensitivity to the active ingredient, to other bisphosphonates, or to any of the excipients included in section 6.1.
- ÿ Breast-feeding (see section 4.6)

4.4. Special warnings and precautions for use

General

Patients should be assessed prior to administration of the drug to ensure that they are adequately hydrated.

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

Common metabolic parameters related to hypercalcaemia, such as serum calcium, phosphate and magnesium concentrations, should be closely monitored after initiation of zoledronic acid therapy. Additional short-term treatment may be necessary if hypocalcaemia, hypophosphatemia or hypomagnesaemia occurs. Patients with untreated hypercalcaemia usually have some degree of renal impairment, therefore careful monitoring of renal function should be considered.

Patients being treated with zoledronic acid should not be treated with any medicinal product containing zoledronic acid or another bisphosphonate concomitantly, since the combined effects of these agents are unknown.

Kidney failure

Patients with HIT and evidence of impaired renal function should be appropriately evaluated, taking into consideration 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 take into consideration 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 risk of deterioration of renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid and other bisphosphonates and also the use of other nephrotoxic drugs.
Although the risk is reduced with a dose of 4 mg zoledronic acid administered over 15 minutes, deterioration of renal function may still occur. Cases of deterioration of renal function with progression to renal failure and dialysis have been reported following administration of the initial dose or a single dose of 4 mg zoledronic acid. Increases in serum creatinine have also occurred in some patients on chronic administration of zoledronic acid at the 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.
When initiating treatment in patients with bone metastases and mild to moderate renal impairment, lower doses of zoledronic acid are recommended. In patients who show evidence of renal impairment during treatment, zoledronic acid should be discontinued.
Treatment should only be resumed when serum creatinine returns to within 10% of baseline.
Treatment with Zoledronic Acid Normon should be resumed at the same dose as before treatment was discontinued.

In view of the potential impact of zoledronic acid on renal function, the absence of clinical safety data in patients with severe renal impairment (defined in clinical trials as serum creatinine ÿ400 ÿmol/l or ÿ4.5 mg/dl for patients with HIT and ÿ265 ÿmol/l or ÿ3.0 mg/dl for patients with cancer and bone metastases, respectively) at baseline and the limited pharmacokinetic data in patients with severe renal impairment at baseline (creatinine clearance <30 ml/min), use of Zoledronic Acid Normon in patients with severe renal impairment is not recommended.

Liver failure

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

Osteonecrosis

Osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) has been observed uncommonly in clinical trials. Post-marketing experience and literature suggest a higher frequency of ONJ reports depending on tumour type (advanced breast cancer, multiple myeloma). One study showed that ONJ was higher in patients with myeloma compared to other cancers (see section 5.1).

Initiation of treatment or a new course of treatment should be delayed in patients with open, unhealed soft tissue lesions in the mouth except in situations involving a medical emergency.

A dental examination with appropriate preventive dentistry and an individual risk-benefit assessment is recommended before treatment with bisphosphonates in patients with concomitant risk factors.

The following risk factors should be considered when assessing the individual risk of developing ONJ: •Potency of the bisphosphonate (higher risk for more potent compounds), route of administration (higher risk for parenteral administration) and cumulative bisphosphonate dose. • Cancer, co-morbid conditions (e.g. anaemia, coagulopathies, infection), patient smoker •Concomitant therapies: chemotherapy, angiogenesis inhibitors (see section 4.5), head and neck radiotherapy, corticosteroids
• History of dental disease, poor oral hygiene, periodontal disease, invasive dental procedures (e.g. tooth extractions) and ill-fitting dentures.

All patients should be advised to maintain good oral hygiene, undergo regular dental check-ups, routine dental check-ups and to promptly report any oral symptoms such as tooth mobility, pain or swelling, or poor healing of ulcers or discharge during treatment with Zoledronic Acid Normon. During treatment, invasive dental procedures should be performed only after careful consideration and should be avoided in close proximity to administration of zoledronic acid.

Dental surgery may aggravate the condition in patients who develop osteonecrosis of the jaw duringbisphosphonate therapy. There are no data available to indicate whether discontinuation of bisphosphonate therapy reduces the risk of osteonecrosis of the jaw in patients requiring dental procedures.

The management plan for patients who develop ONJ should be established in close collaboration between the physician and a dentist or oral surgeon with experience in ONJ.

Whenever possible, temporary discontinuation of zoledronic acid therapy should be considered until thissituation resolves and contributing risk factors are mitigated.

Osteonecrosis of other anatomical locations

Cases of osteonecrosis of the external auditory canal have been reported with the use of bisphosphonates, mainly in association with long-term treatment. Possible risk factors for osteonecrosis of the external auditory canal include steroid use and chemotherapy;local risk factors such as infection or trauma also exist. The possibility of osteonecrosis of the external auditory canal should be considered in patients receiving bisphosphonates who have auditory symptoms such as chronic ear infections.

In addition, there have been sporadic reports of osteonecrosis at other sites, including the hip and femur,reported primarily in adult cancer patients treated with Acidophilus.
Zoledronic acid Normon.

Musculoskeletal pain

In post-marketing experience, cases of severe and occasionally disabling bone, joint and muscle pain have been reported in patients taking zoledronic acid. However, these reports have been rare. The time to onset ofsymptoms ranged from one day to several months after initiation of treatment. Most patients improved when treatment was discontinued. A subset experienced recurrence of symptoms when zoledronic acid or another bisphosphonate was restarted.

Atypical fractures of the femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in association with bisphosphonatetherapy, mainly in patients on long-term treatment for osteoporosis.

These short transverse or oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar crest. These fractures occur after minimal or no trauma and somepatients have thigh or groin pain, often associated with imaging characteristics of stress fractures, weeks to weeks.

months before complete femoral fracture occurs. Fractures are usually bilateral; therefore, the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. A poor rate of union of these fractures has also been reported. Discontinuation of bisphosphonate therapy should be considered, on an individualized benefit/risk basis, inpatients with suspected atypical femoral fracture pending evaluation.

During bisphosphonate therapy, patients should be advised to report any thigh, hip or groin pain. Any patient presenting with suchsymptoms should be evaluated for an incomplete femur fracture.

Hypocalcemia
Hypocalcaemia has been reported in patients treated with zoledronic acid. Cardiac arrhythmias and neurological adverse reactions(including convulsions, hypoaesthesia and tetany) have been reported secondary to severe hypocalcaemia. Cases of severe hypocalcaemia requiring hospitalisation have been reported. In some cases, hypocalcaemia may be life-threatening (see section 4.8).
Caution is advised when administering zoledronic acid with medicinal products known to cause hypocalcaemia, as they may havea synergistic effect and lead to severe hypocalcaemia (see section 4.5). Prior to initiation of treatment with zoledronic acid, serum calcium levels should be monitored and hypocalcaemia corrected. Patients should receive adequate calcium and vitamin D supplementation.

Warning on excipients:
This medicine contains less than 1 mmol sodium (23 mg) per sachet, that is essentially 'sodium-free'.

4.5. Interaction with other medicinal products and other forms of interaction

In clinical trials, zoledronic acid has been administered concomitantly with commonly used anticancer agents, diuretics, antibiotics and analgesics without clinically apparent interactions. *In vitro,* zoledronic acid is not extensively bound to plasma proteins and doesnot inhibit human cytochrome P450 enzymes (see section 5.2), although no formal clinical interaction studies have been performed.

Caution is advised when administering bisphosphonates with aminoglycosides, calcitonin or loop diuretics, since these agents mayexert an additive effect, resulting in lower serum calcium concentrations for longer periods than necessary (see section 4.4).

Caution is advised when using zoledronic acid in combination with other potentially nephrotoxic drugs. Attention should also be paidto the possibility of developing hypomagnesemia during treatment.

In patients with multiple myeloma, the risk of renal dysfunction may be increased when zoledronic acid is

administered in combinationwith thalidomide.

Caution is advised when administering zoledronic acid with antiangiogenic drugs since an increased incidence of ONJ has beenobserved in patients concomitantly treated with these drugs.

4.6. Fertility, pregnancy and lactation

Pregnancy

There are no sufficient data on the use of zoledronic acid in pregnant women.
Reproduction studies in animals with zoledronic acid have shown reproductive toxicity (see section 5.3).
The risk for humans isunknown. This medicine must not be used during pregnancy.

Women of childbearing potential should be advised to avoid becoming pregnant.

Lactation

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

Fertility

Zoledronic acid was studied in rats to assess potential adverse effects on fertility in the parental and F1 generations. This resulted in exaggerated pharmacological effects considered to be related to the product-related inhibition of bone calcium metabolism, resulting in periparturient hypocalcaemia, a bisphosphonate class effect, dystocia and early termination of the study. Therefore, these results preclude a clear effect of zoledronic acid on fertility in humans.

4.7. Effects on ability to drive and use machines

Adverse reactions such as dizziness and drowsiness may have an influence on the ability to drive or use machines, therefore caution should be exercised when using Zoledronic Acid Normon when driving and using machines.

4.8. Adverse reactions

Summary of the safety profile

An acute phase reaction, with symptoms including bone pain, fever, fatigue, arthralgia, myalgia, chills and arthritis with associated joint swelling, has been reported commonly within three days following administration of zoledronic acid; these symptoms usually resolve within a few days (see description of selected adverse reactions).

The following important risks have been identified with zoledronic acid in the approved indications:

Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcemia, atrial fibrillation, anaphylaxis, interstitial lung disease. Frequencies for each of these identified risks are shown in Table 2.

Tabulated list of adverse reactions

The following adverse reactions, listed in Table 2, have been collected from clinical trials and post-marketing reports, mainly following chronic treatment with 4 mg zoledronic acid:

Table 2

Adverse reactions are grouped by frequency, most frequent first, using the following convention: Very common (ÿ1/10), common(ÿ1/100 to <1/10), uncommon (ÿ1/1,000 to <1/100), rare (ÿ1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot beestimated from the available data).

Blood and lymphatic system disorders	Anemia
Frequent:	Thrombocytopenia, leukopenia
Uncommon:	Pancytopenia
Rare:	
Immune system disorders	Hypersensitivity reaction
Uncommon:	Angioneurotic edema
Rare:	

Psychiatric disorders	
Uncommon:	Anxiety, sleep disturbances
Rare:	Confusion
Nervous system disorders	Headache
Frequent:	Dizziness, paresthesia, dysgeusia, hypoesthesia, hyperesthesia, tremor, somnolence.
Uncommon:	Seizures, hypoesthesia and tetany (secondary to hypocalcemia)
Very rare:	
Eye disorders	Conjunctivitis
Frequent:	Blurred vision, scleritis and orbital inflammationUveitis
Uncommon:	Episcleritis
Rare:	
Very rare:	
Cardiac disorders	Hypertension, hypotension, atrial fibrillation, hypotensioncausing syncope or circulatory collapse
Uncommon:	
Rare:	Bradycardia, cardiac arrhythmias (secondary to hypocalcemia)
Respiratory, thoracic and mediastinal disorders	Dyspnea, cough, bronchoconstriction
Uncommon:	
Rare:	Interstitial lung disease
Gastrointestinal disorders	Nausea, vomiting, decreased appetite
Frequent:	Diarrhea, constipation, abdominal pain, dyspepsia, stomatitis,dry mouth
Uncommon:	
Skin and subcutaneous tissue disorders	Pruritus, rash (including erythematous and macular rash),increased sweating *Musculoskeletal and*
Uncommon:	
connective tissue disorders	Bone pain, myalgia, arthralgia, generalized pain Common: Muscle spasms, osteonecrosis of the jaw
Uncommon:	Osteonecrosis of the external auditory canal (class effect of thebisphosphonate group) and other anatomical sites including femur and hip.
Very rare:	
Kidney and urinary disorders	Frequent: Uncommon:Rare:

	failure, hematuria, proteinuriaAcquired
Kidney failure	Fanconi syndrome
A c u t e	
r e n a l	
General disorders and administration site conditions	
Common:	Fever, flu-like syndrome (including fatigue, chills, malaise and hot flushes)
Uncommon:	Asthenia, peripheral edema, injection site reactions (includingpain, irritation, swelling, induration), chest pain, weight gain, anaphylactic reaction/shock, urticaria
Rare:	Arthritis and joint swelling as a symptom of acute phase reaction
Additional explorations	

Very common: Frequent: Uncommon :Rare:	Hypophosphatemia Increased blood creatinine and urea,hypocalcemia Hypomagnesemia, hypokalemiaHyperkalemia, hypernatremia

Description of selected adverse reactions

Impaired kidney function

Zoledronic acid has been associated with reports of renal impairment. In a pooled analysis of safety data from registrational trials of zoledronic acid for the prevention of skeletal-related events in patients with advanced malignancies affecting bone, the frequency of adverse events of renal impairment suspected to be related to zoledronic 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%). The potential for deterioration in renal function may be increased by factors including dehydration, pre-existing renal impairment, multiple courses of zoledronic acid or other bisphosphonates, and concomitant use of nephrotoxic medicinal products or shorter infusion times than currently recommended. Cases of renal impairment, progression to renal failure and dialysis have been reportedin patients following 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 medicinalproducts that inhibit bone resorption such as Zoledronic Acid Normon (see section 4.4). Many of these patients were also receiving chemotherapy and corticosteroids and presented signs of local infection including osteomyelitis. Most reports refer to cancer patients following tooth extraction or other dental surgery.

Atrial fibrillation

In a 3-year, double-blind, randomized, controlled clinical trial evaluating the efficacy and safety of zoledronic acid5 mg once annual versus placebo in the treatment of postmenopausal osteoporosis (PMO), the overall incidenceof atrial fibrillation in patients receiving zoledronic acid 5 mg and placebo was 2.5% (96 of 3,862) and 1.9% (75 of 3,852), respectively. The proportion of serious adverse reactions of atrial fibrillation was 1.3% (51 of 3,862) and 0.6% (22 of 3,852) in patients receiving zoledronic acid 5 mg and placebo, respectively. The difference observed in this trial has not been seen in other trials with zoledronic acid, including trials with zoledronic acid 4 mg, administered every 3-4 weeks in cancer patients. The mechanism causing the increased incidence of atrial fibrillation in this particular clinical trial is unknown.

Acute phase reaction

This adverse drug reaction consists of a group of symptoms including fever, myalgia, headache, pain in extremity,nausea, vomiting, diarrhea, arthralgia and arthritis with subsequent joint swelling. The onset time is ÿ 3 days after zoledronic acid infusion, and the reaction is also described with the terms “flu-like” or “post-administration” symptoms.

Atypical fractures of the femur
The following adverse reactions have been reported during post-marketing experience (frequency rare):

Atypical subtrochanteric and diaphyseal femoral fractures (class adverse reaction to bisphosphonates).

Adverse reactions associated with hypocalcemia
Hypocalcemia is an important identified risk in the approved indications for zoledronic acid.
Based on the review of cases from clinical trials and post-marketing experience, there is sufficient evidence to establish an association between treatment with zoledronic acid,

Hypocalcaemia has been reported as an event and the secondary development of cardiac arrhythmias. There is also evidence of the association of neurological events secondary to hypocalcaemia including: convulsions, hypoaesthesia and tetany (see section4.4).

Reporting suspected adverse reactions: It is important to
report suspected adverse reactions to the medicinal product after its authorisation. This allows for continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are encouraged to report any suspected adverse reactionsvia the Spanish Pharmacovigilance System for Medicinal Products for Human Use: https://www.notificaram.es.

4.9. Overdose

Clinical experience with overdose with zoledronic acid is limited. Doses of up to 48 mg
zoledronic acid have been reported to be administered in error. Patients who have received doses
higher than those recommended (see section 4.2)
should be closely monitored since impaired renal function (including renal failure) and abnormal serum electrolyte levels (includingcalcium, phosphorus and magnesium) have been observed. If hypocalcaemia occurs, calcium gluconate infusions should be administered as clinically indicated.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

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

Mechanism of action

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

Pharmacodynamic effects

The selective bone action of bisphosphonates is based on their high affinity for mineralized bone, but the precise molecular mechanism leading to the inhibition of osteoclastic activity remains unclear. In ~~long-term animal studies, z~~oledronic acid inhibitsbone resorption without impairing bone formation, mineralization or mechanical properties.

In addition to being a highly potent inhibitor of bone resorption, zoledronic acid also possesses several

antitumor properties thatmay contribute to its overall efficacy in the treatment of bone metastases. The following properties have been demonstrated in preclinical trials:
- *In vivo:* Inhibition of osteoclastic bone resorption, which alters the bone marrow microenvironment making it less favorable totumor cell growth, antiangiogenic activity and analgesic activity.

- *In vitro:* Inhibition of osteoblastic proliferation, direct cytostatic and proapoptotic activity on tumor cells, synergistic cytostatic effectwith other anticancer drugs, anti-adhesive/invasive activity.

Clinical efficacy and safety

Results of clinical trials in the prevention of skeletal-related events in patients with advanced malignancies with bone involvement

The first randomized, double-blind, placebo-controlled study compared 4 mg zoledronic acid with placebo for the prevention of skeletal-related events (SREs) in patients with prostate cancer. Administration of 4 mg zoledronic acid significantly decreased theproportion of

patients who experienced at least one skeletal-related event (SRE), delayed the median time to first SRE by more than 5 monthsand reduced the annual incidence of events per patient – Skeletal morbidity rate. Multiple event analysis showed a 36% risk reduction in the development of SRE in the 4 mg zoledronic acidgroup compared with placebo. Patients receiving 4 mg zoledronic acid had a smaller increase in pain than those receiving placebo,with significant differences at months 3, 9, 21, and 24. Fewer patients treated with 4 mg zoledronic acid had pathological fractures. Treatment effects were less pronounced in patients with blast lesions. Efficacy results are shown in Table 3.

In a second study, which included solid tumors other than breast and prostate cancer, 4 mg of zoledronic acid significantly reducedthe proportion of patients with an SRE, delayed the median time to first SRE by more than 2 months, and reduced the rate of skeletal morbidity.
Multiple event analysis showed a 30.7% risk reduction in the development of SRE in the 4 mg zoledronic acid group compared withplacebo. Efficacy results are shown in Table 4.

Table 3: Efficacy results (prostate cancer patients receiving hormone therapy)

	Any ERE (+HIT)		Fractures*		Radiotherapy 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 ERE (%)	38	49	17	25	26	33
p-value	0.028		0.052		0.119	
Median time until ERE (days)	488	321	NA	NA	NA	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	
Reducing the risk of suffering multiple events** (%)	36	-	NAp	NAp	NAp	NAp
p-value	0.002		NAp		NAp	

* Includes vertebral and non-vertebral fractures

** Takes into account all skeletal events, the total number as well as the time until each event during the trial

NA Not

Achieved NAp

Not applicable

Table 4: Efficacy results (solid tumors other than breast or prostate cancer)

	Any ERE (+HIT)		Fractures*		Radiotherapy 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 ERE (%)	39	48	16	22	29	34
p-value	0.039		0.064		0.173	
Median time to ERE (days)	236	155	NA	NA	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	
Reducing the risk of suffering multiple** events (%)	30.7	-	NAp	NAp	NAp	NAp
p-value	0.003		NAp		NAp	

* Includes vertebral and non-vertebral fractures

** Takes into account all skeletal events, the total number as well as the time until each event during the trial

NA Not Achieved NAp Not applicable

In a third randomized, double-blind phase III trial, zoledronic acid 4 mg was compared with pamidronate 90 mg every 3 to 4 weeks in patients with multiple myeloma or breast cancer with at least one bone lesion. Results demonstrated that zoledronic acid 4 mg showed comparable efficacy to pamidronate 90 mg in preventing SREs. Multiple event analysis revealed a significant risk reductionof 16% in patients treated with zoledronic acid 4 mg compared with patients receiving pamidronate. Efficacy results are shown in Table 5.

Table 5: Efficacy results (patients with breast cancer or multiple myeloma)

	Some ERE (+HIT)		Fractures*		Radiotherapy 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 ERE (%)	48	52	37	39	19	24
p-value	0.198		0.653		0.037	
Median time to ERE (days)	376	356	NA	714	NA	NA

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	
Reducing the risk of sufferi	16	-	NAp	NAp	NAp	NAp
ng multiple events** (%)						
p-value	0.030		NAp		NAp	

* Includes vertebral and non-vertebral fractures
** Takes into account all skeletal events, the total number as well as the time until each event during the trial

NA Not
Achieved NAp
Not applicable

Zoledronic acid 4 mg was also studied in a randomized, double-blind, placebo-controlled trial in 228 patients with documented bone metastases from breast cancer to evaluate the effect of zoledronic acid 4 mg on the rate of skeletal- related events (SREs), calculated as the total number of SREs (excluding hypercalcemia and adjusted for prior fracture)divided by the total period at risk. Patients received zoledronic acid 4 mg or placebo every four weeks for one year.
Patients were equally divided between the zoledronic acid 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 hypercalcemia) was 29.8% in the zoledronic acid group versus 49.6% in the placebo group (p=0.003). The median time to onset of the first SRE was not reached in the zoledronic acid treatment arm at the end of the trial and was significantly prolonged compared with placebo (p=0.007). In a multiple event analysis, 4 mg zoledronic acid reduced the risk of SREs by 41% (RR=0.59, p=0.019) compared with placebo.

In the zoledronic acid group, a statistically significant improvement in pain scores (using the Brief Pain Inventory (BPI))was observed at 4 weeks and at each subsequent time point during the study compared to placebo (Figure 1). The painscore obtained with zoledronic acid was consistently lower than baseline and the reduction in pain was accompanied bya downward trend in the scores obtained on the analgesic use scale.

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

Study CZOL446EUS122/SWOG

The primary objective of this observational study was to estimate the 3-year cumulative incidence of osteonecrosis of the jaw (ONJ) in patients with cancer with bone metastases who received zoledronic acid. Osteoclast inhibition therapy, other anticancer therapies, and dental care were administered at clinical discretion to best represent community-based and academic-based care. A baseline dental examination was recommended but not required.

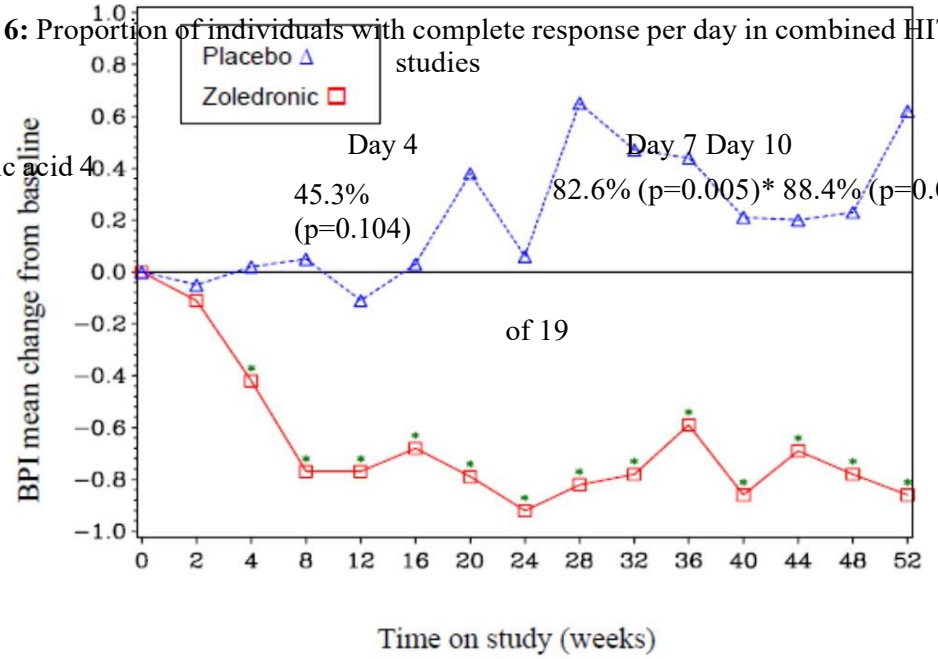
Among 3491 evaluable patients, 87 cases of ONJ diagnosis were confirmed. The estimated overall cumulative incidence of confirmed ONJ at 3 years was 2.8% (95% CI: 2.3-3.5%). Rates were 0.8% inyear 1 and 2. Rates of confirmed ONJ at 3 years were highest in patients with myeloma (4.3%) and lowest in patients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

Results of clinical trials in the treatment of HIT
Clinical trials in tumor-induced hypercalcemia (TIH) demonstrated that zoledronic acid is characterizedby decreasing serum calcium and urinary calcium excretion. In Phase I dose-finding studies in patientswith mild to moderate tumor-induced hypercalcemia (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 90 mg pamidronate, the results of two pivotal multicentre trials in patients with HIT were combined in a pre-planned analysis. There was a more rapidnormalisation of corrected serum calcium concentrations at day 4 for 8 mg zoledronic acid, and at day7 for 4 mg and 8 mg zoledronic acid. The following response proportions were observed:

Table 6: Proportion of individuals with complete response per day in combined HIT studies

	Day 4	Day 7	Day 10
Zoledronic acid 4 mg	45.3% (p=0.104)	82.6% (p=0.005)*	88.4% (p=0.002)*



(N=86)			
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% *p values comparedto pamidronate.		63.6%	69.7 %

The median time to normocalcaemia was 4 days. The median time to relapse (re-emergence of albumin-corrected serum calcium levels ÿ2.9 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 thetwo doses of zoledronic acid.

In clinical trials, 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg)were re-treated with 8 mg of zoledronic acid.
The response rate in these patients was approximately 52%. Since these patients were re-treated with the 8 mg dose only, no dataare available to allow comparison with the 4 mg dose of zoledronic acid.

In clinical trials in patients with tumor-induced hypercalcemia (TIH), the overall safety profile of the three treatment groups (4mg and 8 mg zoledronic acid and 90 mg pamidronate) was similar in type and severity.

Pediatric population

Pediatric population

Results of the clinical trial in the treatment of severe osteogenesis imperfecta in pediatric patients aged 1 to 17 years

The effects of intravenous zoledronic acid in the treatment of pediatric patients (1 to 17 years) with severe osteogenesis imperfecta (types I, III, and IV) were compared with the effects of intravenous pamidronate in an open-label, international, multicenter, randomized trial with 74 and 76 patients in each treatment group, respectively. The study treatment period was 12 months precededby 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 program, 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 trial was conducted to examine the long-term overall and renal safety of once-yearly or twice-yearly zoledronic acid administration during the 12-month extension treatment period in children who had completed one year of treatment with zoledronic acid or pamidronate in the main study.

The primary endpoint of the study was the percentage change in lumbar spine bone mineral density (BMD) from baseline to 12 months after treatment. The estimated treatment effects on BMD were similar, but the trial design was not sufficiently robust to establish non-inferiority of efficacy for zoledronic acid. In particular, no clear evidence of efficacy on the incidence of fractures or pain was observed. Adverse events of fractures of the long bones in the lower extremities were reported in approximately 24% (femur) and 14% (tibia) of patients with severe osteogenesis imperfecta treated with zoledronic acid versus 12% and 5% of patients treated with pamidronate, regardless of disease type and causality but the overall incidence of fractures was comparable for patients treated with zoledronic acid and pamidronate: 43% (32/74) versus 41% (31/76). Interpretation of fracture risk 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 observed in adults with advanced malignancies affecting bone (see section 4.8). Adverse reactions,

grouped by frequency, are presented in Table 7. The following conventional classification is used: very common (ÿ1/10), common(ÿ1/100 to <1/10), uncommon (ÿ1/1,000 to <1/100), rare (ÿ1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 7: Adverse reactions observed in pediatric patients with osteogenesis imperfecta1

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

1 Adverse reactions occurring with frequencies <5% were evaluated medically and these cases were shown to be consistent with the well-established safety profile of zoledronic acid (see section 4.8).

In pediatric patients with severe osteogenesis imperfecta, zoledronic acid appeared to be associated with higher risks of acutephase reaction, hypocalcemia, and unexplained tachycardia compared with pamidronate, but this difference diminished after subsequent infusions.

The European Medicines Agency has exempted the holder of the reference medicine for zoledronic acid from the obligation topresent the results of the trials carried out with this medicine in the different groups of the paediatric population in the treatmentof tumour-induced hypercalcaemia. and the prevention of skeletal-related events in patients with advanced malignancies involving bone (see section 4.2 forinformation on paediatric use).

5.2. Pharmacokinetic properties

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

After initiation of the zoledronic acid infusion, plasma concentrations of zoledronic acid increased rapidly, reaching a 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 before the second zoledronic acid infusion on day 28.

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic elimination from the systemic circulation, with half-lives of t1/2ÿ 0.24 and t1/2ÿ 1.87 hours, followed by a prolonged elimination phase with a terminal elimination half-life of t1/2ÿ 146 hours. After multiple doses every 28 days there was no accumulation of zoledronic acid in plasma. Zoledronic acid is not metabolized.

Zoledronic acid is metabolised and excreted unchanged via the kidneys. During the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is mainly bound to bone tissue. It is released very slowly from bone tissue backinto the systemic circulation and eliminated via the kidneys. Total body clearance is 5.04 ± 2.5 L/h, is independent of dose, and is not affected by sex, age, race or body weight. Increasing the infusion time from 5 to 15 minutes produced a 30% decrease in the concentration of zoledronic acid at the end of infusion, without affecting the area under the plasma concentration-time curve.

Interpatient variability in pharmacokinetic parameters for zoledronic acid was high, as has been seen with other bisphosphonates.

Pharmacokinetic data on zoledronic acid are not available in patients with hypercalcaemia or in patients with hepatic impairment.Zoledronic acid does not inhibit human cytochrome P450 enzymes *in vitro,* does not undergo biotransformation, and in animal studies, < 3% of the administered dose was recovered in faeces, indicating that hepatic function does not play a major role in thepharmacokinetics of zoledronic acid.

Renal clearance of zoledronic acid was significantly positively correlated with creatinine clearance, with renal clearance accountingfor 75 ± 33% of 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 a creatinine clearance of 20 ml/min (severe renal impairment), or 50 ml/ min (moderate renal impairment), the corresponding expected clearance of zoledronic acid would be 37% or 72% respectively, of that of a patient with a creatinine clearance of 84 ml/min. Only limited pharmacokinetic data are available in patients with severe renal impairment (creatinine clearance < 30 ml/min).

In an *in vitro* study , zoledronic acid showed low affinity for cellular components of human blood, with a mean whole blood to plasmaconcentration ratio of 0.59 over a concentration range of 30 ng/ml to 5,000 ng/ml. Plasma protein binding is low, with an unbound fraction ranging from 60% at 2 ng/ml to 77% at 2,000 ng/ml zoledronic acid.

~~Special populations~~

~~*Pediatric patients*~~

Limited pharmacokinetic data in children with severe osteogenesis imperfecta suggest that the pharmacokinetics of zoledronic acidin children aged 3 to 17 years are similar to those in adults at similar mg/kg dose levels. Age, weight, gender and creatinine

clearance do not appear to have any effect on the systemic exposure to zoledronic acid.

5.3. Preclinical safety data

Acute toxicity
The maximum non-lethal single intravenous dose was 10 mg/kg of body weight in mice and 0.6 mg/kg inrats.

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

The most frequent finding in repeated dose studies was an increase in primary spongy substance in the metaphyses of long bonesof growing animals at virtually all doses, reflecting the antiresorptive pharmacological activity of the compound.

Safety margins for renal effects were narrow in long-term animal studies with repeated parenteral doses but cumulative no- adverse-effect levels (NOAELs) from single-dose (1.6 mg/kg) and one-month multiple-dose (0.06–0.6 mg/kg/day) studies did notindicate renal effects at doses equivalent to or in excess of the highest recommended human therapeutic dose. Longer-term administration of repeated doses close to the highest recommended human therapeutic dose of zoledronic acid produced toxicological effects in other organs including the gastrointestinal tract, liver, spleen and lungs and at intravenous injection sites.

~~Reproductive toxicity~~

Zoledronic acid was teratogenic in rats at subcutaneous doses ÿ0.2 mg/kg. No teratogenicity or fetotoxicity was observed in rabbits, but maternal toxicity was observed. Dystocia was observed at the lowest dose tested in rats (0.01 mg/kg body weight).

Mutagenicity and carcinogenic potential

Zoledronic acid was not mutagenic in mutagenicity assays and carcinogenicity assays revealed no evidence of carcinogenicpotential.

6. PHARMACEUTICAL DATA

6.1. List of excipients

Mannitol (E-421)

Sodium citrate

(E-331)Water for

injections

6.2. Incompatibilities

This medicine should not come into contact with other solutions containing calcium, and should not be mixed oradministered intravenously with any other medicine in the same infusion line.

6.3. Shelf Life

Unopened bag: 24 Months

After first opening: From a microbiological point of view, the infusion solution should be used immediately. If not used immediately,storage time and conditions prior to use are the responsibility of the user and should not be longer than 24 hours at 2°C –
8°C under normal conditions. The solution stored in a refrigerator should be allowed to reach

room temperature beforeadministration.

6.4. Special precautions for storage

The unopened bag does not require any special storage conditions. Store in the original packaging.For storage conditions after first opening the medicinal product, see section 6.3.

6.5. Nature and contents of the container

Zoledronic Acid Normon is supplied as a solution in a clear, colourless plastic bag. One bag contains 100 ml of solution.

Zoledronic Acid Normon is supplied in packages containing 1 or 4 bags.

6.6. Special precautions for disposal and other handling

Additional information on the handling of Zoledronic Acid Normon, including instructions for the preparationof reduced doses using the ready-to-use Zoledronic Acid Normon bag, is provided in section 4.2.

Aseptic techniques must be used during preparation of the infusion. For single use only.Only clear solutions free of particles and without discoloration should be used.

Healthcare professionals are advised not to dispose of any unused portion of Zoledronic Acid Normon viahousehold wastewater.

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

7. MARKETING AUTHORIZATION HOLDER

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8.REGISTRATION NUMBER / MARKETING AUTHORISATION NUMBER

082059

9.DATE OF FIRST MARKET AUTHORIZATION / RENEWAL OF REGISTRATION

Date of first Registration / Market Authorization:08th Nov 2016Date of latest renewal: 07th Nov 2026

10. DATE OF TEXT REVISION