Public Assessment Report

Decentralised Procedure

ZOLEDRONIC ACID 4 MG/5 ML CONCENTRATE FOR SOLUTION FOR INFUSION

UK/H/1698/001/DC
UK Licence No: PL 17871/0030

JENSON PHARMACEUTICAL SERVICES LIMITED
LAY SUMMARY

On 14th May 2012, the UK granted Jenson Pharmaceuticals Limited a Marketing Authorisation (licence) for the medicine Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion.

Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion contains the active ingredient zoledronic acid. Zoledronic acid belongs to a group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change.

Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion is used:

- **To prevent bone complications**, e.g. fractures, in adult patients with bone metastases (spread of cancer from primary site to the bone).

- **To reduce the amount of calcium in the blood** in adult patients where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour induced hypercalcaemia (TIH).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion outweigh the risks and a Marketing Authorisation was granted.
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3 Non-clinical aspects
4 Clinical aspects
5 Overall conclusions

Module 6: Steps taken after initial procedure  Not applicable
**Module 1**

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic, Article 10.1</td>
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<td><strong>Drug Substance</strong></td>
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<td><strong>Form</strong></td>
<td>4 mg/5 ml Concentrate for Solution for Infusion</td>
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<td><strong>MA Holder</strong></td>
<td>Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London, N3 3LF United Kingdom</td>
</tr>
<tr>
<td><strong>Reference Member State (RMS)</strong></td>
<td>United Kingdom (UK)</td>
</tr>
<tr>
<td><strong>Concerned Member States (CMS)</strong></td>
<td>Iceland (IS)</td>
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<td><strong>Procedure Number</strong></td>
<td>UK/H/1698/001/DC</td>
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<tr>
<td><strong>End of Procedure</strong></td>
<td>Day 172: 2nd April 2012</td>
</tr>
</tbody>
</table>
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Zoledronic Acid 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 (anhydrous).
One ml concentrate contains zoledronic acid corresponding to 0.8 mg zoledronic acid (anhydrous).
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Concentrate for solution for infusion.
Clear and colourless solution.

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

4.2 Posology and method of administration
Zoledronic acid must only be prescribed and administered to patients by healthcare professionals experienced in the administration of intravenous bisphosphonates.

**Posology**

**Prevention of skeletal related events in patients with advanced malignancies involving bone**
Adults and elderly. The recommended dose in the prevention of skeletal related events in patients with advanced malignancies involving bone is 4 mg zoledronic acid every 3 to 4 weeks.
Patients should also be administered an oral calcium supplement of 500 mg and 400 IU vitamin D daily.
The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2-3 months.

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

**Renal impairment**

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

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

In patients with bone metastases presenting with mild to moderate renal impairment prior to initiation of therapy, which is defined for this population as CLcr 30–60 ml/min, the following zoledronic acid dose is recommended (see also section 4.4):
Baseline creatinine clearance (ml/min) | Zoledronic acid recommended dose*  
--- | ---  
>60 | 4.0 mg zoledronic acid  
50-60 | 3.5 mg* zoledronic acid  
40-49 | 3.3 mg* zoledronic acid  
30-39 | 3.0 mg* zoledronic acid  

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

Following initiation of therapy, serum creatinine should be measured prior to each dose of zoledronic acid and treatment should be withheld if renal function has deteriorated. In the clinical trials, renal deterioration was defined as follows:
- For patients with normal baseline serum creatinine (< 1.4 mg/dl or < 124 μmol/l), an increase of 0.5 mg/dl or 44 μmol/l;
- For patients with abnormal baseline creatinine (> 1.4 mg/dl or > 124 μmol/l), an increase of 1.0 mg/dl or 88 μmol/l.

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

**Paediatric population**
The safety and efficacy of zoledronic acid in children aged 1 year to 17 years have not been established. Currently available data are described in sections 4.4 and 5.1 but no recommendation on a posology can be made.

**Method of administration**
Intravenous use.
Zoledronic acid 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 doses are recommended (see section "Posology" above and section 6.3).

**Instructions for preparing reduced doses of Zoledronic Acid**
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
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 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.

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4.3 **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)

4.4 **Special warnings and precautions for use**
**General**
Patients must be assessed prior to administration of zoledronic acid to ensure that they are adequately hydrated.

Overhydration should be avoided in patients at risk of cardiac failure.
Standard hypercalcaemia-related metabolic parameters, such as serum levels of calcium, phosphate and magnesium, should be carefully monitored after initiating zoledronic acid therapy. If hypocalcaemia,
hypophosphataemia, or hypomagnesaemia occurs, short-term supplemental therapy may be necessary. Untreated hypercalcaemia patients generally have some degree of renal function impairment, therefore careful renal function monitoring should be considered. Zoledronic acid contains the same active substance as found in Aclasta (zoledronic acid). Patients being treated with Zoledronic acid should not be treated with Aclasta or any other bisphosphonate concomitantly, since the combined effects of these agents are unknown.

**Renal insufficiency**
Patients with TIH and evidence of deterioration in renal function should be appropriately evaluated with consideration given as to whether the potential benefit of treatment with zoledronic acid outweighs the possible risk. The decision to treat patients with bone metastases for the prevention of skeletal related events should consider that the onset of treatment effect is 2–3 months.

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

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

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

**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 of the jaw**
Osteonecrosis of the jaw has been reported in patients, predominantly those with cancer, receiving treatment with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures such as tooth extraction. Many had signs of local infection including osteomyelitis.

A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, corticosteroids, poor oral hygiene).

While on treatment, these patients should avoid invasive dental procedures if possible. 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. Clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

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

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

Caution is advised when bisphosphonates are administered with aminoglycosides, since both agents may have an additive effect, resulting in a lower serum calcium level for longer periods than required. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic medicinal products. Attention should also be paid to the possibility of hypomagnesaemia developing during treatment.

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

4.6 Fertility, Pregnancy and lactation
Pregnancy
There are no adequate data on the use of zoledronic acid in pregnant women. Animal reproduction studies with zoledronic acid have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Zoledronic acid should not be used during pregnancy.

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

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

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

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

The following are the important identified risks with zoledronic acid in the approved indications: Renal function impairment, osteonecrosis of the jaw, acute phase reaction, hypocalcaemia, ocular adverse events, atrial fibrillation, anaphylaxis. 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:

**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, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

<table>
<thead>
<tr>
<th>Blood and lymphatic system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common:</strong> Anaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon:</strong> Thrombocytopenia, leukopenia</td>
<td></td>
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<tr>
<td><strong>Rare:</strong> Pancytopenia</td>
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<table>
<thead>
<tr>
<th>Immune system disorders</th>
<th></th>
</tr>
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<tbody>
<tr>
<td><strong>Uncommon:</strong> Hypersensitivity reaction</td>
<td></td>
</tr>
<tr>
<td><strong>Rare:</strong> Angioneurotic oedema</td>
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<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Uncommon:</strong> Anxiety, sleep disturbance</td>
<td></td>
</tr>
<tr>
<td><strong>Rare:</strong> Confusion</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common:</strong> Headache</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon:</strong> Dizziness, paraesthesia, taste disturbance, hypoaesthesia, hyperaesthesia, tremor, somnolence</td>
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</table>

<table>
<thead>
<tr>
<th>Eye disorders</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Common:</strong> Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon:</strong> Blurred vision, scleritis and orbital inflammation</td>
<td></td>
</tr>
<tr>
<td><strong>Very rare:</strong> Uveitis, episcleritis</td>
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<th>Cardiac disorders</th>
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<tbody>
<tr>
<td><strong>Uncommon:</strong> Hypertension, hypotension, atrial fibrillation, hypotension leading to syncope or circulatory collapse</td>
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</tr>
<tr>
<td><strong>Rare:</strong> Bradycardia</td>
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<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
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<tbody>
<tr>
<td><strong>Uncommon:</strong> Dyspnoea, cough, bronchoconstriction</td>
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<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Common:</strong> Nausea, vomiting, anorexia</td>
<td></td>
</tr>
<tr>
<td><strong>Uncommon:</strong> Diarrhoea, constipation, abdominal pain, dyspepsia, stomatitis, dry mouth</td>
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<table>
<thead>
<tr>
<th>Skin and subcutaneous tissue disorders</th>
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</thead>
<tbody>
<tr>
<td><strong>Uncommon:</strong> Pruritus, rash (including erythematous and macular rash), increased sweating</td>
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<table>
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<tr>
<th>Musculoskeletal and connective tissue disorders</th>
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<tbody>
<tr>
<td><strong>Common:</strong> Bone pain, myalgia, arthralgia, generalised pain</td>
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</tr>
<tr>
<td>Uncommon:</td>
<td>Muscle cramps, osteonecrosis of the jaw*</td>
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### Renal and urinary disorders

<table>
<thead>
<tr>
<th>Common:</th>
<th>Renal impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon:</td>
<td>Acute renal failure, haematuria, proteinuria</td>
</tr>
</tbody>
</table>

### General disorders and administration site conditions

<table>
<thead>
<tr>
<th>Common:</th>
<th>Fever, flu-like syndrome (including fatigue, rigors, malaise and flushing)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon:</td>
<td>Asthenia, peripheral oedema, injection site reactions (including pain, irritation, swelling, induration), chest pain, weight increase, anaphylactic reaction/shock, urticaria</td>
</tr>
</tbody>
</table>

### Investigations

<table>
<thead>
<tr>
<th>Very common:</th>
<th>Hypophosphataemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common:</td>
<td>Blood creatinine and blood urea increased, hypocalcaemia</td>
</tr>
<tr>
<td>Uncommon:</td>
<td>Hypomagnesaemia, hypokalaemia</td>
</tr>
<tr>
<td>Rare:</td>
<td>Hyperkalaemia, hypernatraemia</td>
</tr>
</tbody>
</table>

* Based on clinical trials with adjudication of possible cases of osteonecrosis of the jaw. Since these reports are subject to confounding factors, it is not possible to reliably establish a causal relationship to exposure to the medicinal product.

**Description of selected adverse reactions**

### Renal function impairment

Zoledronic acid has been associated with reports of renal dysfunction. Factors that may increase the potential for deterioration in renal function include dehydration, pre-existing renal impairment, multiple cycles of zoledronic acid or other bisphosphonates, as well as concomitant use of nephrotoxic medicinal products or using a shorter infusion time than currently recommended. Renal deterioration, progression to renal failure and dialysis have been reported in patients after the initial dose or a single dose of 4 mg zoledronic acid (see section 4.4).

### Osteonecrosis of the jaw

Cases of osteonecrosis (primarily of the jaws) have been reported, predominantly in cancer patients treated with medicinal products that inhibit bone resorption, such as zoledronic acid. Many of these patients had signs of local infection including osteomyelitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaws has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and comorbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing oral disease). Although causality has not been determined, it is recommended to avoid dental surgery as recovery may be prolonged (see section 4.4).

### Atrial fibrillation

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

### Acute phase reaction

This adverse drug reaction consists of a constellation of symptoms that includes fever, myalgia, headache, extremity pain, nausea, vomiting, diarrhoea and arthralgia. The onset time is ≤ 3 days post-zoledronic acid infusion, and the reaction is also referred to using the terms “flu-like” or “post-dose” symptoms.
Atypical fractures of the femur
During post-marketing experience the following reactions have been reported (frequency rare):
Atypical subtrochanteric and diaphyseal femoral fractures (bisphosphonate class adverse reaction).

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

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Drugs for treatment of bone diseases, bisphosphonates,
ATC code: M05 BA 08.
Zoledronic acid belongs to the class of bisphosphonates and acts primarily on bone. It is an inhibitor of
osteoclastic bone resorption.

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

In addition to being a potent inhibitor of bone resorption, zoledronic acid also possesses several anti-
tumour properties that could contribute to its overall efficacy in the treatment of metastatic bone
disease. The following properties have been demonstrated in preclinical studies: In vivo: Inhibition of
osteoclastic bone resorption, which alters the bone marrow microenvironment making it less conducive
to tumour cell growth, anti-angiogenic activity and anti-pain activity.
In vitro: Inhibition of osteoblast proliferation, direct cytostatic and pro-apoptotic activity on tumour
cells, synergistic cytostatic effect with other anti-cancer drugs, anti-adhesion/invasion activity.

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

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

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

<table>
<thead>
<tr>
<th></th>
<th>Any SRE (+TIH)</th>
<th>Fractures*</th>
<th>Radiation therapy to bone</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Zoledronic acid 4 mg</td>
<td>Placebo</td>
<td>Zoledronic acid 4 mg</td>
</tr>
<tr>
<td>N</td>
<td>214</td>
<td>208</td>
<td>214</td>
</tr>
<tr>
<td>Proportion of patients with SREs (%)</td>
<td>38</td>
<td>49</td>
<td>17</td>
</tr>
<tr>
<td>p-value</td>
<td>0.028</td>
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<td>0.119</td>
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</tr>
<tr>
<td>Median time to SRE (days)</td>
<td>488</td>
<td>321</td>
<td>NR</td>
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<tr>
<td>0.009</td>
<td>0.020</td>
<td>0.055</td>
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</tr>
<tr>
<td>Skeletal morbidity rate</td>
<td>0.77</td>
<td>1.47</td>
<td>0.20</td>
</tr>
<tr>
<td>0.005</td>
<td>0.023</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>Risk reduction of suffering from multiple events** (%)</td>
<td>36</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>0.002</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

* 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)

<table>
<thead>
<tr>
<th>Any SRE (+TIH)</th>
<th>Fractures*</th>
<th>Radiation therapy to bone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4 mg</td>
<td>Placebo</td>
<td>Zoledronic acid 4 mg</td>
</tr>
<tr>
<td>N</td>
<td>257</td>
<td>250</td>
</tr>
<tr>
<td>Proportion of patients with SREs (%)</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>p-value</td>
<td>0.039</td>
<td>0.064</td>
</tr>
<tr>
<td>Median time to SRE (days)</td>
<td>236</td>
<td>155</td>
</tr>
<tr>
<td>p-value</td>
<td>0.009</td>
<td>0.020</td>
</tr>
<tr>
<td>Skeletal morbidity rate</td>
<td>1.74</td>
<td>2.71</td>
</tr>
<tr>
<td>p-value</td>
<td>0.012</td>
<td>0.066</td>
</tr>
<tr>
<td>Risk reduction of suffering from multiple events** (%)</td>
<td>30.7</td>
<td>-</td>
</tr>
<tr>
<td>p-value</td>
<td>0.003</td>
<td>NA</td>
</tr>
</tbody>
</table>

* includes vertebral and non-vertebral fractures ** accounts for all skeletal events, the total number as well as time to each event during the trial NR Not Reached NA Not Applicable
In a third phase III randomised, double-blind trial, zoledronic acid 4 mg or 90 mg pamidronate every 3 to 4 weeks were compared in patients with multiple myeloma or breast cancer with at least one bone lesion. The results demonstrated that zoledronic acid 4 mg showed comparable efficacy to 90 mg pamidronate in the prevention of SREs. The multiple event analysis revealed a significant risk reduction of 16% in patients treated with zoledronic acid 4 mg in comparison with patients receiving pamidronate. Efficacy results are provided in Table 4.

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

<table>
<thead>
<tr>
<th></th>
<th>Any SRE (+THI)</th>
<th>Fractures*</th>
<th>Radiation therapy to bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Zoledronic acid 4 mg</td>
<td>Pamidronate 90 mg</td>
<td>Zoledronic acid 4 mg</td>
</tr>
<tr>
<td>N</td>
<td>561</td>
<td>555</td>
<td>561</td>
</tr>
<tr>
<td>Proportion of patients with SREs (%)</td>
<td>48</td>
<td>52</td>
<td>37</td>
</tr>
<tr>
<td>p-value</td>
<td>0.198</td>
<td>0.653</td>
<td>0.037</td>
</tr>
<tr>
<td>Median time to SRE (days)</td>
<td>376</td>
<td>356</td>
<td>NR</td>
</tr>
<tr>
<td>p-value</td>
<td>0.151</td>
<td>0.672</td>
<td>0.026</td>
</tr>
<tr>
<td>Skeletal morbidity rate</td>
<td>1.04</td>
<td>1.39</td>
<td>0.53</td>
</tr>
<tr>
<td>p-value</td>
<td>0.084</td>
<td>0.614</td>
<td>0.015</td>
</tr>
<tr>
<td>Risk reduction of suffering from multiple events** (%)</td>
<td>16</td>
<td>-</td>
<td>NA</td>
</tr>
<tr>
<td>p-value</td>
<td>0.030</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

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

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

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

In the zoledronic acid-treated group, statistically significant improvement in pain scores (using the Brief Pain Inventory, BPI) was seen at 4 weeks and at every subsequent time point during the study,
when compared to placebo (Figure 1). The pain score for zoledronic acid 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 vs. Placebo) Clinical trial results in the treatment of TIH Clinical studies in tumour-induced hypercalcaemia (TIH) demonstrated that the effect of zoledronic acid is characterised by decreases in serum calcium and urinary calcium excretion. In Phase I dose finding studies in patients with mild to moderate tumour-induced hypercalcaemia (TIH), effective doses tested were in the range of approximately 1.2-2.5 mg.

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

<table>
<thead>
<tr>
<th></th>
<th>Day 4</th>
<th>Day 7</th>
<th>Day 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid 4 mg</td>
<td>45.3% (p=0.104)</td>
<td>82.6% (p=0.005)*</td>
<td>88.4% (p=0.002)*</td>
</tr>
<tr>
<td>(N=86)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid 8 mg</td>
<td>55.6% (p=0.021)*</td>
<td>83.3% (p=0.010)*</td>
<td>86.7% (p=0.015)*</td>
</tr>
<tr>
<td>(N=90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pamidronate 90 mg</td>
<td>33.3%</td>
<td>63.6%</td>
<td>69.7%</td>
</tr>
<tr>
<td>(N=99)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*p-values compared to pamidronate

Median time to normocalcaemia was 4 days. Median time to relapse (re-increase of albumin-corrected serum calcium ≥ 2.9 mmol/l) was 30 to 40 days for patients treated with zoledronic acid versus 17 days for those treated with pamidronate 90 mg (p-values: 0.001 for 4 mg and 0.007 for 8 mg zoledronic acid). There were no statistically significant differences between the two zoledronic acid doses. In clinical trials 69 patients who relapsed or were refractory to initial treatment (zoledronic acid 4 mg, 8 mg or pamidronate 90 mg) were retreated with 8 mg zoledronic acid. The response rate in these patients was about 52%. Since those patients were retreated with the 8 mg dose only, there are no data available allowing comparison with the 4 mg zoledronic acid dose.
In clinical trials performed in patients with tumour-induced hypercalcaemia (TIH), the overall safety profile amongst all three treatment groups (zoledronic acid 4 and 8 mg and pamidronate 90 mg) was similar in types and severity.

Paediatric population Clinical trial results in the treatment of severe osteogenesis imperfecta in paediatric patients aged 1 to 17 years
The effects of intravenous zoledronic acid in the treatment of paediatric patients (age 1 to 17 years) with severe osteogenesis imperfecta (types I, III and IV) were compared to intravenous pamidronate in one international, multicentre, randomised, open-label study with 74 and 76 patients in each treatment group, respectively. The study treatment period was 12 months preceded by a 4- to 9-week screening period during which vitamin D and elemental calcium supplements were taken for at least 2 weeks. In the clinical programme patients aged 1 to < 3 years received 0.025 mg/kg zoledronic acid (up to a maximum single dose of 0.35 mg) every 3 months and patients aged 3 to 17 years received 0.05 mg/kg zoledronic acid (up to a maximum single dose of 0.83 mg) every 3 months. An extension study was conducted in order to examine the long-term general and renal safety of once yearly or twice yearly zoledronic acid over the 12-month extension treatment period in children who had completed one year of treatment with either zoledronic acid or pamidronate in the core study.

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

The type of adverse reactions observed in this population 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>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Headache</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cardiac disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Tachycardia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory, thoracic and mediastinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Nasopharyngitis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Vomiting, nausea</td>
</tr>
<tr>
<td>Common: Abdominal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Musculoskeletal and connective tissue disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common: Pain in extremities, arthralgia, musculoskeletal pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administration site conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Pyrexia, fatigue</td>
</tr>
<tr>
<td>Common: Acute phase reaction, pain</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common: Hypocalcaemia</td>
</tr>
<tr>
<td>Common: Hypophosphataemia</td>
</tr>
</tbody>
</table>
Adverse events occurring with frequencies < 5% were medically assessed and it was shown that these cases are consistent with the well established safety profile of zoledronic acid (see section 4.8).

In paediatric patients with severe osteogenesis imperfecta, zoledronic acid seems to be associated with more pronounced risks for acute phase reaction, hypocalcaemia and unexplained tachycardia, in comparison to pamidronate, but this difference declined after subsequent infusions. The European Medicines Agency has waived the obligation to submit the results of studies with zoledronic acid 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).

5.2 Pharmacokinetic properties

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

After initiating the infusion of zoledronic acid, the plasma concentrations of zoledronic acid rapidly increased, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after 24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak prior to the second infusion of zoledronic acid on day 28. Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2 \alpha} 0.24$ and $t_{1/2 \beta} 1.87$ hours, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2 \gamma} 146$ hours. There was no accumulation of zoledronic acid in plasma after multiple doses given every 28 days. Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hours, 39 ± 16% of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is $5.04 \pm 2.5$ 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 concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

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

No pharmacokinetic data for zoledronic acid are available in patients with hypercalcaemia or in patients with hepatic insufficiency. Zoledronic acid does not inhibit human P450 enzymes in vitro, shows no biotransformation and in animal studies < 3% of the administered dose was recovered in the faeces, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid. The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing 75 ± 33% of the creatinine clearance, which showed a mean of 84 ± 29 ml/min (range 22 to 143 ml/min) in the 64 cancer patients studied. 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 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).

Zoledronic acid shows no affinity for the cellular components of blood and plasma protein binding is low (approximately 56%) and independent of the concentration of zoledronic acid.

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

5.3 Preclinical safety data

Acute toxicity
The highest non-lethal single intravenous dose was 10 mg/kg bodyweight in mice and 0.6 mg/kg in rats.
Subchronic and chronic toxicity
Zoledronic acid 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 produced toxicological effects in other organs, including the gastrointestinal tract, liver, spleen and lungs, and at intravenous injection sites.

Reproduction toxicity
Zoledronic acid 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 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 dihydrate
Water for injection

6.2 Incompatibilities
To avoid potential incompatibilities, zoledronic acid concentrate is to be diluted with 0.9% w/v sodium chloride solution or 5% w/v glucose solution.

Zoledronic acid 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.

Studies with glass bottles, as well as several types of infusion bags and infusion lines made from polyvinylchloride, polyethylene and polypropylene (prefilled with 0.9% w/v sodium chloride solution or 5% w/v glucose solution), showed no incompatibility with zoledronic acid.

6.3 Shelf life
24 months.
Chemical and physical in-use stability has been demonstrated for 24 hours at 2°C-8°C when diluted with 100ml of physiological saline or 5%w/v glucose.

From a microbiological point of view, the diluted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total time between dilution, storage in a refrigerator at 2°C–8°C and end of administration must not exceed 24 hours.

6.4 Special precautions for storage
No special precautions for storage. For storage conditions of the medicinal product after dilution, please see section 6.3.

6.5 Nature and contents of container
Zoledronic acid 4 mg/5 ml concentrate for solution for infusion is supplied as packs containing 1, 4 or 10 vials. Not all pack sizes may be marketed.
Vial: 5 ml plastic vial made of clear, colourless cycloolefine copolymer with bromobutyl rubber stopper and flip-off aluminium seals.

6.6 Special precautions for disposal
Prior to administration, 5 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). If refrigerated, the solution must be allowed to be reach room temperature before administration.

7 MARKETING AUTHORISATION HOLDER
Jenson Pharmaceutical Services Ltd.,
Carradine House,
237 Regents Park Road,
London, N3 3LF, United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)
PL 17871/0030

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
14/05/2012

10 DATE OF REVISION OF THE TEXT
14/05/2012
Module 3
Product Information Leaflet

Package Leaflet: Information for the user

Zoledronic Acid 4 mg/5ml Concentrate for Solution for Infusion (zoledronic acid)

Read all of this leaflet carefully before you are given this medicine

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

In this leaflet:
1. What Zoledronic Acid is and what it is used for
2. Before you are given Zoledronic Acid
3. How Zoledronic Acid is used
4. Possible side effects
5. How to store Zoledronic Acid
6. Further information

1. What Zoledronic Acid is and what it is used for

Zoledronic Acid belongs to the group of substances called bisphosphonates. Zoledronic acid works by attaching itself to the bone and slowing down the rate of bone change. It is used:

- To prevent bone complications, e.g. fractures, in adults with bone metastases (spread of cancer from primary site to the bone).
- To reduce the amount of calcium in the blood in adults where it is too high due to the presence of a tumour. Tumours can accelerate normal bone change in such a way that the release of calcium from bone is increased. This condition is known as tumour-induced hypercalcaemia (TIH).

2. Before you are given Zoledronic Acid

Follow carefully all instructions given to you by your doctor.
Your doctor will carry out blood tests before you start treatment with Zoledronic Acid and will check your response to treatment at regular intervals.

You should not be given Zoledronic Acid:

- if you are breast feeding
- if you are allergic (hypersensitive) to Zoledronic Acid, another bisphosphonate (the group of substances to which zoledronic acid belongs), or any of the other ingredients of Zoledronic Acid.

Before you are given Zoledronic Acid, tell your doctor:

- if you have or have had a kidney problem.
- if you have or have had pain, swelling or numbness of the jaw, a feeling of heaviness in the jaw or loosening of a tooth.
- if you are having dental treatment or are due to undergo dental surgery, tell your dentist that you are being treated with Zoledronic Acid.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. It is especially important that you tell your doctor if you are also taking:

- Aminoglycosides (medicines used to treat severe infections), since the combination of these with bisphosphonates may cause the calcium level in the blood to become too low.

(continued overleaf)
- **Thalidomide** (a medicine used to treat a certain type of blood cancer involving the bone) or any other medicines which may harm your kidneys.

- **Aclasta** (a medicine that also contains zoledronic acid and is used to treat osteoporosis and other non-cancer diseases of the bone), or any other bisphosphonate, since the combined effects of these medicines taken together with Zoledronic Acid are unknown.

**Patients aged 65 years and over**

Zoledronic Acid can be given to people aged 65 years and over. There is no evidence to suggest that any extra precautions are needed.

**Use in children and adolescents**

Zoledronic Acid is not recommended for use in adolescents and children below the age of 18 years.

**Pregnancy and Breast-feeding**

You should not be given Zoledronic Acid if you are pregnant. Tell your doctor if you are or think that you may be pregnant.

You must not be given Zoledronic Acid if you are breast-feeding.

Ask your doctor for advice before taking any medicine while you are pregnant or breast-feeding.

**Driving and using machines**

There have been very rare cases of drowsiness and sleepiness with the use of Zoledronic Acid. You should therefore be careful when driving, using machinery or performing other tasks that need full attention.

---

3. **How Zoledronic Acid is used**

- Zoledronic Acid must only be given by healthcare professionals trained in administering bisphosphonates intravenously, i.e. through a vein.

- Your doctor will recommend that you drink enough water before each treatment to help prevent dehydration.

- Carefully follow all the other instructions given to you by your doctor, nurse or pharmacist.

**How much Zoledronic Acid is given**

- The usual single dose given is 4 mg.

- If you have a kidney problem, your doctor will give you a lower dose depending on the severity of your kidney problem.

**How often Zoledronic Acid is given**

- If you are being treated for the prevention of bone complications due to bone metastases, you will be given one infusion of Zoledronic Acid every three to four weeks.

- If you are being treated to reduce the amount of calcium in your blood, you will normally only be given one infusion of Zoledronic Acid.

**How Zoledronic Acid is given**

- Zoledronic Acid is given as a **drip (infusion) into a vein** which should take at least 15 minutes and should be administered as a single intravenous solution in a separate infusion line.

Patients whose blood calcium levels are not too high will also be prescribed calcium and vitamin D supplements to be taken each day.

**If you are given more Zoledronic Acid than you should be**

If you have received doses higher than those recommended, you must be carefully monitored by your doctor. This is because you may develop serum electrolyte abnormalities (e.g. abnormal levels of calcium, phosphorus and magnesium) and/or changes in kidney function, including severe kidney impairment. If your level of calcium falls too low, you may have to be given supplemental calcium by infusion.
4. Possible side effects

Like all medicines, Zoledronic Acid can cause side effects, although not everybody gets them. The most common ones are usually mild and will probably disappear after a short time.

The frequency of possible side effects listed below is defined using the following convention:
- very common: affects more than 1 user in 10
- common: affects 1 to 10 users in 100
- uncommon: affects 1 to 10 users in 1,000
- rare: affects 1 to 10 users in 10,000
- very rare: affects less than 1 user in 10,000
- not known: frequency cannot be estimated from the available data.

Tell your doctor about any of the following serious side effects straight away:

Common:
- Severe kidney impairment (will normally be determined by your doctor with certain specific blood tests).
- Low level of calcium in the blood.

Uncommon:
- Pain in the mouth, teeth and/or jaw, swelling or sores inside the mouth, numbness or a feeling of heaviness in the jaw, or loosening of a tooth. These could be signs of bone damage in the jaw (osteonecrosis). Tell your doctor and dentist immediately if you experience such symptoms.
- Irregular heart rhythm (atrial fibrillation) has been seen in patients receiving zoledronic acid for postmenopausal osteoporosis. It is currently unclear whether zoledronic acid causes this irregular heart rhythm but you should report it to your doctor if you experience such symptoms after you have received zoledronic acid.
- Severe allergic reaction: shortness of breath, swelling mainly of the face and throat.

Tell your doctor about any of the following side effects as soon as possible:

Very common:
- Low level of phosphate in the blood.

Common:
- Headache and a flu-like syndrome consisting of fever, fatigue, weakness, drowsiness, chills and bone, joint and/or muscle ache. In most cases no specific treatment is required and the symptoms disappear after a short time (couple of hours or days).
- Gastrointestinal reactions such as nausea and vomiting as well as loss of appetite.
- Conjunctivitis.
- Low level of red blood cells (anaemia).

Uncommon:
- Hypersensitivity reactions.
- Low blood pressure.
- Chest pain.
- Skin reactions (redness and swelling) at the infusion site, rash, itching.
- High blood pressure, shortness of breath, dizziness, sleep disturbances, tingling or numbness of the hands or feet, diarrhoea.
- Low counts of white blood cells and blood platelets.
- Low level of magnesium and potassium in the blood. Your doctor will monitor this and take any necessary measures.
- Sleepiness.
- Tearing of the eye, eye sensitivity to light.
- Sudden coldness with fainting, limpness or collapse.
- Difficulty in breathing with wheezing or coughing.
- Urticaria.
Rare:
- Slow heart beat.
- Confusion.
- Unusual fracture of the thigh bone particularly in patients on long-term treatment for osteoporosis may occur rarely. Contact your doctor if you experience pain, weakness or discomfort in your thigh, hip or groin as this may be an early indication of a possible fracture of the thigh bone.

Very rare:
- Painting due to low blood pressure.
- Severe bone, joint and/or muscle pain, occasionally incapacitating.
- Painful redness and/or swelling of the eye.

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor, nurse or pharmacist.

5. How to store Zoledronic Acid

Your doctor, nurse or pharmacist knows how to store Zoledronic Acid properly (see section 6).

6. Further information

What Zoledronic Acid contains
The active substance is Zoledronic Acid 4 mg per 5 ml concentrate. The other ingredients are: mannitol, sodium citrate dihydrate, water for injections.

What Zoledronic Acid looks like and the contents of the pack
Zoledronic Acid is supplied as a liquid concentrate in a vial. One vial contains 4 mg of zoledronic acid. Zoledronic Acid is available in pack sizes of 1, 4 or 10 vials. Not all pack sizes may be marketed.
Information for the healthcare professional

How to prepare and administer Zoledronic Acid
To prepare an infusion solution containing 4 mg zoledronic acid, further dilute the Zoledronic Acid concentrate (5.0 ml) with 100 ml of calcium-free or other divalent cation-free infusion solution. If a lower dose of Zoledronic Acid is required, first withdraw the appropriate volume as indicated below and then dilute it further with 100 ml of infusion solution. To avoid potential incompatibilities, the infusion solution used for dilution must be either 0.9% w/v sodium chloride or 5% w/v glucose solution.

Do not mix Zoledronic Acid concentrate with calcium-containing or other divalent cation containing solutions such as lactated Ringer's solution.

Instructions for preparing reduced doses of Zoledronic Acid:
Withdraw the appropriate volume of the liquid concentrate 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 single use only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used. Aseptic techniques must be followed during the preparation of the infusion.

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.

(continued overleaf)

The solution containing zoledronic acid is given as a single 15-minute intravenous infusion in a separate infusion line. The hydration status of patients must be assessed prior to and following administration of Zoledronic Acid to ensure that they are adequately hydrated.

Studies with several types of infusion lines made from polyvinylchloride, polyethylene and polypropylene showed no incompatibility with Zoledronic Acid.

Since no data are available on the compatibility of Zoledronic Acid with other intravenously administered substances, Zoledronic Acid must not be mixed with other medications/substances and should always be given through a separate infusion line.

How to store Zoledronic Acid
- Keep Zoledronic Acid out of the reach and sight of children
- Do not use Zoledronic Acid after the expiry date stated on the pack.
- The unopened vial does not require any specific storage conditions.
- The diluted Zoledronic Acid infusion solution should be used immediately in order to avoid microbial contamination.
5 ml vial
Read the package leaflet before use.
PL 17871/0030
Zoledronic Acid 4 mg/5 ml
Concentrate for Solution for Infusion
Batch:
EXP:
Module 5
Scientific discussion during initial procedure

1 INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Iceland and the UK considered that the application for Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion could be approved. This prescription only medicine (POM) is indicated as monotherapy for the:

- 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).

This application for Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion is submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, claiming to be a generic medicinal product of Zometa 4 mg Powder and solvent for solution for infusion, centrally authorised in the EEA to Novartis Europharma Limited on 20th March 2001.

Zoledronic acid is a heterocyclic imidazole bisphosphonate that acts primarily on bone and is an inhibitor of osteoclastic bone resorption. It is used to prevent skeletal related events (SRE) in patients with advanced bone malignancies and to treat tumour-induced hypercalcaemia.

No new non-clinical studies were conducted, which is acceptable given that the product contains a widely-used, well-known drug substance. The pharmacology of zoledronic acid is well-established.

No clinical studies have been performed and none are required for this application as the proposed product is an aqueous solution at the point of administration and contains the same concentration of drug substance as the already approved reference product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the drug substance(s) (INN)</td>
<td>Zoledronic acid</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Drugs for treatment of bone diseases, bisphosphonates (M05 BA 08)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength(s)</td>
<td>4 mg/5 ml Concentrate for Solution for Infusion</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/1698/001/DC</td>
</tr>
<tr>
<td>Reference Member State (RMS)</td>
<td>United Kingdom (UK)</td>
</tr>
<tr>
<td>Member States concerned (CMS)</td>
<td>Iceland (IS)</td>
</tr>
<tr>
<td>Marketing Authorisation Number(s)</td>
<td>PL 17871/0030</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Jenson Pharmaceutical Services Limited, Carradine House, 237 Regents Park Road, London, N3 3LF, United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 QUALITY ASPECTS

S. Drug substance

INN/Ph.Eur name: Zoledronic acid

Chemical name: [1-Hydroxy-2-(1H-imidazol-1-yl)ethylidene]-Bisphosphonic acid monohydrate

Structural formula:

\[
\begin{align*}
\text{N} & \quad \text{PO}_2\text{H}_2 \\
\text{O} & \quad \text{N} \quad \text{C}_5\text{H}_{10}\text{N}_2\text{O}_7\text{P}_2 \quad \text{H}_2\text{O}
\end{align*}
\]

Molecular formula: \( C_{5}H_{10}N_{2}O_{7}P_{2} \times H_{2}O \)

Appearance: White or practically white, odourless crystalline powder

Solubility: Soluble in sodium hydroxide solution, slightly soluble in water

Molecular mass: 290.11

The source of zoledronic acid used in this product complies with in-house specifications.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents and these are supported by relevant Certificates of Analysis.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the specification. Batch analysis data are provided and comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines.

Stability studies have been performed with the active substance and no significant changes of the parameters were observed. On the basis of the results, a suitable re-test period could be approved.

P. Drug Product

Other Ingredients

Other ingredients are the pharmaceutical excipients mannitol, sodium citrate dihydrate and water for injection.
All of the excipients comply with the relevant European Pharmacopoeia monographs.

None of the excipients used contain material of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

**Pharmaceutical Development**
The objective of the development programme was to produce a safe, efficacious product containing zoledronic acid that could be considered a generic medicinal product of Zometa 4 mg Powder and solvent for solution for infusion.

The applicant has provided suitable product development information. Valid justification for the use and amount of each excipient has been provided.

**Manufacturing Process**
A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data have been provided and are satisfactory.

**Finished Product Specification**
The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.

**Container-Closure System**
This product is packaged in 5 ml vials made of clear, colourless cyclo olefine copolymer each with a bromobutyl stopper and a flip off aluminium seal.

The product comes in pack sizes of 1, 4 and 10 vials. Not all pack sizes may be marketed.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary packaging complies with the current guidelines.

**Stability of the product**
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 24 months with no special storage instructions.

Once diluted, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. The total time between dilution, storage in a refrigerator at 2 °C – 8 °C and end of administration must not exceed 24 hours. Chemical and physical in-use stability has been demonstrated for 24 hours at 2 °C- 8 °C when diluted with 100 ml of physiological saline or 5 % w/v glucose.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK approved SmPC, PIL and labelling are included in modules 2, 3 and 4 of this report.
User testing results have been submitted for the PIL for this product. The results indicate that the PIL is in accordance with Article 59 of Council Directive 2001/83/EC, as amended and is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**MAA form**
The MAA form is pharmaceutically satisfactory.

**Overall Summary**
The quality overall summary has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

**Conclusion**
It is recommended that a Marketing Authorisation is granted for this application from a quality point of view.
III.2  NON-CLINICAL ASPECTS

The pharmacodynamics, pharmacokinetics and toxicological properties of zoledronic acid are well-known. As this is a widely used, well-known drug substance, the applicant has not provided any additional studies and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Environmental Risk Assessment
The manufacturing, testing and supply of Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion is not known to have any extraordinary effect on the quality of the Environment, therefore an Environmental Risk Assessment was not provided and is not required.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a non-clinical point of view.
III.3 CLINICAL ASPECTS

This assessment report represents an evaluation of the key elements of the information provided by the company in the dossier.

Clinical Pharmacology
The applicant’s product is a generic product of the reference product; both products contain the same quantitative and qualitative composition of the drug substance. As per the Note for Guidance on the Investigation of Bioavailability and Bioequivalence CPMP/EWP/QWP/1401/98 Rev 1, no new pharmacokinetic or pharmacodynamic data were submitted with this generic application and none were required. The test and reference products are equivalent at the point of administration; therefore a human bioavailability study is not required for this application.

Efficacy
No new efficacy data were submitted with this application and none were required.

Safety
No new safety data were submitted with this application and none were required.

The Pharmacovigilance System and Risk Management Plan
The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Following the outcome of the Article 31 referral on bisphosphonates and atypical femoral fracture, it has been agreed recently by the Pharmacovigilance Working Party (PhVWP) and the Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMD(h)) that a risk management plan will be required for all bisphosphonate products. A Letter of Commitment has been provided agreeing to (1) adopt the abbreviated core RMP for bisphosphonates and atypical femoral fractures; and (2) to adhere to the planned pharmacovigilance activities outlined in the abbreviated core RMP. This is acceptable.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product.

Clinical Overview
The clinical overview has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

MAA Form
The MAA form is clinically satisfactory.

Conclusion
It is recommended that a Marketing Authorisation is granted for this application from a clinical point of view.
IV OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

QUALITY
The important quality characteristics of Zoledronic Acid 4 mg/5 ml Concentrate for Solution for Infusion are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Given the composition of the product and its intended route of administration, no bioequivalence studies have been performed and none are required for this application.

No new or unexpected safety concerns arose from this application.

The SmPC, PIL and labelling are satisfactory and consistent with those for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with zoledronic acid is considered to have demonstrated the therapeutic value of the compound. The risk-benefit ratio is therefore considered to be positive.
## Module 5

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

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<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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