Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Zoledronic Acid

Proprietary Product Name: Aclasta/Osteovan

Sponsor: Novartis Australia Pty Ltd

**August 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

### Submission Details

| | |
|---|---|
| *Type of Submission* | Major Variation |
| *Decision:* | Approved |
| *Date of Decision:* | 29 July 2011 |
| | |
| *Active ingredient(s):* | Zoledronic acid |
| *Product Name(s):* | Aclasta/Osteovan |
| *Sponsor's Name and Address:* | Novartis Australia Pty Ltd, PO Box 101, North Ryde, NSW 1670 |
| *Dose form(s):* | Solution for Injection |
| *Strength(s):* | 5 mg/100 mL |
| *Container(s):* | Vial |
| *Pack size(s):* | One vial. Also Multipacks of 3 or 6 vials. |
| *Approved Therapeutic use:* | Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures.<br>Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fracture.<br>To increase bone mineral density in men with osteoporosis.<br>To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use.<br>To prevent glucocorticoid-induced bone mineral density loss.<br>Treatment of Paget's disease of bone. |
| *Route(s) of administration:* | Intravenous (IV) |
| *Dosage:* | Single IV infusion of 5 mg Aclasta administered once a year.[a] |
| *ARTG Number (s)* | 134665 and 13466 |

All published references referred to in this AusPAR are listed under the heading *References* at the end of the document.

## Product Background

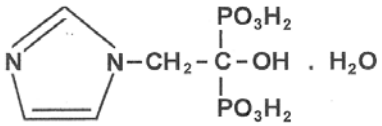
Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates which act primarily on bone. The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid is rapidly distributed to bone and, like other bisphosphonates, localises preferentially at sites of bone resorption and inhibits of osteoclast-mediated bone resorption. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase (FPPS), but this does not exclude other mechanisms.

Most agents currently employed in the treatment of osteoporosis, including zoledronic acid (ZA), are osteoclast inhibitors. ZA, like other amino-bisphosphonates, acts in a stepwise fashion. (1) It

[a] For osteoporosis, the duration of therapy should be restricted to no more than three annual doses, that is, three years.

has a strong binding affinity for hydroxyapatite1 which takes up some 50% of the injected dose within minutes. (2) The drug is ingested by osteoclasts at resorbing surfaces of bone, so that the concentration within these cells is several orders of magnitude greater than in other cells. (3) Within the osteoclast, amino bisphosphonates act as cellular toxins. They competitively inhibit farnesyl diphosphate synthase[2], an enzyme in the mevalonate pathway. Inhibition of this enzyme prevents the biosynthesis of farnesyl diphosphate and geranyl diphosphate, hydrophobic lipids which combine with guanosine triphosphate (GTP)-binding proteins (such as Ras, Rab and Rho) and without which, the signalling pathways of these proteins are impaired. While osteoblastic activity is also diminished by bisphosphonates, the anti-osteoclastic action of these agents (which may be due to other mechanisms as well as those associated with the inhibition of farnesyl diphosphate synthase) predominates, so that bone mineral loss is prevented and the incidence of fractures is reduced.

**Figure 1. The structure of zoledronic acid.**




The P-C-P backbone is common to all bisphosphonates. The affinity for hydroxyapatite and the inhibition of farnesyl diphosphate synthase varies with the structure of the side-chain. For reasons that are probably related to its heterocyclic ring structure (see Figure 1), ZA has a greater affinity for hydroxyapatite than most other bisphosphonates,[3] and it is a more effective inhibitor of farnesyl diphosphate synthase. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of FPPS and its strong binding affinity to bone mineral.

On a milligram for milligram basis, ZA is the most potent amino-bisphosphonate currently available regardless of the assay employed.[4]

The Advisory Committee for Prescription Medicines (ACPM) has considered zoledronic acid on several occasions. The Committee recommended that treatment be restricted to three annual doses at its April 2008 meeting; this was mainly because there were safety concerns relating to bisphosphonates that were not fully addressed in the limited data set submitted.

In the current Australian submission, the sponsor has not requested any changes to the currently approved indications. However, the sponsor would like to remove the three year limit to treatment duration for the osteoporosis indications.

The currently approved indications are:

1. *Treatment of osteoporosis in postmenopausal women (maximum treatment duration: 3 years).*
2. *Treatment of osteoporosis in patients over 50 years with a history of low trauma hip fracture (maximum treatment duration: 3 years).*
3. *Treatment of osteoporosis in men.*
4. *Treatment of osteoporosis in long-term glucocorticosteroid users.*
5. *Prevention of glucocorticosteroid-induced bone loss.*
6. *Treatment of Paget's disease.*

The registered formulation contains the following excipients: mannitol, sodium citrate and Water for Injection.

Zoledronic acid is also marketed as "Zometa" which is currently approved for a variety of malignancies affecting the skeleton.

## Regulatory Status

The current international regulatory status is tabulated below (Table 1).

### Table 1. International regulatory status

| Country/ Region | Trade-name | Approved Indication |
|---|---|---|
| EU (including Sweden) | Aclasta | Treatment of osteoporosis<br>• in post-menopausal women<br>• in men<br>at increased risk of fracture, including those with a recent low-trauma hip fracture.<br>Treatment of osteoporosis associated with long-term systemic glucocorticoid therapy<br>• in post-menopausal women<br>• in men<br>at increased risk of fracture.<br>Treatment of Paget's disease of the bone in adults. |
| USA | Reclast | **1.1 Treatment of Osteoporosis in Postmenopausal Women**<br>Reclast is indicated for treatment of osteoporosis in postmenopausal women. In postmenopausal women with osteoporosis, diagnosed by bone mineral density (BMD) or prevalent vertebral fracture, Reclast reduces the incidence of fractures (hip, vertebral and non-vertebral osteoporosis-related fractures). In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Reclast reduces the incidence of new clinical fractures.<br>**1.2 Prevention of Osteoporosis in Postmenopausal Women**<br>Reclast is indicated for prevention of osteoporosis in postmenopausal women.<br>**1.3 Osteoporosis in Men**<br>Reclast is indicated for treatment to increase bone mass in men with osteoporosis.<br>**1.4 Glucocorticoid-Induced Osteoporosis**<br>Reclast is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months. |

| Country/ Region | Trade-name | Approved Indication |
|---|---|---|
| USA (cont) | Reclast | **1.5 Paget's Disease of Bone**<br>Reclast is indicated for treatment of Paget's disease of bone in men and women. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase of two times or higher than the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease.<br>**1.6 Important Limitations of Use**<br>The safety and effectiveness of Reclast for the treatment of osteoporosis is based on clinical data of three years duration. The optimal duration of use has not been determined. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. |
| Canada | Aclasta | ACLASTA* (zoledronic acid 5 mg/100 mL) is indicated for:<br>• The treatment of osteoporosis in postmenopausal women, as a once-yearly intravenous infusion, to reduce the incidence of hip, vertebral and non-vertebral fractures.<br>• The treatment to increase bone mineral density in men with osteoporosis, as a once-yearly intravenous infusion.<br>• The treatment and prevention of glucocorticoid-induced osteoporosis, to increase bone mineral density, as a once-yearly intravenous infusion.<br>• The prevention of postmenopausal osteoporosis in women with osteopenia as a single intravenous infusion.<br>• The treatment of Paget's disease of the bone in men and women, as a single-dose intravenous infusion. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase (SAP) of at least two times the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease to induce remission (normalization of serum alkaline phosphatase). The effectiveness of ACLASTA* is based on serum alkaline phosphatase (SAP) levels. |
| New Zealand | Aclasta | • Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density.<br>• Treatment of osteoporosis in men.<br>• Treatment of Paget's disease of bone.<br>• Treatment and prevention of glucocorticoid-induced osteoporosis.<br>• Prevention of clinical fractures in patients after hip fracture.<br>• Prevention of postmenopausal osteoporosis. |

The approved indications in USA, Canada and Europe are similar to those approved in Australia. However, there are no limitations placed on treatment duration in these countries.

## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

There was no requirement for a quality evaluation in a submission of this type.

# III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

# IV. Clinical Findings

### Introduction

Clinical data provides an account of Extension Trial 2301E which compared some 600 osteoporotic women who received ZA (5 mg /year) for 6 years with a matched group of patients who received ZA for three years followed by three years of placebo treatment. The results of this trial which was prospective, randomised and double-blinded was recently published in abstract form.[5]

Clinical data also contained a summary of the pivotal HORIZON trial[6] which established the efficacy and safety of zoledronic acid in the treatment of postmenopausal osteoporosis. It was on the basis of this placebo-controlled trial that ZA (5 mg /year for 3 years) became established as a therapeutic agent

A declaration was made by the sponsor that the submitted study was conducted in compliance with good clinical practice including the archiving of essential documents.

### Pharmacokinetics

No new pharmacokinetic data were submitted with this application. In view of the scarcity of human data, a brief summary based on data from a previous application, [7] will be provided here.

After a single intravenous infusion the drug rapidly disappears from the circulation at multiphasic exponential rates with a slow terminal rate (167 h half-life). Some 40% of the administered dose is excreted by the kidney within the first 96 h of administration. The kidney is the only route of bisphosphonate excretion in mammals. After the administration of different doses of zoledronic acid to human subjects, the renal: non-renal clearance ratio was maintained, indicating that at doses of 4-16 mg the renal excretory pathways are not saturated (see Table 2). Second and third injections (4 and 8 weeks after the first) produce similar renal excretory patterns (see Table 2). ZA does not bind to any tissues except bone where its terminal half-life was measured in years. ZA at concentrations of up to 100µmol/L does not inhibit or stimulate nine human hepatic P450 enzymes including several drug metabolising enzymes. This finding makes it unlikely that zoledronic acid affects the metabolism of other drugs. ZA, like other bisphosphonates, is not metabolised significantly by mammalian tissues and there is some evidence that this statement applies to humans.[8] Table 2 which is based on the data of Chen *et al*. [9] summarises one of the few available studies of the pharmacokinetics of ZA in human subjects.

Skerjanec *et al*.,[10] using carbon radiolabelled ($^{14}C$) ZA as well as a sensitive radio-immunoassay in 19 patients with metastatic malignancies, showed that although some 30% of intravenously administers ZA is excreted by the kidneys within 24 h, mild renal impairment affects maximum plasma concentrations and drug clearance rates to only a minor extent (see Table 3). On the basis of these results the sponsors concluded that no dosage adjustments are necessary for patients with renal impairment so long as the pre-infusion creatinine clearance exceeds 30 mL/min.

**Table 2. Pharmacokinetic data for zoledronic acid.**

| | ZA First Dose | | ZA Second Dose | | ZA Third Dose | |
|---|---|---|---|---|---|---|
| **Dose(mg)/ infusion time (min)** | AUC | $C_{max}$ | AUC | $C_{max}$ | AUC | $C_{max}$ |
| **4/5** | 378 ±116 (n=5) | 403 ±118 (n=5) | 593 (n=2) | 654 (n=2) | 401 (n=2) | 271 (n=2) |
| **4/15** | 420 ± 218 (n=7) | 264 ± 86 (n=7) | 593 (n=1) | 551 (n=1) | 323 (n=2) | 229 (n=2) |
| **8/15** | 769 ± 256 (n=12) | 523 ± 186 (n=12) | 746 ± 66 (n=3) | 641± 189 (n=3) | 1153 ±272 (n=3) | 642 ± 152 (n=3) |
| **16/15 (n=11)** | 2004 ± 559 | 2252 ± 2636 | 2103 ± 526 (n=3) | 1210 ± 297 (n=3) | 2150 ± 334 (n=3) | 1296 ± 362 (n=3) |

Means ± standard deviation (S.D.) from IV doses of 4-16 mg , over 5 or 15 mins on three occasions (28 days apart) to 35 patients with various malignancies. AUC= Area under the curve (0-24h) in ng.h/ mL, $C_{max}$ = maximum plasma concentration in ng/ mL. (Modified from Chen *et al*.[8])

In some experiments the numbers of patients were too small for statistical evaluation.

The effects of renal impairment on the pharmacokinetic parameters of ZA following repeated IV infusions (4 mg over 15 min on 3 occasions at 4 weekly intervals) are shown below (Table 3).

**Table 3. Pharmacokinetic parameters of ZA. Effects of renal impairment.**

| **Creatinine clearance** | **>80** mL**/min** | **>50** mL**/min<80** mL**/min** | **<50** mL**/min** |
|---|---|---|---|
| **Infusion 1** | | | |
| ***n*** | **9** | **7** | **3** |
| $C_{max}$ (ng/ mL) | 309 ± 71 | 339 ± 56 | 365 ± 121 |
| $AUC_{0\text{-}24h}$ (ng•h/ mL) | 408 ± 90 | 519 ± 97 | 603 ± 270 |
| $Ae_{0\text{-}24h}$ (% dose) | 36 ± 15 | 40 ± 19 | 28 ± 10 |
| $CL_R$ ( mL/min) | 59 ± 24 | 53 ± 28 | 32 ± 3 |
| **Infusion 2** | | | |
| ***n*** | **9** | **7** | **3** |
| $C_{max}$ (ng/ mL) | 334 ± 138 | 358 ± 93 | 312 ± 53 |
| $AUC_{0\text{-}24h}$ (ng•h/ mL) | 419 ± 160 | 546 ± 127 | 520 ± 180 |
| $Ae_{0\text{-}24h}$ (% dose) | 39 ± 16 | 45 ± 19 | 31 ± 14 |
| $CL_R$ ( mL/min) | 67 ± 32 | 57 ± 31 | 39 ± 6 |
| **Infusion 3** | | | |
| ***n*** | **7** | **7** | **2** |
| $C_{max}$ (ng/ mL) | 323 ± 94 | 379 ± 133 | 315 (267-363)[a] |
| $AUC_{0\text{-}24h}$ (ng•h/ mL) | 430 ± 149 | 559 ± 205 | 587 (488-86)[a] |
| $Ae_{0\text{-}24h}$ (% dose) | 33 ± 14 | 48 ± 25 | 30 (18-42)[a] |
| $CL_R$ ( mL/min) | 53 ± 20 | 57 ± 29 | 33 (25-41)[a] |

[a]= mean (range). Table has been slightly modified from that of Skerjanec *et al*.[10]

## Pharmacodynamics

No new pharmacodynamic data were presented with this application. Like human pharmacokinetic data, human pharmacodynamic data are sparse and a few early studies are summarised here. The markers investigated at early time points by Skerjanec *et al*.[8] included serum calcium, which fell by some 15% immediately after the first infusion but returned to baseline values within 10 days and remained stable thereafter. There were no falls after the second and third infusions. Serum N-terminal and C-terminal telopeptides of Type I collagen fell by some 60% within 24 h of the first infusion and remained suppressed throughout the period of observation.

The large published clinical studies did not report on measurements of ZA effects within the first 24 hours of administration. In two controlled trials comparing the effects of ZA with those of disodium pamidronate in hypercalcemia of malignancy,[11] the earliest measurements were made on Day 4, when serum calcium had become normal in approximately half the patients who had received zoledronic acid (4 mg ) on Day 1. In one of the major Pagetic trials,[12] a reduction in markers of osteoclastic activity was observed on Day 10 after the infusion of 5 mg ZA while at this time point, there was also a significant reduction in serum alkaline phosphatase.

In postmenopausal women with low bone densities, ZA in doses of 0.25 to 4.0 mg resulted in significant changes in osteoclastic markers at 1 month,[14] while the markers of bone formation (such as bone specific alkaline phosphatase) fell more slowly, reaching a lowest point (nadir) of approximately 50% at 3 months.[14] Bone density changes are observable at 6 months [6], while a

reduction in fracture rates is, in general, not observed until 12 months after the administration of ZA. Some of the pharmacodynamic effects of ZA are listed in Table 4.

**Table 4. Time courses of pharmacodynamic and clinical effects of ZA.**

| Effect | Population Studied | N | Time point when first observed | Reference |
|---|---|---|---|---|
| Fall in serum calcium | Women with metastatic malignancies | 19 | At end of first infusion. Returns to pre-infusion values within 10 days | Skerjanec *et al*.[10] |
| Falls in serum osteoclastic markers | Women with metastatic malignancies | 19 | Within 24 h. Remain suppressed. | Skerjanec *et al*.[10] |
| Falls in serum osteoblastic markers. | Patients with Paget's disease | 182 | Day 10. Then continue to fall. Nadir at 90 days. Then remain suppressed | Reid *et al*. [11] |
| Increases in bone densities (femoral neck) | Women with postmenopausal osteoporosis | 3851 | 6 months. Continues to rise | Black *et al*. [6] |
| Reduction in fracture rates (vertebral X–ray) | Women with postmenopausal osteoporosis | 2822 | 1 year | Black *et al*. [6] |

## Dosage Selection for the Pivotal Studies

One of the weaknesses of ZA therapy is that the standard doses of 4 mg per month for malignancies and 5 mg per year for various forms of osteoporosis have not been completely validated. During the early dose finding studies, Body *et al*.[13] used single doses of 0.002-0.04 mg per kg body weight in the treatment of hypercalcemia of malignancy (HCM). Only the two highest doses (0.02 and 0.04 mg /kg = 1.2 and 2.4 mg for a 60kg individual) resulted in normocalcemia. In the pivotal HCM trials comparing ZA to pamidronate, [11] the ZA doses employed were 4 mg and 8 mg, with the smaller dose as efficacious as the larger. Presumably, on the basis of this trial, 4 mg became the standard dose in patients with malignancies. It was unclear how the frequency of 3-4 weeks (for the treatment of skeletal metastases) was established.

*Evaluator Comment*

The osteoporotic population will not necessarily have the same risk for adverse reactions as the patients with malignancies but some safety data are comparable (such as renal effects).

The dose-finding studies for osteoporosis were also incomplete. Reid *et al*.[14] used annual doses of 1.0-4.0 mg in the treatment of postmenopausal women with low bone mineral densities. The end points were the increases in bone mineral density of the lumbar spine and the suppression of osteoblastic and osteoclastic markers. The patients in the five active treatment groups received ZA according to five regimens: (1) Four doses of 0.25 mg each every 3 months; (2) four doses of 0.5 mg each every 3 months; (3) four doses of 1.0 mg each every 3 months; (4) two doses of 2.0 mg each every 6 months; (5) one dose of 4 mg. There was also a placebo group. There were no significant differences between the five active treatment groups but all groups differed significantly different from the placebo group. The choice of 5 mg /year was therefore somewhat arbitrary and the favourable results obtained in the pivotal trials[6, 15] might well have been obtained with lower doses.

No attempt seems to have been made to determine the minimum dose or frequency of administration required to maintain bone densities after 3 years.

## Efficacy

### Novartis CZOL446H2301E1 Study

Only one efficacy study (Novartis CZOL446H2301E1) was submitted with this application. It was a double blind, placebo-controlled extension trial designed to evaluate the efficacy and safety of ZA taken continuously for 6 years, compared with a three year course followed by discontinuation of the drug at the end of three years.

#### *Study design*

The study was an international, multi-centre, randomised, double-blind 3 year extension trial involving 1233 women with postmenopausal osteoporosis who had already received ZA (5 mg/year) for 3 years. At the end of the third year these patients were randomised on a 1:1 basis to either receive ZA (5 mg/year, n=616) for a further 3 years or placebo infusions (n=620) over this period.

#### *Study objectives*

The primary objective of this study was to determine whether the bone mineral density (BMD) of the femoral neck (as assessed by Dual X-Ray Absorptiometry( DEXA) measurements at the end of six years of observation) was affected by the continuation (or discontinuation) of ZA at the end of the initial three years' treatment.
Secondary efficacy objectives included bone mineral densities at various intermediate time points and at sites other than the femoral neck, changes in biochemical markers of bone turnover and the evaluation of the incidence of fractures in the two treatment groups.

Secondary safety objectives included the evaluation of adverse events during the second three years of treatment. In particular, the more recently described bisphosphonate-associated problems (osteonecrosis of the jaws,[16] atypical fractures[17] and cardiac arrhythmias[18]) were specifically looked for and, in relevant cases, reviewed by special committees.

#### *Trial Location*

Patients were recruited at multiple sites in the USA, Australia, Russia, Poland, Germany and various other countries where the original pivotal HORIZON trial had been conducted.

#### *Study Dates*

The study began on 17 May 2005 when the first patient was screened and ended on 24 November 2010 when the investigations of the last patient were completed.

#### *Inclusion criteria*

The patients were ambulatory postmenopausal osteoporotic women aged 93 years or less, who had participated in the HORIZON trial,[6] who had been randomised to receive ZA in that trial and who had completed the first 3 years as per protocol. The definition of osteoporosis for entrance into that trial had been: (1) A femoral neck bone mineral density T-score of ≤ -1.5 *and* the presence of at least one moderate or two mild vertebral fractures. (2) Women without base-line fractures were also eligible, provided their femoral neck T scores were in the osteoporotic range (≤ -2.5).[6]
Patients able to walk with the aid of a mechanical walker or a stick were considered ambulant.

#### *Exclusion criteria*

There were 34 exclusion criteria and only those considered the most significant will be listed here:

(1) Patients considered "not appropriate" to participate in the extension study (not further defined). The context suggests that this criterion was aimed principally at protocol violators and at patients who had been lax in their attendances during the initial three years.

(2) Patients who had taken potentially confounding medications (such as oral bisphosphonates, corticosteroids, teriparatide, strontium, fluoride and tamoxifen) either during the core trial or during the interval between the completion of that trial and their randomisation to the extension trial.

(3) Patients with hypo- or hypercalcemia (serum calcium < 2.0mmol/L or > 2.75mmol/L).

(4). Patients with a variety of malignancies.

(5). Patients with a life expectancy of less than 3 years.

(6). Patients with "uncontrolled seizure disorders associated with falls" (not further defined).

(7). Patients with "uncontrolled" diabetes defined as a history of glycosylated haemoglobin (Hb) (HbA1c) > 10%

*Evaluator Comment*

While these exclusion criteria would not affect the randomisation process, they would be expected to produce a study population less "frail" and more compliant than the general population of 75 year old osteoporotic women. The sponsors do not provide details concerning the numbers of patients who were screened but rejected for the extension trial.

### *Study treatments*

The participants were randomised to receive either 5 mg ZA (in 100 mL) or 100 mL normal saline by intravenous infusion once yearly for 3 years. As part of the study, each patient also received calcium supplements (1000-1500 mg elemental calcium per day and 400-1200 units vitamin D per day, but compliance with these medications was only checked in North America. The patients were contacted by telephone every three months and they underwent a "complete physical examination" during each annual visit. The physical examination does not seem to have included a formal examination of the oral cavity or a specific determination whether or not the pulse was regular. During the annual visits (including a visit 12 months after the last infusion) a variety of measurements were made (DEXA, Quantitative Computed Tomography (QCT), standard haematological and biochemical tests (including creatinine clearance) and biochemical markers of bone turnover. Routine electrocardiograms (ECGs) were performed before, 9-11 days after and 90 days after the third infusion. X-ray examinations (lateral views) of the thoracic and lumbar vertebrae were performed at the beginning of the study and at the end of the third year.

The use of non-bisphosphonate anti-osteoporotic agents, for example estrogens and Selective Estrogen Receptor Modulators (SERM's), was permitted, but the use of other bisphosphonates, teriparatide and strontium was considered a protocol violation (see Table 5).

### *Efficacy variables and outcomes*

The main efficacy variables were:

- Bone Mineral Density (BMD) measurements at the femoral neck and other sites
- QCT of the hip and spine in a subset of randomised patients.
- Biochemical measurements of bone turnover markers such as the c-terminal of Type I collagen.
- Incidence of clinical fractures.
- Incidence or worsening of radiological vertebral fractures.

*Evaluator Comment*

Radiological vertebral fractures, most of which are without symptoms, are defined by arbitrary criteria depending on the anterior and posterior heights of individual vertebrae as seen in lateral X-rays of the spine.

The primary efficacy outcome was the increase in the BMD of the femoral neck between Year 3 and Year 6 with a difference of 1.04% (confidence interval (CI) 0.43-1.65, p = 0.009) between the ZA and the placebo groups (for details see Table 8 and Figure 2)

Other efficacy outcomes included:

ZA treatment was superior to placebo in increasing the BMD's of the total hip, the trochanter and the lumbar spine between Year 3 and Year 6 (P< 0.01)

The incidence of new or worsening radiological vertebral fractures was lower in the ZA than in the placebo group (P<0.05).

### *Sample size*

By analogy with results obtained by Black *et al* [19] in the alendronate extension trial, the ZA investigators assumed that standard deviations for the bone density measurements in the treatment groups would be approximately 5.5% and that the difference between the treated and untreated groups would be approximately 1.1%. In order to provide an approximately 90% power to detect such a difference with a 5% significance, some 526 patients were required in each group. To allow for dropouts and patients with missing data, 1240 patients were recruited (620 for each treatment group) and a total of 1233 were randomised (see Table 5).

### *Randomisation and blinding methods*

The active drug (5 mg ZA in 100 mL) and the placebo (100 mL 0.9% saline) were sent to the investigational centres in plastic bottles, indistinguishable from each other. The randomised allocation to one or the other treatment group was performed by an Interactive Voice Response System (IVRS) which had to be contacted by telephone. The IVRS centre recorded the patient's identification number and her suitability for inclusion in the study, and then allocated a unique medication number. This process was repeated before each infusion.

**Table 5. The Intent-to-Treat (ITT) Population and the Dropouts.**

| Treatment groups | ZA | Placebo | Total |
|---|---|---|---|
| | N(%) | N(%) | N(%) |
| Randomised | 616 | 617 | 1233 |
| Completed | 474 (76.95) | 493 (79.90) | 967 (78.43) |
| Discontinued* | 142 (23.05) | 124 (20.10) | 266 (21.57) |
| **Reason for Discontinuation** | | | |
| Withdrawal of Consent | 77 (12.50) | 72 (11.67) | 149 (12.08) |
| Death | 26 (4.22) | 18 ( 2.92) | 44 (3.57) |
| Adverse Event(s) | 14 (2.27) | 11 ( 1.78) | 25 (2.03) |
| Lost to follow-up | 9 (1.46) | 14 (2.27) | 23 (1.87) |
| Protocol Violation | 2(0.32) | 0 | 2 (0.16) |
| Other* | 14 (2.27) | 9 (1.74) | 23 (1.87) |

*One patient with missing data has been included in the "Discontinuation" group

**Table 6. The ITT, Modified Intent to Treat (MITT), Per Protocol (PP) and Safety Populations**

| Treatment Group | ZA | Placebo | Total | Comments |
|---|---|---|---|---|
| | | | | |
| **ITT population** | 616 | 617 | 1233 | Includes all randomized patients |
| **MITT population** | 451 | 470 | 921 | Includes all patients with DEXA measurements at baseline and at 3 years |
| **Per protocol population** | 429 | 453 | 882 | |
| **Safety population** | 613 | 616 | 1229 | Includes all patients who received at least one dose of ZA or placebo |

### *Baseline data*

The patients in the two treatment groups were remarkably well matched for all baseline values (see Table 7). The large majority in each group were Caucasian. The mean age in both groups was 75.5 years, the mean weight was 60.4 kg in the ZA group and 61.1kg in the placebo group and the mean heights of the patients in the two groups were almost identical. With respect to each subject's "Relevant Past Medical History", no finding seemed overrepresented in any group. Similarly, the participants in the study took literally hundreds of concomitant medications but these were evenly distributed between the two treatment arms.

At baseline, the two treatment groups were well matched for their skeletal measurements. The mean T score for the body mass index (BMD) of the femoral neck was minus 2.58 for the ZA group and minus 2.55 for the placebo group. However, the number of women with two or more vertebral fractures at baseline was smaller in the ZA group (183/616 versus 222/617, $P< 0.05$).

### *Protocol Amendments*

The protocol was amended five times. Most of the changes were administrative in nature but two of them could affect the overall findings of the trial: (1)"The requirement that patients complete 3 years of participation in the core study to be eligible for the extension was removed." The effect of this amendment would be to reduce the cumulative dose of the drug received by the ZA group. (2)The time interval from the completion of the core trial to the time of randomization was extended to 16 months from the time of the last dose. The effect of this amendment would be to increase the study period from 6 years to 6 years and 4 months.

**Table 7. Baseline characteristics of ITT patients in extension Study 2301E1.**

| **Treatment**<br>**Total n=1233** | **Zoledronic acid 5 mg/yr**<br>n=616 | **Placebo**<br>n=617 |
|---|---|---|
| **% Caucasian** | 85.1% | 86.1% |
| **Age (yr)**<br>**Mean ± S.D** | 75.5 ± 4.88 | 75.5 ± 4.89 |
| **Weight (kg) Mean ± S.D** | 60.4± 9.92 | 61.1± 11.28 |
| **Stadiometer height (mm) Mean ± S.D** | 1558.5 ± 65.89<br>(n=367) | 1553.0 ± 65.31<br>(n=370) |
| **Creatinine clearance (mL/min) Mean ± S.D** | 56.65± 13.95 | 57.04± 16.11 |
| **Femoral neck T-score Mean ± S.D** | -2.58±0.55 | -2.55±0.57 |
| **Femoral neck BMD (g/cm2) Mean ± S.D** | 0.562 ± 0.06 | 0.566 ± 0.06 |
| **No. (%) with ≥1 vertebral fractures at baseline** | 360 (58.4) | 390 (63.2) |
| **No. (%) with ≥2 vertebral fractures at baseline** | 183 (29.7) | 222 (36.0) |

All patients were postmenopausal, osteoporotic women who had already received ZA for 3 years.

### *Results for the primary efficacy outcome*

The percentage changes in the bone mineral densities of the femoral neck over the three years of the study are shown in Table 8. The treatment associated difference was small but significant regardless of whether the calculations were performed for the "Modified Intent to Treat" (MITT) patients (all patients who had DEXA measurements performed at the relevant times) or the Per Protocol groups. However, as Figure 2 shows, the values in both groups were well above those observed 6 years earlier when the patients began their initial course of ZA.

**Table 8. Change in bone mineral densities (femoral neck). Three years of additional zoledronic acid treatment.**

| **Treatment Group** | **N** | **Least Square Mean(±S.E)** | **Treatment Difference (95% CI)** | **p value** |
|---|---|---|---|---|
| | | | | |
| **ZA (MITT)** | 451 | 0.24 (0.25) | 1.04 (0.43, 1.65) | 0.0009 |
| **Placebo (MITT)** | 470 | -0.80 (0.25) | | |
| **ZA (PP)** | 429 | -0.02 (0.29) | 0.99 (0.37, 1.62) | 0.0019 |
| **Placebo (PP)** | 453 | -1.01 (0.28) | | |

**Figure 2: Change in bone mineral density (femoral neck )over 6 years of zoledronic acid treatment.**

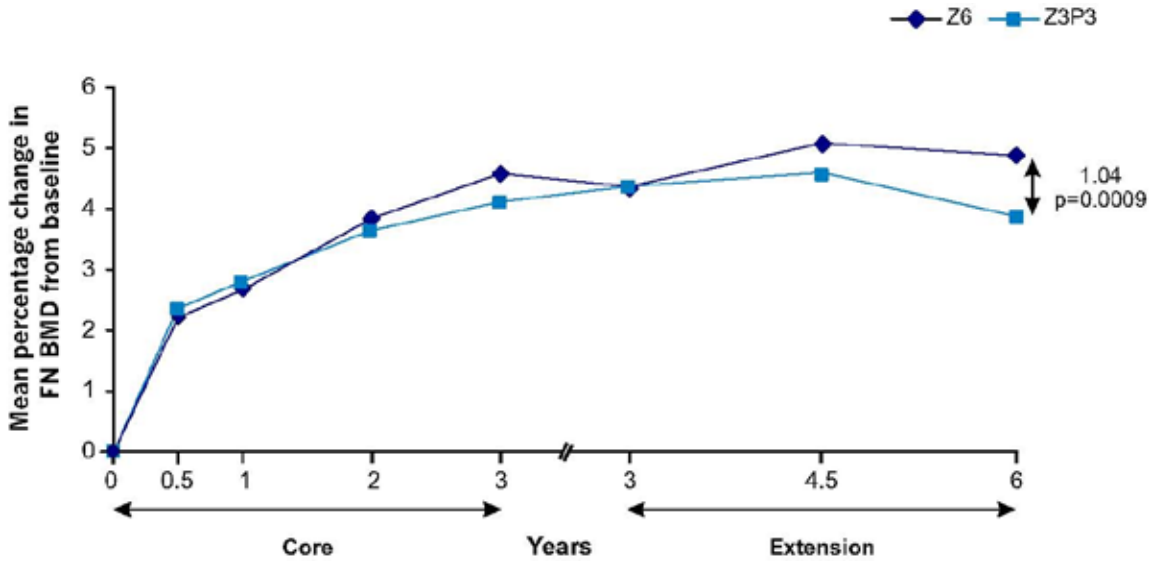



Figure from Black *et al*. [5] The diamonds represent patients who took zoledronic acid for the entire 6 years (Z6) the squares represent patients who took ZA for 3 years and were then randomised to the placebo group(Z3P3).

The difference between ZA and placebo groups was significant at 6 years (1.04%) but not at 4.5 years.

### *Results for other efficacy outcomes*

Table 9 shows DEXA-determined bone mineral changes at times other than 3 years and at sites other than the femoral neck. With the exception of the femoral neck at 18 months and the distal radius at 36 months, ZA was significantly superior to placebo in inducing increases in BMDs.

**Table 9. Changes in the bone mineral densities (various sites) over 18 and 36 months of additional zoledronic acid treatment. (ITT population).**

| Site | Time (month) | Treatment | n | LS Mean (SE) | Treatment difference (95% CI of difference) | p-value |
|---|---|---|---|---|---|---|
| **Femoral Neck** | 18 | ZA | 525 | 0.59 (0.22) | 0.53 (-0.02,1.08) | 0.0568 |
| | | Placebo | 544 | 0.06 (0.22) | | |
| **Total Hip** | 18 | ZA | 525 | 0.37 (0.15) | 0.55 ( 0.18, 0.92) | 0.0037 |
| | | Placebo | 544 | -0.18 | | |
| **Total Hip** | 36 | ZA | 451 | -0.36 (0.20) | 1.22 (0.75, 1.70) | <0.0001 |
| | | Placebo | 470 | -1.58 (0.19) | | |
| **Trochanter** | 18 | ZA | 525 | 0.62 (0.22) | 0.78 ( 0.25, 1.31) | 0.0042 |
| | | Placebo | 544 | -0.15 (0.22) | | |
| **Trochanter** | 36 | ZA | 451 | 0.03 (0.27) | 1.52 (0.87, 2.17) | <0.0001 |
| | | Placebo | 470 | -1.49 (0.27) | | |
| **Lumbar Spine (subset)** | 18 | ZA | 101 | 2.41 (0.38) | 1.40 (0.38, 2.42) | 0.0075 |
| | | Placebo | 102 | 1.01 (0.37) | | |
| **Lumbar Spine (subset)** | 36 | ZA | 100 | 3.20 (0.44) | 2.03 (0.76, 3.29) | 0.0018 |
| | | Placebo | 84 | 1.18 (0.49) | | |
| **Distal Radius (subset)** | 18 | ZA | 100 | 0.45 (0.34) | 1.32 ( 0.40, 2.24) | 0.0053 |
| | | Placebo | 99 | -0.86 (0.34) | | |
| **Distal Radius (subset)** | 36 | ZA | 96 | -0.12 (0.38) | 0.37 ( -0.71, 1.45 ) | 0.5036 |
| | | Placebo | 82 | -0.49 (0.41) | | |

Lateral X-rays of the lumbar spine, taken at the beginning and the end of the three-year extension trial, were available for comparison from 469 ZA patients and 486 placebo patients. Table 10 shows that patients treated with ZA sustained significantly fewer radiological (=non-clinical) fractures than those receiving placebo infusions. By contrast, the incidence of clinical spinal fractures did not differ statistically between the two groups.

**Table 10. Radiological and clinical vertebral fractures in patients treated with ZA or placebo during the three year extension trial.**

| Type of Fracture | No. of fractures (patients with available data) | | P value for difference | Relative risk reduction (95% CI) |
|---|---|---|---|---|
| | ZA | Placebo | | |
| **New radiological** | **14 (469)** | **(30) 486** | **0.0348** | **52% (10, 74)** |
| **New or worsening radiological** | **16 (469)** | **34 (486)** | **0.0302** | **51% (13, 63)** |
| **Clinical (radiologically confirmed)** | **7 (616)** | **4 (617)** | **NS** | |

The incidence of the total number of confirmed fractures involving any site was almost identical in the two treatment groups (51 in each group). The time points at which clinical fractures occurred were not significantly different in the two treatment groups so that the Kaplan-Meier time plots for the first fracture in each group were superimposable.

QCT observations were presented for some 20 patients in each group. Some results suggested methodological problems. None of the QCT studies produced any statistical differences between the treatment groups and there were too few bone biopsies for any meaningful conclusions.

The sponsors measured several serum biochemical markers of bone turnover including the C-terminal peptide of Type I collagen (a marker of bone resorption), the N-terminal propeptide of Type I collagen (a marker of bone formation) and bone-specific alkaline phosphatase (also a marker of bone formation). In the ZA group the values remained constant while they tended to rise in the placebo group but remained suppressed compared with baseline.

**Other Efficacy Studies**

As far as clinical evaluator was aware, there is only one other study involving the use of ZA for more than 3 years in the treatment of osteoporosis. Devogelaer *et al*[20] who treated 22 patients with ZA (4 mg per year for 5 years), measured bone density changes in the "proximal femur" (presumably the femoral neck) at 3 years and 5 years. The percentage increases (5.81% at 3 years and 5.16% at 5 years were very similar to those observed in the current trial (5.06 at 3 years and relatively little change over the next three years).

**Evaluator's Conclusions on Clinical Efficacy**

The applicants have shown in a randomised, multi-centre, placebo-controlled, double blind study that patients who continue taking ZA (5 mg /year) for 6 years have significantly higher bone densities and significantly fewer radiological fractures than patients who discontinued treatment at the end of three years. However, the difference between bone mineral densities of the two treatment groups was relatively small when compared to the residual ZA effect, which was still present after 3 years' discontinuation of treatment (see Figure 2). The absolute increase in the risk of sustaining a radiological vertebral fracture because of discontinuation of ZA was only 3.0%. There are at present no data to distinguish subsets of patients who will benefit from a 3-year extension of treatment from those who will not.

## Safety

The following studies provided evaluable safety data:

### 1. Pivotal efficacy studies

In the pivotal efficacy studies,[5, 6, 15] the following safety data were collected:

- General adverse events (AE's) were assessed by the individual investigators at each site.
- AE's of particular interest, including atrial fibrillation, jaw necrosis, atypical fractures, and deterioration in renal function) were assessed by committees set up specifically to deal with these putative complications.
- Laboratory tests, including haematological and routine biochemical investigations including liver and kidney functions were performed at the individual clinical centres. The investigators were notified if the results were outside a pre-determined range.
- Biochemical tests measuring bone turnover were performed at a central laboratory.
- DEXA scans were sent to a central reader for evaluation. In the HORIZON trial[6] this evaluation was performed at the central laboratory and although the applicants do not say so specifically, it was presumed that the same readers were employed during the extension trial.
- Similarly, the spinal X-rays were evaluated for incident and worsening fractures at the central laboratory.[6]

- Clinical (non-spinal) fractures were evaluated at the same medical centre based on an X-ray report, a surgical report or an X-ray film.

### 2. Pivotal studies that assessed safety as a primary outcome

There were no studies submitted this application which assessed safety as a primary outcome. A brief perusal of the list of 221 clinical ZA trials (ongoing and completed) registered in the USA,[21] and the recent literature suggests that safety was a secondary outcome in all studies regardless of the underlying indication for treatment.

The major safety issues emerging from the pivotal and the smaller trials include: (1) The occurrence of a influenza like illness occurring within 3 days of the infusion and attributed to the acute phase response. (2) Deterioration in renal function. (3) Hypocalcemia. (4) Uveitis and other ocular inflammations. (5) Atrial fibrillation. Rare but serious events that emerged in the post-marketing period include: (6) Jaw necrosis. (7) Atypical, "insufficiency" type femoral fractures.

### 3. Dose-response and non-pivotal efficacy studies

The following selected dose-response and non-pivotal efficacy studies provided safety data:

- In their early dose-finding studies Arden-Cordone *et al*.[22] and Buckler *et al*.[23] used different microgram doses of ZA (maximum 400 µg, infused over 1 h) into patients with Paget's disease (total number of patients for all doses in the two studies =157). Under these conditions, adverse events (other than the "flu-like illness" which appeared dose-dependent) were similar to those observed with placebo infusions.
- Subsequent studies by Reid *et al*.[12] and Hosking *et al*.[24] compared the effects of a single ZA dose (5 mg given over 15 min) with those of oral risedronate (30 mg /day for 60 days) on the long-term (2 years) biochemical control of Paget's disease. They showed that the 182 patients randomised to receive ZA achieved earlier, more intense and more prolonged falls in biochemical markers of bone turnover than those receiving risedronate. From a safety point of view, patients in the ZA group were twice as likely as the risedronate patients to develop the early "flu-like illness." The number of patients with hypocalcemia was greater in the ZA than in the risedronate group. Otherwise, there was no difference between the two groups in relation to deaths and serious adverse events.[24]
- Reid *et al*.[14] who performed dose-finding studies in postmenopausal women with low bone densities found that the transient "flu-like syndrome" occurred more frequently after the first than after subsequent infusions of ZA and that it was not dose-related.
- In a series of papers, Rosen *et al*. [25-27] and Saad *et al*.[28] described their experiences with ZA treatment in a variety of malignancies. One of the studies of Rosen *et al*.[27] involved 519 patients with documented skeletal metastases from lung carcinoma and other cancers (not breast or prostate) who were randomised to receive ZA (4 mg or 8 mg over 5 min) or placebo (n==247) every 3 weeks. The drop-out rate was greater than 80% in each group. After the protocol was changed from an infusion time of 5 min to 15 min and after the 8 mg dose was reduced to 4 mg, the patients who remained in the study (133 at 9 months and 18 at 21 months) sustained no greater rises in serum creatinine than the placebo patients. Similar results were obtained in placebo-controlled studies involving breast cancer, prostate cancer and myeloma patients.[25, 26, 28]. The acute phase response was not well defined in the early trials involving patients with advance malignancies, and osteonecrosis of the jaw was not mentioned.

## Patient Exposure

### *The influenza-like illness*

Tables 11 and 12 list some of the trials during which patients were exposed to ZA. Some of these trials involved hundreds[27, 28, 33] or even thousands [6, 15, 25, 31] of patients. Other studies,

involving special populations, were smaller, but carefully conducted.[30, 35-7] Some were placebo controlled, others used an active comparator. Almost all these studies agree that within a few days of a ZA infusion a proportion of patients will develop a flu-like syndrome (fever, myalgia, and arthralgia) which subsides spontaneously and does not seem to be associated with long-term sequelae. The various symptoms associated with this "acute phase reaction" are more common after the first than after subsequent infusions[38] and rarely lead to discontinuation of treatment.

### *Renal impairment*

The early clinical literature on ZA contains multiple case reports describing the nephrotoxic effects of this drug.[39] In a retrospective analysis of patients with prostatic carcinoma attending the Dana Farber Institute in Boston, Oh *et al*.[40] observed rises in serum creatinine in 23.8% of patients. Boonen *et al*.[41] subsequently pointed out that in controlled osteoporosis trials employing ZA doses of 5 mg/year, transient post-infusional rises in serum creatinine were indeed more common in the ZA than in the placebo groups, but that all elevated serum creatinine values recovered within 12 months (see *Adverse Events*).

**Table 11. Safety results of selected ZA trials involving patients with malignancies.**

| Indication Reference | Population studied | No. exposed to ZA; mean duration | Dose | Comparator | Adverse Events | Comments |
|---|---|---|---|---|---|---|
| Hypercalcemia of malignancy [29] (Major *et al* 2001) | 50% male; mean age 59.4 yr. Various malignancies. | 184; single infusion | 4 or 8 mg | Pamidronate | Acute phase response, renal impairment, hypocalcemia not significantly different from pamidronate | |
| Metastatic prostate cancer.[28] | Mean age 71.5 yr. 99% with skeletal meta-stases | 419; 9.1 mo | 4 or 8 mg , every 3 weeks | Placebo | Acute phase response more common with ZA. Renal impairment comparable. | 8 mg dose changed to 4 mg |
| Non-metastatic pro-state cancer. Androgen deprivation.[30] | Mean age 71.1 yr. | 55; 12 mo | 4 mg every 3 mo | Placebo. | No changes in renal function from baseline to end of study | |
| Multiple myeloma or metastatic breast cancer.[25] | Mean age (breast carcinoma) 57.5 yr. | 1090; 60 % drop-out by 13 mo | 4 or 8 mg every 3-4 weeks | Pamidronate. No placebo | Renal impairment in 10.7% of patients after protocol amendment. Not significantly different from pamidronate | Dose changed from 8 to 4 mg , infusion time from 5 to 15 min, and infusate volume from 50 to 100 mL |
| Metastatic lung cancer and other solid tumors.[27] | Median age 63 yr; 66% male;50% non-small cell lung ca, 10% renal cell ca. | 519; 84 % drop-out by 21mo | 4 or 8 mg every 3 weeks | Placebo | Acute phase response more common with ZA. Renal impairment not significantly different from placebo. | Dose changed from 8 to 4 mg , infusion time from 5 to 15 min, and infusate volume from 50 to 100 mL |
| Metastatic breast cancer.[31] | Mean age 56.5yr | 1013; 17 mo | 4 mg (adjusted for creatinine clearance) every 4 weeks. | Denosumab. No placebo | Acute phase response significantly more common with ZA. Renal impairment more common with ZA | Hypocalcemia more common with denosumab. Jaw necrosis (34 cases) equal frequency |

**Table 12. Safety Results of Previous ZA Trials Involving Patients with Low Bone Densities.**

| | | | | | |
|---|---|---|---|---|---|
| Postmenopausal osteoporosis. Pivotal study[6] | Mean age 73.1 yr | 3875<br>3 yr | 5 mg /year | Placebo | Acute phase response, transient renal impairment, atrial fibrillation more common in ZA group |
| Patients with hip fracture[15] (77% ♀) | Mean age 74.4yr. ZA commenced ≤90 days after fracture | 1065<br>1.9yr | 5 mg /yr | Placebo | Acute phase response more common after ZA. Otherwise comparable. ZA improved survival |
| Male osteoporosis ("idiopathic" or hypogonadal) [32] | Men, mean age 64.5 yr, with low BMD and /or fractures | 153;<br>2 yr | 5 mg /year | Oral alendronate. No placebo | Acute phase response in 5% of ZA subjects. Other AE's comparable. |
| Glucocorticoid-induced osteoporosis[33] | Mean age 53.0 yr; 68% ♀; | 416;1 yr | 5 mg | Oral risedronate. No placebo | Acute phase response more common in ZA group. Other AE's comparable |
| Postmenopausal women, low BMD, previously on alen-dronate[34] | Alendronate for at least 12 mo before randomisation; Mean age 67.6 yr | 113<br>Single infusion | 5 mg | Oral alendronate. No placebo | No acute phase response. AE comparable in the two groups |
| Stroke patients (11♂, 4♀)[35] | ZA for prevention of fall in BMD. Mean age 67.8 yr | 15<br>Single infusion | 4 mg | Placebo | Hypocalcemia, hypophosphatemia, more common in ZA group. Other AE's comparable |
| Liver transplantation (26♂, 6♀) [36] | ZA for prevention of fall in BMD. Mean age 47.4yr | 32 | 5x4 mg over 9mo | Placebo | Hypocalcemia more common in ZA group. No renal impairment |
| Cystic Fibrosis (7♂, 3♀)[37] | ZA for enhancement of BMD. Mean age 30.1 yr | 10<br>2 years | 2 mg every 3 mo (8 mg /yr) | Placebo | Severe acute phase response in 27/63 ZA infusions v. 4/73 placebo infusions. |

Mo=months. Yr=years

## Adverse Events

### *All adverse events (irrespective of relation to study treatment)*

Table 13 shows that the incidence of the most frequently reported adverse events did not differ significantly between the two treatment groups.

The list differs in one respect from that published with the pivotal HORIZON trial. In that study, some 30% of ZA patients developed symptoms indicative of the acute phase reaction (pyrexia, myalgia, and arthralgia) in the immediate post-infusion period, especially after the first dose.[6, 38] In the current trial, all patients had previously received zoledronic acid so that by definition there were no "zoledronic acid-naïve" individuals. The number of adverse events considered "mild," "moderate" or "severe" did not differ significantly between the groups.

### *Suspected study drug related events*

Adverse events suspected as due to the administered drug, were attributable, predominantly, to the acute phase response. Table 14 shows that these AE's occurred mainly during the first 3 days after infusions, whereas for the remainder of the three years the various "events" happened with equal frequency in the two treatment groups.

**Table 13. Most frequent AEs irrespective of relationship to study treatment.**

| Preferred Term (Number/percentage reporting particular event) | ZA (N=613) | Placebo (N=616) |
|---|---|---|
| **Arthralgia** | 119( 19.4) | 108( 17.5) |
| **Back pain** | 117( 19.1) | 114( 18.5) |
| **Urinary tract infection** | 77(12.6) | 94 (15.3) |
| **Nasopharyngitis** | 61(10.0) | 61( 9.9) |
| **Osteoarthritis** | 59( 9.6) | 52( 8.4) |
| **Fall** | 53( 8.6) | 62( 10.1) |
| **Pain in extremity** | 53( 8.6) | 54( 8.8) |
| **Bronchitis** | 48( 7.8) | 52( 8.4) |
| **Hypertension** | 48( 7.8) | 93 ( 15.1) |
| **Cataract** | 37( 6.0) | 45( 7.3) |
| **Headache** | 37( 6.0) | 41( 6.7) |
| **Musculoskeletal pain** | 35( 5.7) | 32( 5.2) |
| **Influenza** | 32( 5.2) | 31( 5.0). |
| **Confusion** | 31( 5.1) | 26( 4.2) |
| **Diarrhoea** | 31( 5.1) | 32( 5.2) |
| **Bone pain** | 30( 4.9) | 16( 2.6) |
| **Pyrexia** | 30( 4.9) | 20( 3.2) |
| **Dizziness** | 29( 4.7) | 31( 5.0) |

**Table 14. Most frequent AE's reported during the first 3 days after infusions, compared with those occurring at other time points.**

| Preferred Term (Number/ percentage reporting a particular event) | Events reported ≤ 3 days after infusions | | Events reported > 3 days after infusions | |
|---|---|---|---|---|
| | ZA (N=613) | Placebo (N=616) | ZA (N=613) | Placebo (N=616) |
| **Headache** | 20 (3.3) | 16 (2.6) | 19 (3.1) | 26 (4.2) |
| **Myalgia** | 19 (3.1) | 15 (2.4) | 11 (1.8) | 10 (1.6) |
| **Pyrexia** | 19 (3.1) | 10 (1.6) | 13 (2.1) | 10 (1.6) |
| **Bone pain** | 18 (2.9) | 9 (1.5) | 12 (2.0) | 7 (1.1) |
| **Back pain** | 14 (2.3) | 9 (1.5) | 106 (17.3) | 107 (17.4) |
| **Arthralgia** | 10 (1.6) | 8 (1.3) | 112 (18.3) | 102 (16.6) |
| **Nasopharyngitis** | 6 (1.0) | 0 | 56 (9.1) | 61 (9.9) |
| **Pain in extremity** | 6 (1.0) | 2 (0.3) | 47 (7.7) | 52 (8.4) |
| **Cataract** | 4 (0.7) | 2 (0.3) | 33 (5.4) | 43 (7.0) |
| **Urinary tract infection** | 3 (0.5) | 3 (0.5) | 75 (12.2) | 91 (14.8) |
| **Osteoarthritis** | 3 (0.5) | 2 (0.3) | 56 (9.1) | 50 (8.1) |
| **Musculoskeletal pain** | 3 (0.5) | 2 (0.3) | 33 (5.4) | 30 (4.9) |
| **Bronchitis** | 1 (0.2) | 0 | 47 (7.7) | 52 (8.4) |
| **Hypertension** | 0 | 4 (0.6) | 48 (7.8) | 90 (14.6) |
| **Influenza** | 0 | 1 (0.2) | 32 (5.2) | 30 (4.9) |
| **Fall** | 0 | 1 (0.2) | 53 (8.6) | 61 (9.9) |

### *Deaths and other serious adverse events*

Table 15 gives a rough overview of the 44 patients who died during the study period (26 of them in the ZA group). After adjudication by an eight member committee, 15 of the deaths in the ZA treatment group were reclassified as due to "unknown" causes, compared to four in the placebo group. With respect to *Other treatments* administered there were no major differences between the two treatment groups.

**Table 15. Causes of death in the two treatment groups**

| | ZA | Placebo |
|---|---|---|
| **Safety population** | 613 | 616 |
| | | |
| **Cardiac Disorders (infarct, arrest, failure)** | 8 | 3 |
| **Infections (pneumonia, sepsis)** | 5 | 1 |
| **Nervous System Disorders (haemorrhage, ischemic stroke)** | 4 | 2 |
| **General Disorders (delirium, malignancy unknown origin)** | 3 | 0 |
| **Gastrointestinal Disorders** | 2 | 1 |
| **Respiratory Disorders** | 2 | 3 |
| **Injury** | 1 | 3 |
| **Neoplasms** | 1 | 5 |
| **Total no of deaths** | 26 | 18 |

Similarly, there were more serious adverse events reported for the ZA than for the placebo group (191 versus 168 cases; not statistically significant) but this difference was not drug related. Atrial fibrillation was more common among the ZA than the placebo patients (21 versus 13) but the difference was not statistically significant. The discovery of the arrhythmia seemed unrelated in time to the administration of the study drug.

### *Discontinuation due to adverse events*

Table 16 lists some of the causes that led to discontinuation of the drug. A total of 51 ZA patients discontinued which can be compared to 43 placebo discontinuations, but this difference (which was due mainly to the larger number of cardiac events in the ZA group) was not statistically significant. The numbers of patients who discontinued because of a fall in creatinine clearance showed no treatment-related differences.

**Table 16. Adverse events leading to premature discontinuation.**

| | ZA | Placebo |
|---|---|---|
| **Safety population** | 613 | 616 |
| | | |
| **Cardiac Disorders (infarct, failure, arrhythmia)** | 11 | 3 |
| **Nervous System Disorders (haemorrhage, ischemic stroke, dementia)** | 9 | 6 |
| **Investigations (creatinine clearance diminished** | 7 | 6 |
| **Injury (vehicular accidents)** | 5 | 5 |
| **Neoplasms (breast, colon)** | 5 | 9 |
| **Infections (pneumonia, urinary tract infections)** | 4 | 4 |
| **Renal and urinary disorders** | 3 | 1 |
| **Respiratory Disorders** | 3 | 3 |
| **Hematological Disorders** | 2 | 1 |
| **Gastrointestinal Disorders** | 2 | 1 |
| **General Disorders** | 1 | 2 |
| **Musculoskeletal Disorders (arthralgia, Myalgia)** | 0 | 2 |
| **Total no of premature discontinuations** | 51* | 43* |

* Patients with multiple AE's were counted only once.

### *Laboratory Tests*

*Liver functions*

There were no consistent abnormalities in liver function either in this study or in the larger pivotal studies.[6, 12, 15]

*Kidney functions*

Soon after the release of zoledronic acid for the treatment of malignant disorders, there appeared a number of anecdotal and retrospective reports[39, 40, 42, 43] describing an apparent association between the use of this intravenous bisphosphonate and the development of renal failure. It was subsequently pointed out [41, 43] that many of the patients with post-ZA renal failure suffered from multiple myeloma or other malignancies and were in addition to ZA receiving treatment with other potentially nephrotoxic agents. Moreover, the doses of ZA prescribed for patients with malignancies are significantly larger (about 50 mg/year) than those recommended for osteoporosis.

Nevertheless, in some of the pivotal controlled trials involving single or annual infusions of 5 mg ZA for non-malignant conditions,[6,12] post-treatment serum creatinine elevations were observed in a small but significant proportion of patients when a particular search was made for this complication. In the HORIZON trial[6] 31 patients (1.3%) had an increase of more than 0.5 mg/dl (45 μmol/L) in serum creatinine 9-11 days after ZA infusion, compared with 10 patients (0.4%) after a placebo infusion (P< 0.001). All patients recovered spontaneously and by the end of the observation period serum creatinine and calculated creatinine clearance rates did not differ significantly between the two treatment groups.[6]

Similar findings were reported in the present study. An increase in serum creatinine occurred in 18/612 patients in the ZA group (2.94%) and 4/615 placebo patients (0.65%). However, the statement by Oh *et al*.[40] that the ZA associated deterioration in renal function is aggravated by the duration of exposure was not confirmed in the current trial. The small decline in mean creatinine clearance over the three years of observation was similar in the two treatment groups (minus 3.18±8.06 mL/min in the ZA group versus minus 3.85±9.75 mL/min in the placebo group.)

*Evaluator Comment:*

There is no doubt that a single 5 mg ZA infusion, even when given under trial conditions to individuals with previously normal renal function, can cause mild, transient elevations in serum creatinine in a small percentage of patients. This problem does not appear to become aggravated when the duration of treatment is increased from 3 to 6 years.

### *Other clinical chemistry parameters*

*Serum calcium*

Anti-osteoclastic agents such as bisphosphonates[45] and denosumab [46] are known to cause hypocalcemia. Indeed, the first indication to be approved for the clinical use of ZA was the reduction in serum calcium in patients with hypercalcemia of malignancy. It was therefore not surprising that this potent osteoclast poison may cause hypocalcemia in some patients,[47,48] particularly in the presence of hypomagnesaemia [49] renal failure[49] and vitamin D deficiency. [35,36] However, in vitamin D replete, adult patients with normal renal and parathyroid function ZA rarely causes clinical hypocalcemia with tetany and epileptiform seizures.

In the pivotal HORIZON study[6] 49 patients with available data developed hypocalcemia (serum calcium <2.075 mmol/L) 9-11 days after the first infusion whereas only one placebo patient was reported with the same finding. All the hypocalcemic patients were asymptomatic[50] and in all of them the biochemical abnormality disappeared spontaneously. Moreover, among the zoledronic acid recipients, the incidence of hypocalcemia decreased dramatically between the first infusion (49/2015 = 2.4%) and the second (2/1594 = 0.1%) and third (5/1483 = 0.3%) infusion, this was presumably because by the time the patients presented for their second infusion they had been receiving vitamin D supplements for twelve months and were no longer vitamin D deficient. Hypocalcemia was mild and only 9 of the 56 patients in the ZA group had serum calcium concentrations <1.87 mmol/L. [50]

The patients in the current trial were selected on the basis of having previously received annual ZA infusion for three years (as well as vitamin D and calcium supplements). There was not a single adjudicated case of hypocalcemia in either the ZA extension or in the placebo group.

Similarly, the investigators who studied the use of ZA in the prevention and treatment of corticosteroid induced osteoporosis, who did not accept vitamin D deficient subjects into their trial,[33] found only one case of asymptomatic hypocalcemia 11 days after a ZA infusion.

*Evaluator Comment*

Single ZA infusions cause transient asymptomatic hypocalcemia in 2-3 % of patients. Symptomatic hypocalcemia also occurs but it wa rare. Hypocalcemia (asymptomatic or symptomatic), in general, occurs in the presence of other abnormalities, particularly

vitamin D deficiency. The problem was not aggravated by the prolongation of ZA treatment from three to six years.

*Haematology*

A single case of thrombotic thrombocytopenic purpura attributed to zoledronic acid was reported in 2004.[51] Two ZA patients in had low platelet counts; however, the first who was desperately ill with septicaemia, was receiving multiple other drugs, while the second was suffering from a general myelodysplasia. More worrying is the World Health Organisation (WHO) "Vigisearch" database[52] which lists 79 reports of "Thrombocytopenia" in its Zoledronic Acid file, 44 of them reported in 2009 and 2010. The large controlled trials [6, 15, 32] do not suggest a cause and effect relationship between ZA and haematological disorders and the known pharmacokinetic properties of ZA [3, 4] make such a relationship unlikely. In this study, the haematological findings give no cause for concern.

*Electrocardiogram (ECG) and Atrial Fibrillation*

The large pivotal HORIZON trial[6] produced a totally unexpected finding: atrial fibrillation (AF; reported as a serious adverse event) was more common in the ZA than in the placebo patients (50/3862 versus 20/3852, p <0.001). There was no temporal relationship between the arrhythmic events and the infusions. A subset of 559 patients in the same trial [6] had an ECG performed before and 9-11 days after the third infusion. The prevalence of atrial fibrillation was 2.1% in the ZA group and 2.8% in the placebo group (NS).

In the sponsor's study all patients were supposed to have ECG recordings taken before the third extension infusion (5 years after entering the original trial), 9-11 days later and 90 days later. While less than half the patient in each treatment group actually had their ECG evaluated for conduction and rhythm abnormalities, no consistent treatment-related changes were found. The prevalence of cardiac arrhythmias was greater in the ZA than in the placebo group but the difference was not statistically significant.

Since the publication of the pivotal trial, there have been multiple studies attempting to confirm, refute or explain away the statistical association between atrial fibrillation and bisphosphonate administration. Subsequent controlled trials using ZA,[15, 31, 32, 53] (none as large as the HORIZON study and some[31,53] involving younger patients), have failed to confirm this association. Cummings *et al*.[54] who re-analysed their data from one of the pivotal alendronate /placebo trials found a trend towards serious adverse events involving atrial fibrillation in the alendronate group, but this did not reach statistical significance.

Population-based, retrospective, case-controlled studies (involving mainly oral bisphosphonates) have produced mainly negative results. Sørensen *et al*. [54] compared the case records of 13,586 women with atrial fibrillation with those of 68,054 non-fibrillating age-matched controls (40% over the age of 80 years in each group). The current use of oral bisphosphonates was low (approximately 3%) and did not differ between the two groups.[54] Abrahamsen *et al*. [55] compared case records of 14,302 in patients with fractures exposed to oral bisphosphonates with age- and sex-matched fracture patients not exposed to these drugs. The hazard ratio (HR) for the diagnosis of atrial fibrillation in bisphosphonate users was 1.18 (1.08-1.29) after adjustment for other medications and co-morbidity, but the risk was inversely proportional to drug adherence. Bunch *et al*[56] studied a group of 9,623 patients who underwent coronary angiography at their facility. Ninety eight of these had been treated with bisphosphonates, 9,525 had not. The bisphosphonate users were older and more likely to have hypertension, heart failure and to have had a previous myocardial infarct. Despite these risk factors, bisphosphonate use was not associated with AF in this study. Arslan *et al*. [57] described a small series of patients with metastatic malignancies treated with ZA. The mean age was 55 years, the mean period of

observation was 13.4 months and the mean cumulative ZA dose was 54 mg per patient. ECG examinations showed no atrial fibrillation in any of the patients.

Just when it seemed that the evidence was generally against an association between bisphosphonates and atrial fibrillation, Wilkinson *et al*.[58] published a positive result: Using the "SEER Medicare" database, they identified 6857 patients aged ≥ 65 years suffering from various malignancies and treated with intravenous bisphosphonates (pamidronate or zoledronic acid) between January 1 1995 and December 31 2003. These patients were age, sex and diagnosis-matched on a 1:2 basis with 13,714 cancer patients who had not been treated with any bisphosphonate. Intravenous bisphosphonate treatment was associated with an increased risk for atrial fibrillation (HR =1.30, 95% CI 1.18-1.43), all supraventricular tachycardias (HR =1.28, 95% CI 1.19-1.38) and stroke (HR =1.30, 95% CI 1.09-1.54). The risk of occurrence for all supraventricular tachycardias increased by 7% for each five bisphosphonate doses (4 mg ZA or 90 mg pamidronate).

*Evaluator Comment*

The evidence concerning the association between ZA administration and atrial fibrillation is conflicting. The current trial does not suggest that the prolongation of ZA treatment (5 mg /year) from 3 years to six years increases the risk of cardiac arrhythmias.

### *Other safety issues*

*Inflammatory eye problems*

The association between bisphosphonate administration and uveitis has been known for many years,[59, 60]. Case reports continue to appear describing a temporal relationship between bisphosphonates, including ZA[61-65] and ocular inflammatory disorders. The "Vigisearch" database[52] contains reports of 112 patients who developed "iritis," iridocyclitis," "uveitis," "scleritis," and "episcleritis."

The cause and effect relationship was questioned by French and Margo[66] who performed a retrospective survey of 35,252 US veterans who were given a new prescription for bisphosphonates during the 2006 financial year. Twenty-eight of these were recorded as suffering from "uveitis" or "scleritis" during the six-month period after the drug (mainly alendronate, 70 mg /week) was dispensed (7.9 cases per 10,000 prescriptions). This rate did not differ significantly from that observed among veterans not taking bisphosphonates.[62] Moreover, 12 of the 28 patients with inflammatory eye disorders described by French and Margo [66] suffered from systemic disorders known for their association with ocular complications (ankylosing spondylitis, rheumatoid arthritis, sarcoidosis).

French and Margo's[66] statistical analysis notwithstanding, the evaluator found it difficult to ignore the case reports[62-65] describing severe ocular inflammatory changes within 72 h of zoledronic acid administration. In the sponsor's study (which excluded patients with a history of uveitis), all suspected ocular adverse events (12 in the ZA group, 17 in the placebo group) were adjudicated by an independent, blinded ophthalmologist who considered that none of the 12 ocular events in the ZA group were possibly or probably drug related.

*Evaluator Comment*

Only rarely do ZA users develop inflammatory eye disease within 72 h of the first infusion. There was no evidence either in the current application or in the literature that the risk for this complication may be aggravated by extending the treatment period from three to six years.

*Osteonecrosis of the jaw*

Since Marx[67] and Ruggiero *et al*[68] first published their observations concerning the association between bisphosphonates and osteonecrosis of the jaw (defined as the presence of exposed bone in the maxillofacial region which did not heal within 8 weeks after identification by a health professional [16]) there have been scores of single and multiple case reports confirming this association. Lists of these reports are to be found in the reviews by Woo *et al*.,[69] Khosla *et al*.[16] and in particular in the paper by Palaska *et al*.[70] Attempts to deny[71] or cast doubt[72] on the role of bisphosphonates in the pathogenesis of this condition have been discredited, [73] and while the prevalence[74, 75] and the etiology[76] of bisphosphonate-induced jaw necrosis remain in doubt, the existence of the syndrome seems firmly established. The "Vigisearch" database for ZA[52] contains 1129 reports of osteonecrosis of the jaws.

One of the very few prospective studies of jaw osteonecrosis was performed as part of the "head to head" study comparing denosumab with ZA. [31] In this double blind, double dummy study, 2049 women with metastatic breast cancer were randomized to receive either 4 mg ZA intravenously or 120 mg denosumab subcutaneously, every 4 weeks. Formal examinations of the oral cavity were performed at baseline and every six months. Patients with oral lesions at baseline were excluded. Those who developed oral lesions were seen by members of a blinded adjudication committee who determined whether the diagnosis of osteonecrosis was appropriate. Over the three-year observation period, osteonecrosis of the jaw developed in 14 /1013 ZA patients and in 20/1020 patients in the denosumab group. The cumulative incidence in the ZA group was 0.5% at 1 year, 1.2% at two years and 1.4% at three years. Eleven of the 14 ZA patients with osteonecrosis were receiving or had received cancer chemotherapy, four had previously received oral bisphosphonates and two were receiving anti-angiogenic agents. The earliest osteonecrosis lesion was found at six months.

Fehm *et al*[77] who performed a retrospective analysis of 345 patients who had received bisphosphonate infusions found that their ten patients with osteonecrosis (2.9%) had all been given zoledronic acid. In these ten patients the median number of treatment cycles (4 mg/4weeks) was 21 (range 6-62) whereas in patients treated with ZA who did not develop jaw osteonecrosis the median number of treatment cycles was 8 (range 1-90). The mean cumulative ZA dose among the patients with osteonecrosis (range 24 -136 mg ) was approximately twice that of those who did not.

In view of the difference in dosages, the relevance of these findings to the treatment of osteoporosis has not been established. Among the 3875 ZA patients in the pivotal HORIZON trial [6] there was one case of osteonecrosis of the jaw which can be compared to 1/3861 patients in the placebo group. None of the 416 patients randomized to receive ZA for the prevention or treatment of glucocorticoid-induced osteoporosis[33] developed this complication. In the sponsor's trial, the adjudicating committee found one case of osteonecrosis of the jaw among the 613 ZA patients and one doubtful case among the 616 placebo patients. However, routine examinations of the oral cavity were not performed in any of these studies.

Palaska *et al*.[70] performed a detailed analysis of 112 articles on the subject published since 2003. They calculated mean times of onset and cumulative doses of bisphosphonates prescribed prior to the diagnosis of osteonecrosis of the jaws. Despite the obvious weaknesses of such statistics, they are the only ones currently available, and a summary is presented in Table 17. A cumulative ZA dose of 49 mg is reached after 10 years of conventional osteoporosis treatment.

*Evaluator Comment*

By mechanisms that are not understood, bisphosphonates (±other factors) cause osteonecrosis of the jaws in a dose and drug type dependent manner. Zoledronic acid, the most potent bisphosphonate currently available, causes osteonecrosis more frequently, after shorter periods of administration and after smaller cumulative doses than other bisphosphonates. A cumulative ZA dose of 52 mg (4 mg every 4 weeks for 1 year, equivalent to 10 years conventional treatment for osteoporosis) produced osteonecrosis in 14/1013 patients.

**Table 17. Osteonecrosis of jaws after different bisphosphonates.**

| **Type of Bisphosphonate** | **Indication** | **No of patients** | **Mean duration of treatment** (years) | **Median minimum duration of treatment** | **Mean** (range) **minimum cumulative dose** (mg) |
|---|---|---|---|---|---|
| **Alendronate (oral), Risedronate (oral)** | Osteoporosis, osteopenia Paget's | 103 | 4.6 | 3 yr | 13,870 (900-72,000) |
| **Pamidronate (IV)** | Malignancies | 145 | 2.8 | 1.5 yr | 2217 (90-6480) |
| **Zoledronic acid (IV)** | Malignancies | 388 | 1.8 | 10 mo | 49 (4-192) |

Data from multiple case reports collated by Palaska *et al*.[70]

### *Other safety issues*

*Atypical fractures (with oral bisphosphonates).*

In 2005, Odvina *et al*.[78] published a widely cited[79] and much criticised paper drawing attention to an unusual type of fracture that occurs in patients exposed to bisphosphonates. These fractures involve predominantly the subtrochanteric regions of the femora, they occur with little trauma while patients "perform their normal daily activities,"[78] stand on a crowded train [80] or walk in the street.[81] A characteristic X-ray pattern consists of lateral cortical thickening of the femoral shaft, a transverse or short oblique fracture pattern and "beaking" of the fractured cortex.[82] Most importantly, many of the patients have prodromal symptoms (such as pain in the thigh when weight-bearing), and radiological abnormalities in the contralateral femur with increased isotope uptake in the relevant areas[83]

The concept that bisphosphonates, which prevent fractures,[84, 85] may in a subset of patients, cause a particular type of fracture in its own right has given rise to a great deal of controversy.[17] A group of Danish investigators denies the existence of this syndrome and regards the "atypical" fractures as due to osteoporosis rather than bisphosphonates.[86] Another Danish group [87] recognises the increased risk of femoral shaft and subtrochanteric fractures among bisphosphonate (not raloxifene) users, but attribute it to conditions that were present before treatment was commenced. On the other hand, Dell *et al*., [88] who identified 102 patients with atypical fractures (out of a total of more than 15,000 femoral fractures) found that 97/102 had been taking oral bisphosphonates (average duration of use 5.5 yr). These authors[88] found a significant correlation between the duration of bisphosphonate treatment and the incidence of atypical fractures. The problem is discussed in considerable detail by Shane *et al* and a task force recently set up by the American Society for Bone and Mineral Research.[89]

What is the relevance of all this to zoledronic acid? Only two of the 310 patients with atypical fractures listed by Shane *et al* [89] had received ZA monotherapy. Black *et al*, [17] who

re-analysed the X-ray reports from the pivotal HORIZON trial[6] found only five patients (two of them placebo recipients) with features suggestive of "atypicality." In the sponsor's study there were several patients in the ZA group with femoral fractures, including at least one with a distal fracture, but there was nothing to suggest anything other than osteoporosis.

However, as the cumulative dose of ZA increased (as it will, if treatment continues for six or more years) skeletal problems may appear. While a cumulative dose of 15 mg produces no bony pathology in humans,[90] larger doses (in mice) cause increased bone stiffness and brittleness.[91] Non-compliant patients,[92] who lose the benefits of oral bisphosphonates,[93] are, to some extent, "protected" from the side effects of these drugs. This kind of "protection" is not available for a drug that is given by intravenous infusion on a once yearly basis.

*Evaluator Comment*

Evidence is accumulating that a very small percentage of patients (? 97/300,000)[88] taking oral bisphosphonates (especially alendronate) develop a specific type of "insufficiency" fracture and that the risk of sustaining such a fracture increases as the cumulative dose increases. Such evidence does not exist for ZA which has been used in the treatment of osteoporosis for only 3 years. The current application seeks to remove any time limit for this drug.

### *Post-Marketing Experience*

Since ZA was approved for use in cancer patients in 2002, for Paget's disease in 2006 and for osteoporosis in 2008, there has been a trickle of reports to bodies such as Adverse Drug Reactions Advisory Committee (ADRAC)43 and the WHO database at Uppsala[52] concerning various adverse events. These include the post-infusion "flu-like illness," renal impairment, hypocalcemia, atrial fibrillation, ocular inflammation, jaw necrosis and atypical fractures. However, from a perusal of the available data it would appear that apart from the "flu-like illness," most of these reports involved cancer patients who receive some ten times the dose recommended for osteoporosis. So far, ZA seems to have been well tolerated in osteoporotic patients. The flu-like illness occurs mainly after the first infusion and can be prevented or at least attenuated with paracetamol.[38] The renal impairment was transient, the hypocalcemia was asymptomatic and ocular inflammatory conditions respond to appropriate therapy. Atrial fibrillation is to be expected in a proportion of elderly individuals and aseptic necrosis of the jaws which occurs in some 3.5 % of myeloma patients treated with ZA [94] is excessively rare in individuals receiving a dose of 5 mg/year. Atypical fractures have, so far, been identified in only two patients.

### *Specific Safety Issues of Regulatory Importance*

*Liver toxicity*

There are very few case reports of hepatotoxicity attributable to bisphosphonates.[95, 96] The Vigisearch data base on ZA[52] contains 38 reports listed as "alanine aminotransferase elevation, and 52 reports of aspartate aminotransferase elevation. There was no evidence that these "transaminitis" cases were due to zoledronic acid. The data submitted with the current Australian application and the previous trials involving ZA [6, 12, 14, 15, 32, 33, 34] give no cause for concern in this regard.

*Haematological toxicity*

In the sponsor's study and in the previously published placebo-controlled trials [6, 15] the number of haematological adverse events did not differ significantly between the ZA and the placebo groups.

*Serious skin reactions*

In the sponsor's study and in the previously published placebo-controlled trials, [6, 15] adverse events affecting the skin and subcutaneous tissues were no more prevalent in the ZA patients than in the placebo controls.

*Cardiovascular safety*

In view of the increased incidence of atrial fibrillation in the ZA group in one of the pivotal trials,[6] the organizers of the sponsor's study made a specific search for ECG abnormalities (see Section 8.5.5 above). There were no significant differences between the ZA and the placebo groups.

*Unwanted immunological events*

ZA did not appear to be different from placebo in this respect.

*Musculoskeletal Pain*

The "incapacitating" bone, joint and muscle pain described by Wysowski and Chang[97] for oral bisphosphonates and which appears in the draft Product Information for ZA is currently too vague an entity and insufficiently differentiated from polymyalgia rheumatica to be listed among the suspected adverse events attributable to this drug.

***Other Safety Issues***

*Safety in special populations*

(a) Elderly Patients. Boonen *et al*.[98] performed a post hoc subgroup analysis of 3872 women aged ≥75 years from the two major HORIZON trials. [6, 15] Adverse events (apart from post-dose fever and myalgia) were similar in the two age groups and did not differ significantly between ZA and placebo patients in either age group.

(b) Children. The sponsors do not recommend the use of ZA in children below the age of 18. Paediatricians who used ZA for the treatment of a variety of indications including immobilisation osteoporosis, steroid-induced osteoporosis or osteogenesis imperfecta [99,100] found that a reduction in dosage (to 0.0125 mg /kg) reduced the incidence of hypocalcemia but not the incidence of the acute phase reaction, which, in the Sydney series,[99] occurred in 77% of children. At this dose 42% of children became hypocalcemic (serum calcium < 2.1 mmol/L). See also (d) below.

(c) Uremic patients. The sponsors do not recommend the use of ZA in patients with a creatinine clearance of < 35 mL/min and the clinical evaluator was unable to find reports of patients in whom this injunction was ignored.

(d) Pregnant patients. The large majority of patients receiving zoledronic acid are in the post-reproductive age group. Exceptions include patients who receive this drug for the treatment of metastatic malignancies,[31] for the prevention of glucocorticoid-induced osteoporosis[33] or for the treatment of juvenile osteoporosis. [98, 99] As bisphosphonates have half-lives that are measured in years [101,102] and since ZA is a known teratogen, this aspect should be carefully considered in all females of childbearing age, even if they are not pregnant at the time of ZA administration. Djokanovic *et al*.[103] performed a literature search of bisphosphonate exposure during or before pregnancy and found 51 cases. With the exception of one case of Apert's Syndrome, there were no infants with congenital abnormalities.

### *Safety related drug-drug interactions*

The sponsors do not present any formal studies concerning the possible interaction of ZA with commonly administered drugs such as anti-hypertensives, anti-depressants and anti-coagulants. However, in the various trials involving the administration of zoledronic acid to thousands of patients, both with and without malignant disorders, many of these patients were taking multiple other medications without obvious associations between any of these drugs and adverse reactions. Moreover, ZA at concentrations of up to100 µmol/L does not inhibit or stimulate nine human hepatic P450 enzymes including several drug metabolising enzymes.[7] Also, as ZA is only 50-60% bound to plasma proteins[7], drug-drug interactions are unlikely to be clinically important.

**Evaluator's Overall Conclusions on Clinical Safety**

The applicants have shown, both in the sponsor's trial and in several previous studies,[6, 12, 14, 15, 32, 33] that intravenous zoledronic acid, given in the recommended doses, and infused according to their instructions, is well tolerated. The data in the current Australian submission shows that the administration of ZA for six consecutive years does not lead to a permanent deterioration in renal function, to clinical hypocalcemia, to cardiac arrhythmias, to ocular complications, to jaw necrosis or to "insufficiency" type fractures. The number of deaths was greater than in the placebo group but the difference was not statistically significant and the study drug was not a likely to be a contributing factor. The acute phase reaction which, when it occurs, can be attenuated by ibuprofen or paracetamol[194] was in this trial no more prevalent in the ZA than in the placebo group.

## Clinical Summary and Conclusions

**Benefits**

The benefits of zoledronic acid in the proposed usage are:

- Patients who are treated with zoledronic acid (5 mg/year) for 6 years sustain fewer radiological vertebral fractures during the 4th 5th and sixth years than patients who cease treatment after 3 years.
- Patients who are treated with zoledronic acid (5 mg/year) for 6 years have significantly higher bone densities at the end of the sixth year of treatment than patients who cease treatment after 3 years and then receive placebo infusions for three years.

**Risks**

The risks of zoledronic acid in the proposed usage are:

- Transient rises in serum creatinine during the post-infusion period (9-11 days) which occur more frequently in the zoledronic acid than in the placebo group. However there was no evidence that six years' treatment with zoledronic acid causes any permanent impairment in renal function.

**Benefit-Risk Balance**

The benefit-risk balance of ZA, given the proposed usage, was considered favourable. However, this balance might not remain favourable if treatment is continued beyond six years (based on experience with other bisphosphonates and with ZA in malignant disorders). A statement to this effect should appear in the product information.

**Recommendation Regarding Authorisation**

The sponsors have shown in a randomized, double-blind, placebo-controlled trial, that the extension of zoledronic acid treatment from three years to six years is of some benefit and

does not give rise to significant adverse events. It was therefore recommended that the time limit imposed on this drug at the time of its introduction, be removed.

It was noted, however, that recently the use of bisphosphonates on a long-term basis has repeatedly been called into question. There is mounting evidence that the risks for jaw osteonecrosis[70] and atypical fractures[88] increase with the duration of treatment. These complications are currently quite rare but if bisphosphonate treatment is continued year after year they may become less rare. Moreover, it has been known for years[105] that the beneficial effects of bisphosphonates may last for many years after discontinuation, so that despite the objections of some physicians,[106] several clinical investigators are now advocating the introduction of "drug holidays."[107, 108] There are no scientific data to support or to oppose this concept. It may well be true, that giving bisphosphonates to everyone with low bone densities for the rest of their lives[106] may result in "the greatest good for the greatest number." However, a few patients (or possibly a lot) would be harmed by such a policy. The guidelines as to who benefits from ongoing treatment are still very rough, so that in our current state of ignorance, individual decisions concerning prolonged treatment have to be made by doctors and their patients.

# V. Pharmacovigilance Findings

### Risk Management Plan

A summary of the ongoing safety concerns as specified by the sponsor are tabulated below (Table 18).

**Table 18. Summary of Safety Concerns.**

| Category | Safety concern |
|---|---|
| Important identified risks | Post dose symptoms |
| | Renal dysfunction |
| | Ocular AEs |
| | Hypocalcemia |
| | Osteonecrosis of the jaw |
| | Anaphylaxis |
| Important potential risks | AVN/fracture nonunion and/or delayed union |
| | Cerebrovascular AEs |
| | Atrial fibrillation |
| | Gastrointestinal AEs |
| | Atypical stress fracture (subtrochanteric) |
| Potential interactions | Products that can significantly affect renal function |
| | Paracetamol/acetominophen |
| Missing infomation | Use in pregnancy/lactation |
| | Patients with severe renal impairment |

**Office of Product Review (OPR) evaluator comment:**

The above summary of the ongoing safety concerns was considered acceptable.

The sponsor proposed to monitor the safety concerns of renal dysfunction, ocular adverse events, hypocalcemia, osteonecrosis of the jaw, anaphylaxis, osteonecrosis outside of the jaw (avascular necrosis)/fracture non-union and/or delayed union, cerebrovascular adverse events, atrial fibrillation and use in patients with severe renal impairment via a targeted questionnaire/checklist. However, a copy of this targeted questionnaire/checklist was not provided in the RMP submission. It was recommended to the Delegate that this targeted questionnaire/checklist be submitted for review.

The study timelines and milestones appear acceptable.

**Summary of Recommendations**

The OPR provides the following recommendations in the context that the submitted RMP was supportive to the application; the implementation of a RMP satisfactory to the TGA imposed as a condition of registration; and the submitted European Union (EU)-RMP applicable without modification in Australia unless so qualified:

It was recommended to the Delegate that the sponsor make the following changes to the RMP:

1. The clinical trial ZOL446H2337E1 was proposed as a pharmacovigilance activity to evaluate the safety concerns:

- Osteonecrosis of the jaw and osteonecrosis outside of the jaw (avascular necrosis)
- Fracture non-union and/or delayed union
- Cerebrovascular adverse events
- Atrial fibrillation

The sponsor should be required to include these safety concerns as secondary outcome measures in this trial and not solely monitored through patient reported adverse event reporting.

2. Provide the target questionnaire/checklist that the sponsor proposes in the pharmacovigilance plan to monitor most safety concerns for review.

3. Undertake routine risk minimisation[2] for the safety concerns of osteonecrosis outside of the jaw (avascular necrosis), fracture non-union and/or delayed union, cerebrovascular adverse events, potential interactions - paracetamol/acetaminophen and atypical stress fracture (subtrochanteric).

4. Provide full details on their special infusion services established in Australia (mentioned in Annex 8) and update the RMP accordingly.

5. Provide clinical study reports to the TGA for all studies (ongoing/proposed) when they become available.

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

There were no new quality data submitted with the current Australian application.

## Nonclinical

There were no new nonclinical data submitted with the current Australian application.

## Clinical

The clinical data submission with this application essentially consisted of the results from the three year extension phase of **Study 2301**. No new pharmacokinetic and pharmacodynamic data were provided.

[2] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

The primary objective of this study was to determine whether the bone mineral density (BMD) of the femoral neck (as assessed by DEXA measurements at the end of six years' observation) was affected by the continuation (or discontinuation) of ZA at the end of the initial three years' treatment.

The primary objective of the extension study was to assess the percentage change in bone mineral density (BMD) of the femoral neck as measured by DXA at year 6 relative to year 3 in group Z 6 patients (zoledronic acid for 6 years) compared to group Z3P3 patients (zoledronic acid three years followed by placebo).

Ambulatory postmenopausal women ≤ 93 years who participated in **Study 2301** (and randomised to receive ZA) and completing three years as per protocol were eligible to participate. Exclusion criteria were comprehensive and were in line with other osteoporosis trials.

The clinical evaluator mentioned that the extensive list of exclusion criteria was likely to "produce a study population less 'frail' and more compliant than the general population of 75-year old osteoporotic women".

The primary efficacy variable was the increase in the BMD of the femoral neck between Year 3 and Year 6, between the ZA group and placebo group.

The clinical evaluator mentioned that the baseline demographics were similar between groups. The femoral neck T score was similar, however the number of women with ≥ 2 vertebral fractures was less in the ZA group (183/616 versus 222/617, P< 0.05).

The clinical evaluator concluded that the treatment associated difference was "small but significant". This was seen in both m ITT and PP populations.

Secondary efficacy endpoints in relation to other BMD measurements also showed statistically significant difference favouring ZA. However, the incidence of clinical fractures which was a secondary endpoint was not statistically significant between groups.

**Safety**

Based on previously submitted data the clinical evaluator stated that within a few days of a ZA infusion, a proportion of patients develop a 'flu like illness which subsides spontaneously and appears not to be associated with long term sequelae.

In relation to renal impairment, in controlled osteoporosis trials (ZA-5 mg /year), there was transient post infusional rise in serum creatinine that "recovered" in 12 months.

In the sponsor's study, the frequently reported AEs are listed in Table 14. There were no significant differences seen between the two treatment groups. In relation to treatment related AEs, the acute phase reactions were higher in the ZA group. Other AEs appeared to be evenly distributed.

The fatalities were reported in a greater number of subjects in the ZA group (n=26) compared to placebo (n=18). This should be included in the PI. However, on reviewing the individual patient data the evaluator mentions that there was no cause for concern. The increase in the ZA group was due to an increased number of cardiac events (11 versus 3). The evaluator mentions that AF, hypocalcaemia, inflammatory eye disease, transient increase in creatinine did not increase with increased duration.

The number and duration were inadequate to assess ONJ and atypical fractures. However, the clinical evaluator stated that "Zoledronic acid, the most potent bisphosphonate currently available, causes osteonecrosis more frequently, after briefer periods of administration and after smaller cumulative doses than other bisphosphonates. A

cumulative ZA dose of 52 mg (4 mg every 4 weeks for 1 year, equivalent to 10 years conventional treatment for osteoporosis) produced osteonecrosis in 14/1013 patients."

### Overall conclusions of the clinical evaluator

The clinical evaluator mentioned those who continued treatment for six years had significantly higher bone densities and fewer radiological fractures than those who discontinued at three years. The difference between two groups at 6 years was small, there being a residual ZA effect in those who had stopped treatment (discontinued) for three years.

In relation to safety, there was no obvious increase in adverse effects noted when increasing the duration from three to six years.

Overall, the clinical evaluator recommended removal of the time limit. It was recommended that the PI include a statement that "the optimum duration of bisphosphonate treatment is currently unknown. The risk: benefit ratio of prolonged therapy should be estimated in each patient".

## Risk Management Plan

The Delegate made no comments regarding the RMP.

## Risk-Benefit Analysis

### Delegate Considerations

1. Risk benefit ratio in those administered Aclasta for over three years (that is, six years) in this study was difficult to assess as the number of subjects recruited was inadequate to detect rare adverse events such as ONJ, atypical fractures that have been reported with bisphosphonates. Thus, the data submitted do not provide adequate evidence of safety with prolonged use (more than three injections). This needs to be addressed in the RMP.
2. Though there was a statistically significant difference in BMD at the end of six years between the group that continued on Aclasta (six years in total) and the group that was administered placebo for the last three of the six years, the clinical fracture incidence was not significantly different. The letter of application states that "no significant difference was observed in risk of clinical fracture between the groups (HR 1.04, 95% CI 0.71 to 1.54, p=0.8368) indicating no higher risk of fracture in those who discontinue zoledronic acid therapy than in those who continue zoledronic acid therapy". Figure 2 shows that discontinuing treatment after three years maintains the BMD at approximately 4% above baseline level. Continuing treatment for the extra three years appears not to result in significant 'clinical fracture' reduction. Efficacy in relation to fracture reduction (between the two groups) was marginal. Thus, there is no overwhelming evidence of a positive risk benefit balance in continuing <u>all</u> patients for six years or <u>indefinitely</u>. In this study, the subset that would benefit from continued treatment has not been identified. The sponsor could in its pre-ACPM response, provide an analysis on BMD in the subgroup that is likely to benefit from more than 3 ZA injections.

3. In this context, the Delegate recommended removal of the time limit, provided the PI include the following statements :
   - The subpopulation that will benefit from prolonged treatment should be stated.
   - In treating patients beyond three years, individual risk benefit should be estimated. There also should be a statement that the duration relating to optimum therapy is not known.

- Patients who have been pretreated with other bisphosphonates are not suitable.
- No statistically significant difference in clinical fracture rates have been reported in the group continuing treatment with ZA for over three years.
- No data are available on recommencing therapy after cessation of treatment.
- The PI should disclose the number needed to treat.

The advice of the Advisory Committee on Prescription Medicines (ACPM) was sought.

## Summary of the Response from Sponsor

Novartis concurred with the Delegate's recommendation and addressed the issues raised in the Delegate's overview below.

**Issue and Recommendation 1:**

> "Risk benefit ratio in those administered Aclasta for over 3 years (that is, 6 years) in this study is difficult to assess as the number of subjects recruited is in adequate to detect rare adverse events such as ONJ, atypical fractures that have been reported with bisphosphonates. Thus, the data submitted do not provide adequate evidence of safety with prolonged use (i.e. more than 3 injections). This needs to be addressed in the RMP. "

Novartis did not agree with the Delegate's conclusion that the data submitted does not provide adequate evidence of safety with prolonged use. As stated in the Delegate's Overview "there was no obvious increase in adverse effects noted by increasing the duration from 3 to 6 years."

Adverse events such as ONJ and atypical fractures occur very rarely. The incidence of ONJ has been estimated at less than 1 in 100,000 patient years of exposure. Subtrochanteric and diaphyseal fractures, with or without atypical features have been estimated as 1 to 3 reports per 1,000,000 patient years of exposure. In addition, a causal association with such adverse events and bisphosphonates has not been established.

As stated in the RMP: "ONJ has been reported predominantly in patients with cancer receiving treatment regimens including bisphosphonates. Many of these patients were also receiving chemotherapy and corticosteroids." ONJ has been reported in patients not treated with bisphosphonates and regions of necrotic bone have been reported in the mandible of elderly individuals. There is currently not enough evidence to establish causal relationship between bisphosphonate use and ONJ.

Furthermore, detailed information on ONJ is available to Australian prescribers and patients (refer to PI and Consumer Medicine Information). Novartis also undertakes routine pharmacovigilance in the form of a targeted checklist for ONJ. The information contained in the RMP and PI on atypical fractures is currently limited. Novartis currently undertakes routine pharmacovigilance, including a targeted checklist follow-up for atypical fractures, and cumulative analysis in the Periodic Safety Update Report (PSUR). The PI includes a warning in relation to this risk.

However, as this risk increases with the duration of treatment, Novartis has collaborated with the ASBMR Task Force to provide information on this risk. The FDA has reviewed the risk of atypical fractures in patients who take bisphosphonates for osteoporosis. As a result, in October 2010 the FDA requested all sponsors of bisphosphonates approved to treat osteoporosis to update the US Prescribing Information and develop a Risk Evaluation and Mitigation Strategy (REMS) including a Medication Guide. The approval for this update was granted on 25 January 2011.

In October 2010, in the European Union (EU) the Committee for Human Medicinal Products (CHMP) at the EMA has begun looking at the possible increased risk of atypical stress fractures in patients taking bisphosphonate containing medicines for the treatment and prevention of bone disorders.

The CHMP will review all available data thoroughly, including published data, nonclinical and clinical data and post-marketing reports, to clarify whether atypical stress fractures are a class effect of bisphosphonates, and will assess their impact on the balance of risks and benefits of these medicines. It was expected that the CHMP assessment and potential list of outstanding issues would be available in March 2011.

In order to ensure a simultaneous communication on the safety changes of the labelling information worldwide, Novartis plans to update the Company Core Data Sheet once the above mentioned assessments are completed. The sponsor was awaiting the decisions of the EU health authorities in relation to any required updates to labelling and other RMP activities.

Due to the concerns raised by the Delegate regarding the safety of prolonged use, Novartis agreed on the inclusion of the recommended risk benefit statement in the PI which relates to prolonged use of zoledronic acid. A statement on the optimum duration of bisphosphonate treatment and a statement regarding the risk benefit ratio being estimated in each patient have been added to the PI.

In the RMP, the following actions will provide additional evidence of safety with prolonged use:

- three year extension study to CZOL446H2301E1 is ongoing, approximately 200 patients (100 patients with 9 years treatment of zoledronic acid) and will be completed in the third quarter of 2013. Adjudication in areas of interest is ongoing.
- Scandinavian registry study (CZOL446H2202), five-year health registry study to compare safety of Aclasta versus oral BPs and untreated controls.

Novartis therefore believed that the submitted RMP addressed the risks associated with the treatment with zoledronic acid.

**Issue and Recommendation 2:**

> "In this study, the subset that would benefit from continued treatment has not been identified. The sponsor could.....provide an analysis on BMD in the subgroup that is likely to benefit from more than 3 ZA injections."

There was no subgroup analysis of BMD to identify patients who would benefit from continued Aclasta use (after 3 years) from the clinical study report. This was not part of the analyses plan. However, there was a significant treatment associated difference in BMD at the femoral neck of patients who continue for 3 years compared to patients who cease therapy at 3 years, as noted by the Delegate. Moreover the DEXA-determined BMD changes at sites other than the femoral neck showed that additional Aclasta treatment was significantly superior to placebo in inducing increases in BMDs. The clinical evaluator concluded that the extension of Aclasta treatment from 3 to 6 years offers benefit without giving rise to significant adverse events. For this reason the sponsor considered that all patients who respond well to Aclasta in the first 3 years should be eligible to continue treatment.

**Issue and Recommendation 3:**

> *Point 3:* Patients who were pretreated with other bisphosphonates are not suitable.

The current application deals with removing the time limit to effectively permit use of Aclasta in patients who have already received three years of Aclasta treatment. The issue of patients pre-treated with oral bisphosphonates was addressed in our original application to register Aclasta. The question of the appropriateness of switching to Aclasta in patients who have received several years of oral bisphosphonate treatment was raised by the Delegate and addressed in our response to TGA at the time.

Important information to address this matter comes from the bone turnover marker results of Study 2313 which were included in our previous application. In this study, women treated with alendronate for at least 12 months (with a mean treatment period of 4 years) were randomised to receive either a single 5 mg dose of zoledronic acid or alendronate 70 mg weekly for 52 weeks. They were monitored over 12 months for change in BMD and the levels of three different validated markers of bone turnover.

As expected, patients who remained on alendronate maintained bone turnover close to, or just below, their baseline level over the 12 month course of the study. For those in the zoledronic arm, bone turnover decreased to below the baseline level at 3 months after dosing, then returned to about the baseline levels at 6 months and continued to increase above the baseline level at the 9- and 12-month time points, while still remaining within the premenopausal reference range. This study demonstrated that patients who have been maintained on oral bisphosphonate therapy can be switched to zoledronic acid without a washout period, and that this switch does not lead to oversuppression of bone turnover.

Novartis therefore did not agree that patients pretreated with other bisphosphonates are not suitable and believe that the current wording in the PI satisfactorily counsels prescribers:

> "Consider carefully before using Aclasta in patients who have been extensively pretreated with other bisphosphonates."

Patients in the Core Study (H2301) included patients who had taken Bisphosphonates in the past and had followed the required washout periods. The washout period consisted of between two months and two years, depending on the duration of pretreatment.

In addition to the precaution stated above, the Aclasta PI also notes that:

> "There are limited 12 month evaluated clinical data on the use of Aclasta in patients who had been extensively treated with bisphosphonates but without a washout period.....This experience should be considered when selecting patients for Aclasta treatment."

Novartis contend that this information was consistent with the current clinical data available in regards to Aclasta and pre-treatment with other bisphosphonates.

**Advisory Committee Considerations**

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

ACPM recommended approval of the submission from Novartis Australia Pty Ltd to register zoledronic acid (ACLASTA / OSTEOVAN) solution 5 mg/100 mL for an extension of indications to remove the current restriction of a maximum of 3 doses (abridged):

> *Treatment of osteoporosis in postmenopausal women; Treatment of osteoporosis in patients over 50 years of age with a history of low trauma hip fracture; Treatment of osteoporosis in men; Treatment of osteoporosis in long-term glucocorticosterioid users; prevention of glucocorticosteroid-induced bone loss; Treatment of Paget's disease.*

The ACPM noted that the three year (3 dose) restriction followed from the evidence submitted in the original pivotal trial. The single clinical trial submitted shows a small but significant difference in bone mineral density (BMD) between treatment and placebo groups at three years which was maintained to six years. The effect of continued therapy was small in comparison to the effect of zoledronic acid in the first three years. A relative risk reduction of 52% was also shown in radiological fractures in the zoledronic acid group versus placebo, but not in clinical fractures.

No significant new safety signals were evident but it was noted that the study provided was underpowered to detect osteonecrosis of the jaw and atypical fractures. Atypical fractures undoubtedly occur but a t a low rate. More data is needed as they were not assessed by the sponsor in the submitted study. Active collection of post market of data on these issues should be considered.

The ACPM was concerned that the standard doses have not been completely validated, nor has the frequency, and this submission provided no better information on the optimal dose and frequency of treatment. All patients on bisphosphonate therapy should have the need for continued therapy re-evaluated on a periodic basis. It was noted that the sponsor has agreed to insert the statement the optimal duration of bisphosphonate therapy is currently unknown. The risk benefit ratio of prolonged therapy should be estimated with each patient. No data are available on recommencing therapy after cessation of treatment.

The ACPM, taking into account the submitted evidence of safety and efficacy, considered there was a favourable benefit-risk profile for this product.
The ACPM considered the specific conditions of registration should include:

- Provision of any reports that might provide safety updates on ONJ or atypical fractures.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Aclasta zoledronic acid 5mg/100mL injection solution vial and Osteovan zoledronic acid 5mg/100mL injection solution vial, indicated for:

> *Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures.*
>
> *Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fracture.*
>
> *To increase bone mineral density in men with osteoporosis.*
>
> *To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use.*
>
> *To prevent glucocorticoid-induced bone mineral density loss.*
>
> *Treatment of Paget's disease of bone.*

The following Special Condition of Registration applies to this product:

- Any reports that might provide safety updates on osteonecrosis of the jaw (ONJ) or atypical fracture must be notified to the TGA immediately.

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# Attachment 1. Product Information

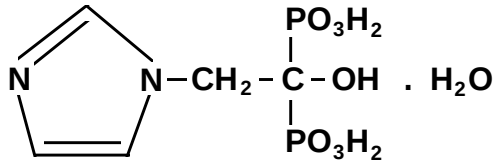
The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

# ACLASTA®
**zoledronic acid**

## NAME OF THE MEDICINE

The active ingredient of Aclasta® is a bisphosphonate, zoledronic acid, or 1-hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diphosphonic acid. Although zoledronic acid is marketed by Novartis as a monohydrate, doses refer to the anhydrous substance.

The chemical structure of zoledronic acid monohydrate is:




## DESCRIPTION

Zoledronic acid monohydrate is a white, crystalline powder. It is soluble in water, most soluble at neutral pH (>290 mg/mL; pH=6.8) and practically insoluble in organic solvents.

| | |
|---|---|
| Empirical formula: | $C_5H_{10}N_2O_7P_2 \cdot H_2O$ |
| Relative molecular mass: | 290.11 |
| CAS number: | 165800-06-6 (zoledronic acid monohydrate)<br>118072-93-8 (zoledronic acid anhydrous) |

Aclasta 5 mg/100 mL solution for infusion contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

Aclasta contains the following excipients: mannitol, sodium citrate, water for injections.

Zoledronic acid is also marketed as a 4 mg/5 mL concentrated injection for infusion and as a powder for injection containing 4 mg of zoledronic acid for use in patients with malignancies under the trade-name Zometa®.

# PHARMACOLOGY

## Pharmacodynamics

**Pharmacotherapeutic group:** Bisphosphonate (ATC code: M05B A08).

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The action of bisphosphonates on bone is based on their high affinity for mineralised bone. Intravenously administered zoledronic acid is rapidly distributed to bone. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms.

### Osteoporosis

Aclasta treatment rapidly reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralisation or the mechanical properties of bone. Histomorphometric data from long-term rat and monkey experiments showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclast activity and activation frequency of new remodelling sites in both trabecular and Haversian bone. Continuing bone remodelling was observed in bone samples from all animals treated with zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid and no woven bone in treated animals.

**Bone Histology:** In the postmenopausal osteoporosis treatment trial, bone biopsy specimens were obtained between months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Aclasta. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76

specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralisation defects.

In the treatment and prevention of glucocorticoid-induced osteoporosis trial, bone biopsy specimens were obtained at month 12 from 23 patients treated with either an annual dose of Aclasta or daily oral risedronate (12 in the Aclasta treatment group and 11 in the risedronate treatment group). All biopsies were adequate for qualitative histomorphometry assessment. Qualitative assessments showed bone of normal architecture and quality without mineralisation defects. Apparent reductions in activation frequency and remodelling rates were seen when compared with the histomorphometry results seen with Aclasta in the postmenopausal osteoporosis population. The long term consequences of this degree of suppression of bone remodelling in glucocorticoid-treated patients is unknown.

**Paget's Disease of Bone**

Paget's disease of bone is a chronic, focal skeletal disorder characterised by greatly increased and disorderly bone remodelling. Excessive osteoclastic bone resorption is followed by irregular osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganised, enlarged and weakened bone structure. Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

In two 6-month randomised comparative, controlled clinical trials in patients with Paget's disease, biochemical markers of bone formation and resorption demonstrated normalisation of bone turnover in more Aclasta treated patients compared to risedronate treated patients (see **CLINICAL TRIALS**).

**Bone Histology:** In the two trials in patients with Paget's disease, bone histology was evaluated in 7 patients 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

**Pharmacokinetics**

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

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

**Distribution**

There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (alpha and beta, with $t_{½}$ values below) presumably represent rapid uptake into bone and excretion via the kidneys.

Zoledronic acid is not highly bound to plasma proteins (approximately 30-60% bound) and binding is concentration and divalent cation ion dependent. Interactions resulting from displacement of highly protein-bound drugs are unlikely.

**Metabolism**

Zoledronic acid is not metabolised in humans. The substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, therefore zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems.

**Elimination**

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½alpha}$ 0.24 and $t_{½beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½gamma}$ 146 hours.

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 ± 2.5 L/h, independent of dose, and unaffected by gender, age,

race or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

No specific drug-drug interaction studies have been conducted with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems.

**Pharmacokinetics in special patient groups**

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 patients studied. Small observed increases in $AUC_{(0\text{-}24hr)}$, by about 30% to 40% in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of drug with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild ($Cl_{cr}$ = 50-80 mL/min) and moderate ($Cl_{cr}$ = 35-50 mL/min) renal impairment are not necessary. The use of Aclasta in patients with creatinine clearance < 35 mL/min is not recommended due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**). No dose adjustment is necessary in patients with creatinine clearance≥ 35 mL/min.

# CLINICAL TRIALS

## Clinical Efficacy for the Treatment of Postmenopausal Osteoporosis

The efficacy and safety of Aclasta were demonstrated in a randomised, double-blind, placebo-controlled, multinational study of 7736 ambulant women aged 65 to 89 years with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Clinical experience in postmenopausal women without a history of low trauma hip fracture is limited to women aged over 63 years. Patients pretreated with other bisphosphonates were excluded except if they complied with a washout schedule of between two months and two years, determined by the duration of pretreatment; for

instance, patients who had used oral bisphosphonates for more than 8 weeks but less than 48 weeks were eligible after a washout period of at least one year; more extensively pretreated patients were eligible after a washout period of at least 2 years. There are limited 12 month evaluated clinical data on the use of Aclasta in patients who had been extensively treated with bisphosphonates but without a washout period. In the pivotal studies, extensively pretreated patients were enrolled after a washout period of two years. This experience should be considered when selecting patients for Aclasta treatment.

Aclasta was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes for a total of three doses. The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years, and the incidence of hip fractures over a median duration of 3 years. 7736 women were evaluated for the incidence of hip and all clinical fractures. Of these, 5661 women were evaluated annually for incidence of vertebral fractures. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day.

**Primary Efficacy Variables**

**Effect on Vertebral Fracture:** Aclasta significantly decreased the incidence of one or more new vertebral fractures over three years and as early as the one year time point (see Table 1).

**Table 1 Summary of vertebral fracture efficacy at 12 months, 24 months and 36 months**

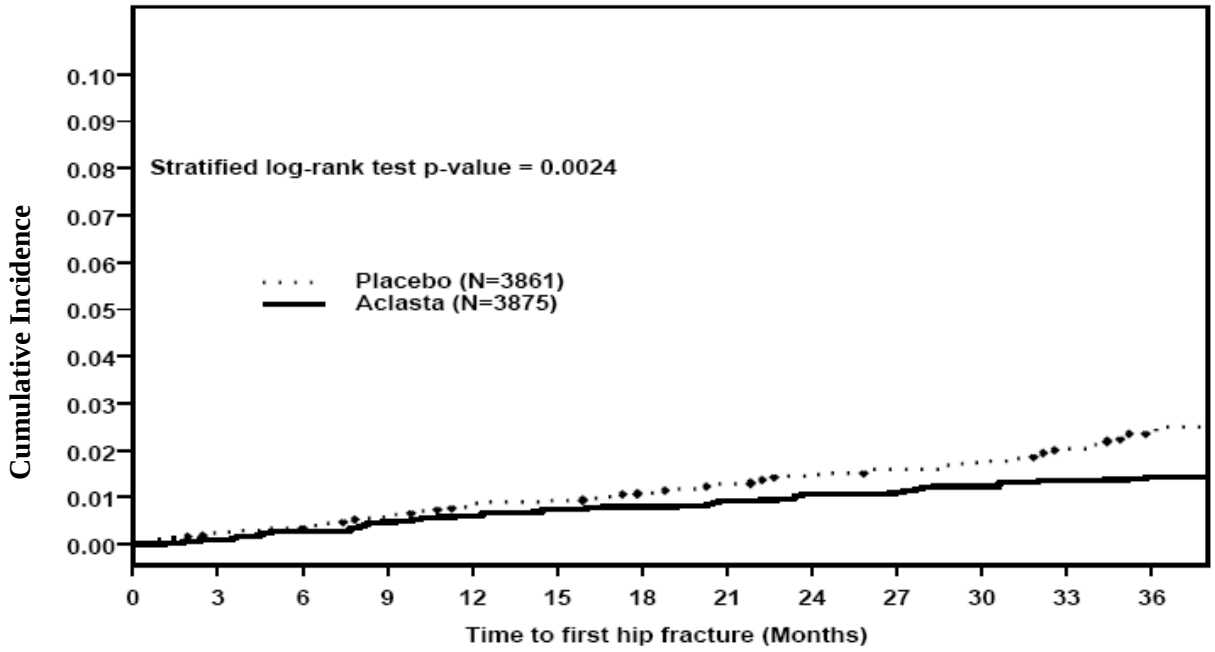
| Outcome | Aclasta<br><br>Event rate (%) | Placebo<br><br>Event rate (%) | Absolute reduction in fracture incidence (%) (95% CI) | Relative reduction in fracture incidence (%) (95% CI) |
|---|---|---|---|---|
| At least one new vertebral fracture (0-1 year) | 1.5 | 3.7 | 2.2 (1.4, 3.1) | 60 (43, 72)** |
| At least one new vertebral fracture (0-2 year) | 2.2 | 7.7 | 5.5 (4.3, 6.6) | 71 (61, 78)** |
| At least one new vertebral fracture (0-3 year) | 3.9 | 10.9 | 7.6 (6.3, 9.0) | 70 (62, 76)** |

** $p < 0.0001$

The reductions in vertebral fractures over three years were consistent and significantly greater than placebo regardless of age, geographical region, race, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score or prior bisphosphonate use. Specifically for patients aged 75 years and older, Aclasta patients had a 61% reduction in the risk of vertebral fractures compared to placebo patients ($p<0.0001$).

**Effect on Hip Fracture:** Aclasta demonstrated a 41% reduction in the risk of hip fractures over 3 years. The hip fracture event rate was 1.4% for Aclasta-treated patients compared to 2.5% for placebo-treated patients. The effect over time is displayed in Figure 1.

**Figure 1 Cumulative incidence of hip fracture over 3 years**




The reduction in the risk of hip fractures was similar in women who did not take concomitant osteoporosis therapy to women who were allowed to take concomitant therapy. In 6084 women who did not take concomitant osteoporosis therapy, Aclasta demonstrated a 41% reduction (95% CI, 13% to 59%) in the risk of hip fractures over this time period. In 1652 women who were allowed to take concomitant osteoporosis therapy, a comparable 42% reduction in the risk of hip fractures was observed (95% CI, -2.7% to 73%). The study was not powered to determine if this difference was statistically significant.

The reductions in hip fractures over three years were greater than placebo regardless of femoral neck BMD T-score.

**Secondary Efficacy Variables**

**Effect on Vertebral Fractures:** Aclasta significantly decreased the risk of one or more new/worsening vertebral fractures at 1 year (58%), 2 years (68%) and 3 years (67%) (all $p<0.0001$). Aclasta significantly decreased the risk of at least one new moderate or severe vertebral fracture at 1 year (60%), 2 years (71%) and 3 years (70%) (all $p<0.0001$).

**Effect on All Clinical Fractures:** Aclasta demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical vertebral and non-vertebral

fractures. All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 2.

**Table 2 Between-treatment comparisons of the incidence of key clinical fracture variables over 3 years**

| **Outcome** | **Aclasta (N = 3875) Event rate (%)** | **Placebo (N = 3861) Event rate (%)** | **Absolute reduction in fracture incidence (%) (95% CI)** | **Relative reduction in fracture incidence (%) (95% CI)** |
|---|---|---|---|---|
| Any clinical fracture (1) | 8.4 | 12.8 | 4.4 (3.0, 5.8) | 33 (23, 42)** |
| Clinical vertebral fracture (2) | 0.5 | 2.6 | 2.1 (1.5, 2.7) | 77 (63, 86)** |
| Non-vertebral fracture (1) | 8.0 | 10.7 | 2.7 (1.4, 4.0) | 25 (13, 36)* |

*p-value < 0.001, **p-value <0.0001

(1) Excluding finger, toe and facial fractures

(2) Includes clinical thoracic and clinical lumbar vertebral fractures

**Effect on Bone Mineral Density (BMD):** Aclasta significantly increased BMD at the lumbar spine, hip and distal radius relative to treatment with placebo at all time points (6, 12, 24 and 36 months). Treatment with Aclasta resulted in a 6.7% increase in BMD at the lumbar spine, 6.0 % at the total hip, 5.1% at the femoral neck and 3.2% at the distal radius over 3 years as compared to placebo.

**Bone Turnover Markers:** Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (beta-CTx) were evaluated in subsets ranging from 517 to 1246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of Aclasta reduces bone turnover markers to the premenopausal range. Repeat dosing does not lead to further reduction of bone turnover markers.

**Effect on Height:** In the 3-year osteoporosis study, standing height was measured annually using a stadiometer. The Aclasta group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively ($p<0.001$)).

**Days of Disability:** Aclasta significantly reduced both the days of limited activity and the days of bed rest due to fractures compared to placebo (both $p<0.01$). Aclasta also significantly reduced both the days of limited activity and the days of bed rest due to back pain compared to placebo (both $p\leq0.008$).

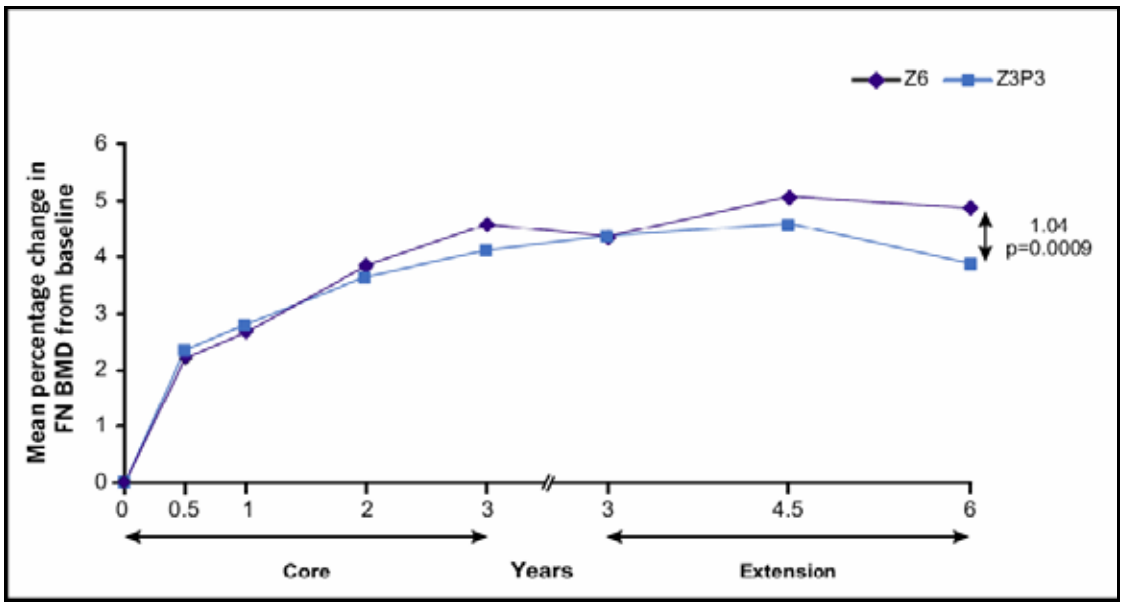
**Effects of Prolonged Therapy and its Discontinuation:** The effects of prolonged zoledronic acid therapy as well as its discontinuation were assessed in a 3 year extension to the treatment of postmenopausal osteoporosis trial. The extension was a randomised, double-blind, multinational study in 2456 ambulatory postmenopausal women who had completed participation in the core study. The same dosing regimen of zoledronic acid was used in the extension study as in the core study (5 mg intravenous infusion once yearly). The trial design did not allow identification of the specific subset of patients likely to benefit.

The extension study demonstrated that the therapeutic benefit of continued annual zoledronic acid therapy on maintaining or increasing BMD in women with postmenopausal osteoporosis is sustained long-term, while the discontinuation of therapy results in a gradual loss of bone mass.

Compared to treatment with zoledronic acid for 3 years followed by 3 years of placebo, treatment with zoledronic acid for 6 years significantly reduced the risk of new morphometric vertebral fractures by 52% ($p<0.05$) and significantly reduced the risk of new or worsening morphometric fractures by 51% ($p<0.05$). No significant differences were observed between the two groups in the risk of clinical, non-vertebral, hip and clinical vertebral fractures. There is no statistically significant difference in clinical fractures between the group who received zoledronic acid for 6 years compared to the group who received zoledronic acid for 3 years followed by 3 years of placebo.

Bone marker levels remained below pre-treatment levels 6 years earlier and mean values remained within the pre-menopausal reference range for all 3 biomarkers.

**Figure 2 Femoral neck BMD percentage change over time**




There were no cases of atypical femoral fractures in the extension study.

**Clinical Efficacy in the Prevention of Clinical Fractures after Hip Fracture**

The efficacy and safety of Aclasta in the prevention of clinical fractures in patients who suffered a recent low trauma hip fracture were demonstrated in a randomised, double-blind, placebo-controlled, multinational endpoint study of 2127 ambulant men and women aged 50-95 years (mean age of 74.5). The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2127 men and women with a recent (within 90 days) low trauma hip fracture (pertrochanteric or femoral neck) but not malignant fractures and fractures associated with previously implanted orthopedic devices. The washout periods for patients who had been pretreated with other bisphosphonates were the same as those in the postmenopausal osteoporosis study described above. Patients were followed for an average of 2 years on study drug. The following concomitant osteoporosis therapies were allowed: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone, DHEA(s), ipriflavone, and testosterone, as hormone replacement in the case of hypogonadal men; but excluded other bisphosphonates and parathyroid hormone.

Aclasta was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes, until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or via the intramuscular route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D

supplementation per day. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

**Primary Efficacy Variable**

**Effect on All Clinical Fractures:** In the prevention of clinical fractures after hip fracture trial, treatment with Aclasta significantly reduced the incidence of any clinical fracture by 35% (see Table 3).

**Secondary Efficacy Variables**

**Other Clinical Fracture Endpoints:** There was also a 46% reduction in the risk of a clinical vertebral fracture; a 27% reduction in the risk for non-vertebral fractures with Aclasta. There was a 30% reduced risk for a subsequent hip fracture that was observed for the Aclasta group that did not meet statistical significance. See Table 3.

**Table 3 Between treatment comparisons of the incidence of key clinical fracture variables**

| Outcome | Aclasta (N=1064) Event rate (%) | Placebo (N=1063) Event rate (%) | Absolute reduction in fracture incidence(%) (95% CI) | Relative risk reduction in fracture incidence (%) (95% CI) |
|---|---|---|---|---|
| Any clinical fracture (1) | 8.6 | 13.9 | 5.3 (2.3, 8.3) | 35 (16, 50)** |
| Clinical vertebral fracture (2) | 1.7 | 3.8 | 2.1 (0.5, 3.7) | 46 (8, 68)* |
| Non-vertebral fracture (3) | 7.6 | 10.7 | 3.1 (0.3, 5.9) | 27 (2, 45)* |
| Hip fracture | 2.0 | 3.5 | 1.5 (-0.1, 3.1) | 30 (-19, 59) |

*p-value <0.05, **p-value <0.005
(1) Excluding finger, toe and facial fractures
(2) Including clinical thoracic and clinical lumbar vertebral fractures
(3) Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

**Effect on Bone Mineral Density (BMD):** In the prevention of clinical fractures after hip fracture trial, Aclasta treatment significantly increased BMD relative to placebo at the hip and femoral neck at all time points (12, 24 and 36 months). Treatment with Aclasta resulted in a 5.4 % increase at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo. Similar significant results were observed for femoral neck BMD measures.

**Treatment of Male Osteoporosis**

The efficacy and safety of Aclasta in men with osteoporosis were assessed in a randomised, multicentre, double-blind, active-controlled study of 302 men aged 25 to 86 years (mean age of 64 years) with either: a femoral neck BMD T-score less than or equal to -2.0 and a lumbar spine BMD T-score less than or equal to -1.0 or a femoral neck BMD T-score less than or equal to -1.0 and at least one vertebral deformity or a history of an osteoporotic fracture. The duration of the trial was two years. Patients were randomised to either Aclasta, which was administered once annually as a single 5 mg dose in 100 mL infused over 15 minutes for a total of two doses, or to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to alendronate was shown with respect to the percentage change in lumbar spine BMD at 24 months relative to baseline.

Aclasta has not been studied in hypogonadal men. Fracture data are not available from the study.

**Effect on Bone Mineral Density (BMD):** An annual infusion of Aclasta was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline (Aclasta 6.1% compared to alendronate 6.2%). The percentage increases in lumbar spine BMD at month 12 were also similar between treatment groups. The criterion for non-inferiority of zoledronic acid by comparison with alendronate was met as the lower bound of the 95% CI (-1.12 for the ITT population, -1.27 per protocol) exceeded the pre-specified non-inferiority margin of -1.5%.

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

The efficacy and safety of Aclasta in the treatment and prevention of glucocorticoid-induced osteoporosis were assessed in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women aged 18 to 85 years (mean age of 54.4 years) treated with $\geq$ 7.5 mg/day oral prednisone (or equivalent). Patients in the prevention subpopulation were treated with glucocorticoids $\leq$ 3 months prior to randomisation, and the treatment subpopulation was treated with glucocorticoids $\geq$ 3 months prior to randomisation. The duration of the trial was one year. Patients were randomised to either Aclasta, which was administered once as a single 5 mg dose in 100 mL infused over 15 minutes, or to oral risedronate 5 mg daily for one year. All participants received 1000 mg elemental calcium plus 400 to 1000 IU vitamin D supplementation per day.

The study was designed to show non-inferiority of a single infusion of Aclasta relative to risedronate in these two subpopulations. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively.

This was not a fracture study and limited data only are available: over the 12 months of the study, new vertebral fractures detected by x-ray morphometry occurred in 5/379 (1.3%) of Aclasta-treated patients and assessed, compared to 3/381 (0.8%) in the risedronate treated group. An analysis of the time to first clinical fracture during the study period showed no difference between the treatment groups. During the 12 month study, 8 Aclasta-treated patients and 7 risedronate treated patients had at least one clinical fracture.

**Effect on Bone Mineral Density (BMD):** Non-inferiority to risedronate was shown. There was a trend to greater increase in BMD in the Aclasta-treated group in both the treatment and prevention sub-populations at all sites, which included the lumbar spine, femoral neck, total hip, trochanter and distal radius at 12 months compared to risedronate. A summary of the key results appears in Table 4.

**Table 4 Effects of Aclasta and risedronate on bone mineral density of the lumbar spine, total hip and femoral neck (modified ITT population)**

| Population | Location | Aclasta n LS Mean* (SE) | Risedronate n LS Mean* (SE) |
|---|---|---|---|
| Treatment | Lumbar spine | 249 4.06 (0.28) | 245 2.71 (0.28) |
| | Total hip | 247 1.65 (0.21) | 239 0.45 (0.20) |
| | Femoral neck | 247 1.45 (0.31) | 239 0.39 (0.30) |
| Prevention | Lumbar spine | 129 2.60 (0.45) | 136 0.64 (0.46) |
| | Total hip | 126 1.54 (0.36) | 135 0.03 (0.36) |
| | Femoral neck | 126 1.30 (0.45) | 135 -0.03 (0.46) |

* LS Mean – Least Square Mean

**Clinical Efficacy for the Treatment of Paget's Disease of Bone**

Aclasta was studied in male and female patients aged above 30 years with mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6-3.0 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Aclasta versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month controlled comparative trials. The

primary objective of these trials was to show non-inferiority of zoledronic acid compared to risedronate with respect to the proportion of patients who achieved a therapeutic response at 6 months. Non-inferiority was defined as: zoledronic acid is non-inferior to risedronate if the lower bound of a two-sided 95% confidence interval for the difference between zoledronic acid and risedronate in the proportion of therapeutic responders exceeded -0.16. If non-inferiority was shown and the pre-defined non-inferiority margin was exceeded, testing for superiority would be performed.

The primary outcome variable was the proportion of patients achieving a therapeutic response defined as either normalisation of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of the normal range.

At 6 months, combined data from both trials showed that 96.0% (169/176) Aclasta-treated patients achieved a therapeutic response as compared with 74.3% (127 of 171) of patients treated with risedronate ($p<0.001$). In addition, at 6 months, 88.6% (156/176) of Aclasta-treated patients achieved remission (normalisation of SAP levels) compared to 57.9% (99/171) of patients treated with risedronate ($p<0.0001$). Non-inferiority was found (the difference between combined groups was 0.22 (0.14, 0.30)).

In combined data from both trials, after 2 months, the therapeutic response rate was 90% (158/176) and the SAP normalisation rate was 63% (111/176) compared to 47% (81/171) and 26% (45/171) respectively for risedronate (all $p<0.001$).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Aclasta and risedronate.

The adverse reaction profile reflects a very common incidence of acute phase reactions in the zoledronic acid group (influenza-like illness, pyrexia, myalgia, arthralgia and bone pain).

**Extended Observation Period**

Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended follow-up period. Of the 152 Aclasta-treated patients and 115 risedronate-treated patients who entered an extended observation study, after a median duration of follow-up of 32 months from time of dosing, 142 Aclasta-treated

patients maintained their therapeutic response compared to 50 risedronate-treated patients ($p<0.0001$).

# INDICATIONS

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures.
- Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures.
- To increase bone mineral density in men with osteoporosis.
- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use.
- To prevent glucocorticoid-induced bone mineral density loss.
- Treatment of Paget's disease of bone.

# CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates; hypocalcaemia; renal impairment (creatinine clearance < 35 mL/min); current or recent uveitis, or a history of bisphosphonate-associated uveitis; pregnancy and lactation.

# PRECAUTIONS

## General

The dose of 5 mg zoledronic acid must be administered intravenously over at least 15 minutes.

Aclasta contains the same active ingredient found in Zometa® (zoledronic acid), used for oncology indications, and a patient being treated with Zometa should not be treated with Aclasta.

Consider carefully before using Aclasta in patients who have been extensively pretreated with other bisphosphonates. Consider discontinuing Aclasta on the occurrence of atypical fractures such as subtrochanteric fractures or atypical stress fractures. The Optimum duration of bisphosphonate treatment is currently unknown. The risk: benefit ratio of prolonged therapy should be estimated in each patient. No data are available on recommencing therapy after cessation of treatment.

**Acute Phase Reaction**

Post-dose symptoms commonly occur within the first three days following Aclasta administration and may include fever, flu-like symptoms, myalgia, arthralgia and headache (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). The incidence of these symptoms can be reduced by approximately 50% with the administration of paracetamol shortly following Aclasta administration. Non-steroidal anti-inflammatory agents are not recommended first line to manage the acute phase reaction.

**Hydration**

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important in the elderly and for patients receiving diuretic therapy. Adequate hydration can be achieved by the patient drinking two glasses of fluid (such as water) before and two glasses of fluid after the infusion.

**Pre-existing Hypocalcaemia or Vitamin D Deficiency**

If there are clinical reasons to suspect hypocalcaemia, vitamin D deficiency or other disturbances of mineral metabolism (e.g. thyroid surgery, parathyroid surgery, calcium malabsorption), the appropriate tests should be performed and, if abnormalities are discovered, these should be corrected before initiating therapy with Aclasta (see **CONTRAINDICATIONS**). Physicians should consider clinical monitoring after treatment in patients with pre-existing disturbances of mineral metabolism.

**Renal Impairment**

Renal impairment has been observed following the administration of Aclasta (see **ADVERSE REACTIONS, Post-marketing Experience**), especially in patients with pre-existing renal compromise or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see **PRECAUTIONS Interactions with Other Medicines**), or dehydration occurring after Aclasta administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

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

- Aclasta should not be used in patients with severe renal impairment (creatinine clearance < 35 mL/min) due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**).
- Aclasta should be used with caution when concomitantly used with other medicinal products that could impact renal function (see **PRECAUTIONS Interactions with Other Medicines**).
- Creatinine clearance should be calculated (e.g. Cockroft-Gault formula) before each Aclasta dose (see **CONTRAINDICATIONS**). Transient increase in serum creatinine may be greater in patients with underlying impaired renal function; interim monitoring of serum creatinine should be considered in at-risk patients.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta (see **PRECAUTIONS Hydration**).
- A single dose of Aclasta should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see **DOSAGE AND ADMINISTRATION**).

**Calcium and Vitamin D Supplementation**

**Treatment of Osteoporosis:** Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis if dietary intake is inadequate.

**Prevention of Clinical Fractures after a Hip Fracture:** Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a hip fracture.

**Treatment of Paget's Disease of Bone:** Elevated bone turnover is a characteristic of Paget's disease of bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Aclasta (see **ADVERSE REACTIONS**). Adequate vitamin D intake is recommended in association with Aclasta administration (see **PRECAUTIONS Pre-existing Hypocalcaemia or Vitamin D Deficiency**). In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration. Patients should be informed about symptoms of hypocalcaemia. Physicians should consider clinical monitoring for patients at risk.

**Musculoskeletal Pain**

Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates including Aclasta.

**Osteonecrosis of the Jaw (ONJ)**

Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including 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. Symptoms include persistent pain and/or non-healing sores of the mouth or jaw. Many had signs of local infection including osteomyelitis.

Discuss with the patient the need to have dental work completed before commencing Aclasta treatment. 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. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

In the treatment of postmenopausal osteoporosis trial in 7714 patients who received Aclasta or placebo, ONJ has been reported in one patient with Aclasta and one patient treated with placebo. Both cases resolved. In the prevention of clinical fractures after hip fracture trial, in 2111 patients who received Aclasta or placebo there were no reports of ONJ. (See **CLINICAL TRIALS.**)

**Effects on Fertility**

Fertility was decreased in rats dosed subcutaneously (SC) with zoledronic acid 0.1 mg/kg/day for 71 days (males) or 15 days (females), with animal/human exposure margins 2-8 (based on cumulative AUC for unbound drug), and preimplantation loss was increased at 0.01 mg/kg/day. Reversible testicular atrophy occurred in rats at 0.003 mg/kg/day SC for 12 months (exposure margin 1). In dogs, testicular and prostatic atrophy and oligospermia were observed at 0.2 mg/kg/day intravenously (IV) for 3 months (exposure margin 160). Testicular atrophy and/or mineralisation were additionally observed in the dog at 0.03 mg/kg IV dosed every 2 to 3 days for 6 months (exposure margin 56), although no such changes were seen at 0.1 mg/kg for 12 months (exposure margin 269). Female dogs had decreased weights of ovaries and uterus, correlated with anoestrus and, in some animals, with vaginal epithelial

degeneration at 0.01 mg/kg IV daily for 3 months (exposure margin 14). There were no effects on reproductive organs in dogs dosed with up to 1 mg/kg zoledronic acid by IV infusion once every 3 weeks for 26 weeks (exposure margin 60).

**Use in Pregnancy**

Category B3. There are no data on the use of zoledronic acid in pregnant women. Teratology studies were performed in rats and rabbits, both via subcutaneous administration. Teratogenicity was observed in rats at doses≥ 0.2 mg/kg (0.2 times clinical exposure based on unbound AUC) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological effects were observed in rabbits, but maternal toxicity and increased embryo/foetal resorption occurred at≥ 0.03 mg/kg (0.14 times clinical exposure based on dose adjusted for body surface area). In the absence of adequate data in pregnant women, Aclasta is contraindicated during pregnancy. Women who might become pregnant at some time in the future should be warned about the long half-life of bisphosphonates.

**Use in Lactation**

Studies have not been performed in lactating animals, and the transfer of zoledronic acid into milk is unknown. Because many drugs are excreted in human milk, breast-feeding should be discontinued before Aclasta administration.

**Paediatric Use**

Aclasta is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

**Use in the Elderly**

The postmenopausal osteoporosis trial included 3868 Aclasta-treated patients who were at least 65 years of age, while 1497 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

The prevention of clinical fractures after hip fracture trial included 893 Aclasta-treated patients who were at least 65 years of age, while 586 patients were at least 75 years old. Those who were 65 years and older had the same reduction in clinical fractures (35%) as those less than 65 years of age. Those 75 years and older had a

42% reduction in clinical fractures. No overall differences in safety were observed between these patients and younger patients.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

**Carcinogenicity**

In carcinogenicity studies, zoledronic acid was administered orally by gavage to rats and mice at daily doses of 0.1, 0.5 and 2.0 mg/kg and 0.1, 0.3 and 1.0 mg/kg, respectively, for at least 104 weeks without evidence of carcinogenic potential. Pharmacological bone changes typically observed following long-term bisphosphonate administration to young animals with growing skeletons were observed in these studies, suggesting systemic exposure to zoledronic acid in both species.

**Genotoxicity**

Zoledronic acid was not mutagenic in bacterial reverse mutation tests in *Salmonella typhimurium* and *Escherischia coli* or in cultured V79 Chinese hamster lung cells. Zoledronic acid did not induce chromosome aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* micronucleus test in rats.

**Interactions with Other Medicines**

Specific drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see **PHARMACOLOGY Pharmacokinetics**). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely. Zoledronic acid is eliminated by renal excretion.

**Drugs that Could Impact Renal Function:** Caution is indicated when Aclasta is administered in conjunction with drugs that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

**Drugs Primarily Excreted by the Kidney:** In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidneys may increase.

**Effects on Ability to Drive and Use Machines**

There are no data to suggest that Aclasta affects the ability to drive or use machines. However, patients should be warned about post-infusion hypocalcaemia which is usually asymptomatic but occasionally causes tetany.

# ADVERSE EFFECTS

## Adverse Events in Clinical Trials

### Postmenopausal Osteoporosis

In the Phase III randomised, double-blind, placebo-controlled, multinational study of 7736 postmenopausal women aged 65-89 years (see **CLINICAL TRIALS**), there were no significant differences in the overall incidence of serious adverse events compared to placebo and most adverse events were mild to moderate. The incidence of all-cause mortality was similar between groups: 3.4% in the Aclasta group and 2.9% in the placebo group. Aclasta was administered once yearly for three consecutive years for a total of three doses.

Consistent with the intravenous administration of bisphosphonates, Aclasta has been most commonly associated with the following post-dose symptoms: fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occur within the first 3 days following Aclasta administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased markedly with subsequent annual doses of Aclasta.

The incidence of post-dose symptoms occurring within the first 3 days after administration of Aclasta can be reduced by approximately 50% with the administration of paracetamol shortly following Aclasta administration.

Adverse events occurring in ≥ 2.0% of postmenopausal women with osteoporosis are shown in Table 5.

**Table 5 Adverse events occurring in ≥ 2.0% of postmenopausal women with osteoporosis and in ≥ 2.0% of men and women following hip fracture receiving Aclasta (5 mg IV infusion once yearly) and more frequently than in placebo-treated patients over 3 years**

| | Postmenopausal osteoporosis trial | Prevention of clinical fracture after hip fracture |
|---|---|---|

| | | | trial | |
|---|---|---|---|---|
| **System Organ Class** | **5 mg IV Aclasta once per year % (N=3862)** | **Placebo once per year % (N=3852)** | **5 mg IV Aclasta once per year % (N=1054)** | **Placebo once per year % (N=1057)** |
| **Infections and infestations** | | | | |
| Urinary tract infection | 12.1 | 11.7 | 10.6 | 9.6 |
| Nasopharyngitis | 11.3 | 11.0 | 4.7 | 4.3 |
| Bronchitis | 5.3 | 6.1 | 3.9 | 3.1 |
| **Blood and the Lymphatic System Disorders** | | | | |
| Anaemia | 4.4 | 3.6 | 5.3 | 5.2 |
| **Metabolism and Nutrition Disorders** | | | | |
| Hypercholesterolaemia | 4.0 | 3.9 | 2.9 | 2.1 |
| Dehydration | 0.6 | 0.6 | 2.5 | 2.3 |
| Anorexia | 2.0 | 1.1 | 1.0 | 1.0 |
| **Nervous System Disorders** | | | | |
| Headache | 12.4 | 8.1 | 3.9 | 2.5 |
| Dizziness | 7.6 | 6.7 | 2.0 | 4.0 |
| **Eye Disorders** | | | | |
| Cataract | 6.3 | 5.8 | 3.0 | 2.3 |
| **Ear and Labyrinth Disorders** | | | | |
| Vertigo | 4.3 | 4.0 | 1.3 | 1.7 |
| **Cardiac Disorders** | | | | |
| Atrial fibrillation | 2.5 | 1.9 | 3.0 | 2.8 |
| Cardiac failure congestive | 3.0 | 2.8 | 2.8 | 2.6 |
| **Vascular Disorders** | | | | |
| Hypertension | 12.7 | 12.4 | 6.8 | 5.4 |
| **Gastrointestinal Disorders** | | | | |

| | | | | |
|---|---|---|---|---|
| Nausea | 8.5 | 5.2 | 4.5 | 4.5 |
| Diarrhoea | 6.0 | 5.6 | 5.2 | 4.7 |
| Vomiting | 4.6 | 3.2 | 3.4 | 3.4 |
| Abdominal pain upper | 4.6 | 3.1 | 0.9 | 1.5 |
| Dyspepsia | 4.3 | 4.0 | 1.7 | 1.6 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | | | |
| Arthralgia | 23.8 | 20.4 | 17.9 | 18.3 |
| Myalgia | 11.7 | 3.7 | 4.9 | 2.7 |
| Pain in extremity | 11.3 | 9.9 | 5.9 | 4.8 |
| Shoulder pain | 6.9 | 5.6 | 0.0 | 0.0 |
| Bone pain | 5.8 | 2.3 | 3.2 | 1.0 |
| Neck pain | 4.4 | 3.8 | 1.4 | 1.1 |
| Muscle spasms | 3.7 | 3.4 | 1.5 | 1.7 |
| Osteoarthritis | 9.1 | 9.7 | 5.7 | 4.5 |
| Musculoskeletal pain | 0.4 | 0.3 | 3.1 | 1.2 |
| **General Disorders and Administrative Site Conditions** | | | | |
| Pyrexia | 17.9 | 4.6 | 8.7 | 3.1 |
| Influenza-like illness | 8.8 | 2.7 | 0.8 | 0.4 |
| Fatigue | 5.4 | 3.5 | 2.1 | 1.2 |
| Chills | 5.4 | 1.0 | 1.5 | 0.5 |
| Asthenia | 5.3 | 2.9 | 3.2 | 3.0 |
| Peripheral oedema | 4.6 | 4.2 | 5.5 | 5.3 |
| Pain | 3.3 | 1.3 | 1.5 | 0.5 |
| Malaise | 2.0 | 1.0 | 1.1 | 0.5 |
| Hyperthermia | 0.3 | <0.1 | 2.3 | 0.3 |
| Chest pain | 1.3 | 1.1 | 2.4 | 1.8 |
| **Investigations** | | | | |
| Weight decreased | 1.8 | 1.2 | 2.4 | 2.1 |
| Creatinine renal | 2.0 | 2.4 | 2.1 | 1.7 |

| | | | | |
|---|---|---|---|---|
| clearance decreased | | | | |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Post procedure complication | 0.0 | 0.0 | 3.8 | 3.3 |
| Contusion | 2.9 | 2.6 | 2.9 | 2.6 |

The safety results in the three year extension to the treatment of postmenopausal osteoporosis trial suggest that the overall safety profile for zoledronic acid 5 mg yearly is similar in patients who continued therapy for 6 years to patients who stopped treatment after 3 years.

**Prevention of Clinical Fractures after Hip Fracture**

In a randomised, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years with a recent (within 90 days) low trauma hip fracture, 1065 patients were exposed to Aclasta (zoledronic acid) and 1062 patients exposed to placebo. Aclasta was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of 2 years on study drug. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day.

Most adverse events were of mild to moderate severity and did not lead to discontinuation. The incidence of serious adverse events was 38% in the Aclasta group and 41% in the placebo group. All cause mortality was 9.6% in the Aclasta-treated group compared to 13.3% in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality (p=0.01).

Aclasta was associated with the following post-dose symptoms: fever (7%) and arthralgia (3%), which occur within the first 3 days following Aclasta administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased with subsequent doses of Aclasta. The main reason for the lower rate of post-dose symptoms in this trial compared to the rate of post-dose symptoms in the treatment of postmenopausal osteoporosis trial was that, in this prevention of clinical fractures after hip fracture trial, paracetamol was provided to patients and its use encouraged to manage post-dose symptoms.

Adverse events occurring in≥ 2.0% of men and women following hip fracture (prevention of clinical fractures after hip fracture) are shown above in Table 5.

**Treatment of Male Osteoporosis**

The safety of Aclasta in men with osteoporosis or significant osteoporosis secondary to hypogonadism was assessed in a two-year randomised, multicentre, double-blind, active-controlled group study of 302 men aged 25-86 years. One hundred and fifty-three patients were exposed to Aclasta administered once annually as a single 5 mg dose in 100 mL infused over 15 minutes for a total of two doses and 148 patients were exposed to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar between the Aclasta and alendronate treatment groups. The percentage of patients experiencing at least one adverse event was comparable between the Aclasta and alendronate treatment groups, with the exception of a higher incidence of post-dose symptoms in the Aclasta group that occurred within 3 days after infusion. The overall safety and tolerability profile of Aclasta in male osteoporosis was similar to that reported in the Aclasta postmenopausal osteoporosis trial.

Adverse events reported in at least 2% of men with osteoporosis and more frequently in the Aclasta treatment group than the alendronate group and either not reported in the postmenopausal osteoporosis trial or reported more frequently in the osteoporosis trial in men are presented in Table 6.

**Table 6 Adverse events occurring in ≥ 2% of men with osteoporosis and more frequently in the Aclasta-treated patients than the alendronate-treated patients and either not reported in the postmenopausal osteoporosis trial or reported more frequently in this trial**

| System Organ Class | 5 mg IV Aclasta once per year % (N=153) | Alendronate 70 mg once weekly % (N=148) |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 4.6 | 3.4 |
| Tooth abscess | 2.6 | 0.7 |
| Cellulitis | 2.0 | 1.4 |
| **Neoplasma Benign, Malignant and Unspecified (including cysts and polyps)** | | |
| Basal cell carcinoma | 3.3 | 0.7 |

| | | |
|---|---|---|
| **Psychiatric disorders** | | |
| Anxiety | 2.6 | 2.0 |
| **Nervous System Disorders** | | |
| Headache | 15.0 | 6.1 |
| Lethargy | 3.3 | 1.4 |
| Paraesthesia | 2.6 | 0.7 |
| Syncope | 2.6 | 1.4 |
| Hypoaesthesia | 2.0 | 1.4 |
| **Eye Disorders** | | |
| Eye pain | 2.0 | 0.0 |
| **Cardiac Disorders** | | |
| Atrial fibrillation | 3.3 | 2.0 |
| Palpitations | 2.6 | 0.0 |
| **Vascular Disorders** | | |
| Hypotension | 2.0 | 1.4 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnoea | 6.5 | 4.7 |
| Chronic obstructive pulmonary disease | 2.6 | 0.7 |
| Pulmonary oedema | 2.0 | 0.7 |
| **Gastrointestinal Disorders** | | |
| Dental caries | 4.6 | 0.0 |
| Abdominal pain* | 7.9 | 4.1 |
| Colonic polyp | 2.0 | 1.4 |
| Haemorrhoids | 2.0 | 1.4 |
| Toothache | 2.0 | 0.7 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Skin lesion | 3.3 | 0.0 |
| Actinic keratosis | 2.6 | 0.7 |
| Hyperhidrosis | 2.6 | 2.0 |
| Alopecia | 2.0 | 0.0 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Myalgia | 19.6 | 6.8 |
| Musculoskeletal pain** | 12.4 | 10.8 |
| Musculoskeletal stiffness | 4.6 | 0.0 |
| Muscular weakness | 2.0 | 1.4 |
| **Renal and Urinary Disorders** | | |
| Urinary retention | 2.0 | 0.7 |
| Blood creatinine increased | 2.0 | 0.7 |
| **General Disorders and Administrative Site Conditions** | | |

| | | |
|---|---|---|
| Fatigue | 17.6 | 6.1 |
| Pain | 11.8 | 4.1 |
| Chills | 9.8 | 2.7 |
| Influenza like illness | 9.2 | 2.0 |
| Malaise | 7.2 | 0.7 |
| Acute phase reaction | 3.9 | 0.0 |
| Chest pain | 2.0 | 1.4 |
| **Investigations** | | |
| C-reactive protein increased | 4.6 | 1.4 |
| Weight decreased | 3.3 | 1.4 |
| **Injury, Poisoning and Procedural Complications** | | |
| Rib fracture | 3.3 | 0.7 |

* Combined abdominal pain, abdominal pain upper and abdominal pain lower as one AE.
** Combined musculoskeletal pain and musculoskeletal chest pain as one AE.

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

The safety of Aclasta in men and women in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in a randomised, multicentre, double-blind, active-controlled, stratified study of 833 men and women aged 18-85 years treated with $\geq$ 7.5 mg/day oral prednisione (or equivalent). Patients in the prevention subpopulation were treated with glucocorticoids $\leq$ 3 months prior to randomisation, and the treatment subpopulation was treated with glucocorticoids > 3 months prior to randomisation.

The duration of the trial was one year, with 416 patients exposed to Aclasta administered once as a single 5 mg dose in 100 mL infused over 15 minutes and 417 patients exposed to oral risedronate 5 mg daily for one year. All participants received 1000 mg elemental calcium plus 400 to 1000 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar between the Aclasta and risedronate treatment groups. Overall safety and tolerability were similar between the Aclasta and risedronate groups, with the exception of a higher incidence of post-dose symptoms in the Aclasta group that occurred within 3 days after infusion. The overall safety and tolerability profile of Aclasta in glucocorticoid-induced osteoporosis was similar to that reported in the Aclasta postmenopausal osteoporosis clinical trial.

Adverse events reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis trial or reported more frequently in the treatment and prevention of glucocorticoid induced osteoporosis trial are presented in Table 7.

**Table 7 Adverse events occurring in ≥ 2% of patients receiving at least 7.5 mg/day or equivalent for the treatment or prevention of glucocorticoid-induced osteoporosis patients and either not reported in the postmenopausal osteoporosis trial or reported more frequently in this trial**

| System Organ Class | 5 mg IV Aclasta once per year % (N=416) | Risedronate 5 mg/day % (N=417) |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 3.4 | 1.9 |
| Upper respiratory tract infection | 2.4 | 1.9 |
| **Nervous System Disorders** | | |
| Sciatica | 2.4 | 0.2 |
| **Gastrointestinal Disorders** | | |
| Nausea | 9.6 | 8.4 |
| Dyspepsia | 5.5 | 4.3 |
| Abdominal pain* | 7.5 | 5.0 |
| Constipation | 2.2 | 1.7 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Rheumatoid arthritis | 6.3 | 5.0 |
| Musculoskeletal pain** | 3.1 | 1.7 |
| **General Disorders and Administrative Site Conditions** | | |
| Oedema peripheral | 2.9 | 2.2 |

* Combined abdominal pain, abdominal pain upper and abdominal pain lower as one AE.

** Combined musculoskeletal pain and musculoskeletal chest pain as one AE.

**Paget's Disease of Bone**

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged > 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Aclasta and 172 patients exposed to risedronate. Aclasta was administered once as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The signs and symptoms of acute phase reaction (influenza-like illness, pyrexia, myalgia, arthralgia and bone pain) were reported in 25% of patients in the Aclasta-treated group compared to 8% in the risedronate-treated group. Symptoms usually occur within the first 3 days following Aclasta administration. The majority of these symptoms resolved within 4 days of onset.

Adverse events occurring in at least 2% of the Paget's patients receiving Aclasta (single 5 mg IV infusion) or risedronate (30 mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 8.

**Table 8 Adverse events reported in ≥ 2% of Paget's patients receiving Aclasta (single 5 mg IV infusion) or risedronate (oral 30 mg daily for 2 months) over a 6-month follow-up period**

| System Organ Class | 5 mg IV Aclasta % (N = 177) | Risedronate 30 mg/day x 2 months % (N = 172) |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 7 | 5 |
| **Metabolism and Nutrition Disorders** | | |
| Hypocalcaemia | 3 | 1 |
| Anorexia | 2 | 2 |
| **Nervous System Disorders** | | |
| Headache | 11 | 10 |
| Dizziness | 9 | 4 |
| Lethargy | 5 | 1 |
| Paraesthesia | 2 | 0 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnoea | 5 | 1 |
| **Gastrointestinal Disorders** | | |
| Nausea | 9 | 6 |
| Diarrhoea | 6 | 6 |
| Constipation | 6 | 5 |
| Dyspepsia | 5 | 4 |
| Abdominal distension | 2 | 1 |
| Abdominal pain | 2 | 2 |
| Vomiting | 2 | 2 |
| Abdominal pain upper | 1 | 2 |
| **Skin and Subcutaneous Tissue Disorders** | | |

| | | |
|---|---|---|
| Rash | 3 | 2 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Arthralgia | 9 | 11 |
| Bone pain | 9 | 5 |
| Myalgia | 7 | 4 |
| Back pain | 4 | 7 |
| Musculoskeletal stiffness | 2 | 1 |
| **General Disorders and Administrative Site Conditions** | | |
| Influenza-like illness | 11 | 6 |
| Pyrexia | 9 | 2 |
| Fatigue | 8 | 4 |
| Rigors | 8 | 1 |
| Pain | 5 | 4 |
| Peripheral oedema | 3 | 1 |
| Asthenia | 2 | 1 |

**Adverse Reactions with Suspected Relationship to Product**

Table 9 lists the adverse reactions suspected (investigator assessment) to be associated with Aclasta in the pooled studies supporting the indications: treatment of osteoporosis in men and postmenopausal women, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone by system organ class and by frequency 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) adverse drug reactions.

**Table 9 Adverse reactions suspected to be associated with Aclasta treatment**

| | |
|---|---|
| **Infections and Infestations** | |
| Uncommon: | Influenza, nasopharyngitis |
| **Blood and Lymphatic System Disorders** | |
| Uncommon: | Anaemia |
| **Metabolism and Nutrition Disorders** | |
| Uncommon: | Anorexia*, decreased appetite |
| **Psychiatric Disorders** | |
| Uncommon: | Insomnia |
| **Nervous System Disorders** | |
| Common: | Headache, dizziness |
| Uncommon: | Lethargy*, paraesthesia, somnolence, tremor, syncope |
| **Eye Disorders** | |
| Uncommon: | Conjunctivitis, eye pain |

| | |
|---|---|
| Rare: | Uveitis*, episcleritis, iritis |
| **Ear and Labyrinth Disorders** | |
| Uncommon: | Vertigo |
| **Vascular Disorders** | |
| Uncommon: | Hypertension, flushing |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| Uncommon: | Cough, dyspnoea* |
| **Gastrointestinal Disorders** | |
| Common: | Nausea, vomiting, diarrhoea |
| Uncommon: | Dyspepsia*, abdominal pain upper, abdominal pain*, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis* |
| **Skin and Subcutaneous Tissue Disorders** | |
| Uncommon: | Rash, hyperhydrosis*, pruritus, erythema |
| **Musculoskeletal Disorders** | |
| Common: | Myalgia*, arthralgia*, bone pain, back pain, pain in extremity |
| Uncommon: | Neck pain, musculoskeletal stiffness*, joint swelling*, muscle spasms, shoulder pain, musculoskeletal chest pain*, musculoskeletal pain, joint stiffness*, arthritis, muscular weakness |
| **Renal and Urinary Disorders** | |
| Uncommon: | Blood creatinine increased, pollakiuria, proteinuria |
| **General Disorders and Administration Site Conditions** | |
| Very common: | Fever |
| Common: | Flu-like symptoms, chills, fatigue*, asthenia, pain*, malaise |
| Uncommon: | Peripheral oedema, thirst*, acute phase reaction*, non-cardiac chest pain |

* Adverse reactions reported more frequently in the individual studies are: *Very common:* myalgia, arthralgia, fatigue, pain *Common:* lethargy, dyspnoea, dyspepsia, oesophagitis, abdominal pain, hyperhydrosis, musculoskeletal (muscle) stiffness, joint swelling, musculoskeletal chest pain, joint stiffness, anorexia, thirst, acute phase reaction *Uncommon:* uveitis.

Additional adverse reactions which were reported in the individual studies but are not included in the Table 9 (due to a lower frequency in the Aclasta group compared with that of the placebo group when the data were pooled) include: ocular hyperaemia, C-reactive protein increased, hypocalcaemia, dysgeusia, toothache, gastritis, palpitation, infusion site reaction.

**Atrial Fibrillation**

In one clinical trial, the overall incidence of atrial fibrillation was 2.5% (96 out of 3862) and 1.9% (75 out of 3852) in patients receiving Aclasta and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving Aclasta (1.3%) (51 out of 3862) compared with patients receiving placebo (0.6%) (22 out of 3852). The mechanism behind the increased incidence of atrial fibrillation is unknown. These imbalances were not observed in other trials; the overall pooled atrial fibrillation incidences were 2.6% for Aclasta and 2.1% for placebo and for serious adverse events, the pooled incidences were 1.3% for Aclasta and 0.8% for placebo.

**Local Reactions**

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

In the prevention of clinical fractures after hip fracture trial, the event rate was comparable for both Aclasta and placebo treatment groups.

**Laboratory Test Abnormalities**

In the treatment of postmenopausal osteoporosis trial, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87 mmol/L) following Aclasta administration. No symptomatic cases of hypocalcaemia were observed.

In the prevention of clinical fractures after hip fracture trial, there were no patients who had treatment emergent serum calcium levels below 1.87 mmol/L.

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

**Class Effects**

**Renal impairment**

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. advanced

age, oncology patients with chemotherapy, concomitant nephrotoxic medications, concomitant diuretic therapy, severe dehydration), the majority of whom received a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In the treatment of postmenopausal osteoporosis trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment were comparable for both the Aclasta and placebo treatment groups over 3 years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of Aclasta-treated patients versus 0.8% of placebo-treated patients.

In the prevention of clinical fractures after hip fracture trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment were comparable for both the Aclasta and placebo treatment groups over 3 years.

In clinical trials in Paget's disease, there were no cases of renal deterioration following a single 5 mg 15-minute infusion.

**Osteonecrosis of the jaw (ONJ)**

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid (uncommon). 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 jaw has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged.

In the treatment of postmenopausal osteoporosis trial in 7736 patients, ONJ has been reported in one patient treated with Aclasta and one patient treated with placebo. Both cases resolved.

In the prevention of clinical fractures after hip fracture trial, there were no reports of osteonecrosis of the jaw.

**Eye disorders**

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates. In the treatment of postmenopausal osteoporosis trial, 9 (0.2%) patients treated with Aclasta and 1 (<0.1%) patient treated with placebo developed iritis/uveitis/episcleritis. Patients who develop ocular symptoms after a zoledronic acid infusion should seek medical help.

**Post-marketing Experience**

The following adverse reactions have been reported during post-approval use of zoledronic acid. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.

Rare cases of renal impairment including renal failure requiring dialysis or with fatal outcome, especially in patients with pre-existing renal compromise or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period have been reported.

In very rare cases, the following events have been reported: dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea; hypotension in patients with underlying risk factors; osteonecrosis of the jaw; scleritis and orbital inflammation. In 2010, the Atypical Femoral Fractures Task Force Report identified that “Subtrochanteric and diaphyseal fractures, with or without atypical features have been estimated as 1 to 3 reports per 1,000,000 patient years of exposure to bisphosphonates.”

# DOSAGE AND ADMINISTRATION

## General

The incidence of post-dose symptoms occurring within the first three days after administration of Aclasta can be reduced with the administration of paracetamol shortly following Aclasta administration.

Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important in the elderly and for patients receiving diuretic therapy (see

**PRECAUTIONS**). Adequate hydration can be achieved by the patient drinking two glasses of fluid (such as water) before and after the infusion.

The inclusion and exclusion criteria of the clinical trials should be used as a basis for patient selection (see **CLINICAL TRIALS**).

**Treatment of Postmenopausal Osteoporosis**

For the treatment of postmenopausal osteoporosis the recommended dose is a single intravenous infusion of 5 mg of Aclasta administered once a year.

Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate. In the treatment of postmenopausal osteoporosis trial, all women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day (see **CLINICAL TRIALS**).

**Prevention of Clinical Fractures After a Hip Fracture**

For the prevention of clinical fractures after a low trauma hip fracture, the recommended dose is a single intravenous infusion of 5 mg Aclasta administered once a year.

In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Aclasta infusion (see **CLINICAL TRIALS**).

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a low trauma hip fracture (see **PRECAUTIONS Calcium and Vitamin D Supplementation**).

**Treatment of Osteoporosis in Men**

For the treatment of osteoporosis in men, the recommended dose is a single intravenous infusion of 5 mg Aclasta administered once a year.

Adequate supplemental calcium and vitamin D intake is important in men with osteoporosis if dietary intake is inadequate (see **PRECAUTIONS**).

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

For the treatment and prevention of glucocorticoid-induced osteoporosis, the recommended dose is a single intravenous infusion of 5 mg Aclasta administered once a year.

Adequate supplemental calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate (see **PRECAUTIONS**).

**Treatment of Paget's Disease of Bone**

For the treatment of Paget's disease, Aclasta should be prescribed only by physicians with experience in treatment of Paget's disease of the bone The recommended dose is a single intravenous infusion of 5 mg Aclasta.

**Re-treatment of Paget's disease:** Specific re-treatment data are not available. After a single treatment with Aclasta in Paget's disease, an extended remission period is observed in responding patients. Of the 152 Aclasta -treated patients who entered the extended observation study of the pivotal studies, after a median duration of follow-up of 32 months from time of dosing, 142 Aclasta -treated patients maintained their therapeutic response (see **CLINICAL TRIALS**).

However, re-treatment with Aclasta may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, in patients who failed to achieve normalisation of serum alkaline phosphatase, or in patients with symptoms, as dictated by medical practice 12 months after the initial dose.

In patients with Paget's disease, adequate vitamin D intake is recommended in association with Aclasta administration (see **PRECAUTIONS Pre-existing Hypocalcaemia or Vitamin D Deficiency)**. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration (see **PRECAUTIONS**).

**Method of Administration**

Aclasta (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes (see **Instructions for Use and Handling**).

**Patients with Renal Impairment**

The use of Aclasta in patients with creatinine clearance < 35 mL/min is not recommended due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**).

No dose adjustment is necessary in patients with creatinine clearance≥ 35 mL/min.

**Patients with Hepatic Impairment**

No dose adjustment is required for patients with hepatic impairment.

**Elderly Patients**

No dose adjustment is necessary (see **PRECAUTIONS**). However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

**Instructions for Use and Handling**

Aclasta must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

Use in one patient on one occasion only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used.

After opening, the solution is chemically and physically stable for at least 24 hours at 2°C to 8°C.

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

**Incompatibilities**

Aclasta solution for infusion must not be allowed to come into contact with any calcium- or other divalent cation-containing solutions.

## OVERDOSAGE

Clinical experience with acute overdosage is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an infusion of calcium gluconate.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Aclasta 5 mg/100 mL solution for infusion is sterile, clear and colourless. It is supplied in a 100 mL transparent plastic vial closed with a fluoro-polymer-coated bromobutyl rubber stopper and an aluminium/polypropylene cap with a flip component.

Aclasta is supplied as packs containing one vial and multipacks comprising three or six packs, each containing one vial. Not all pack sizes may be marketed.

**Storage:** The unopened vial does not require any special storage conditions. Aclasta must be kept out of the reach and sight of children.

## POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4).

## NAME AND ADDRESS OF SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
ABN 18 004 244 160
54 Waterloo Road
North Ryde NSW 2113

® = Registered Trademark

## DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 28 July 2011

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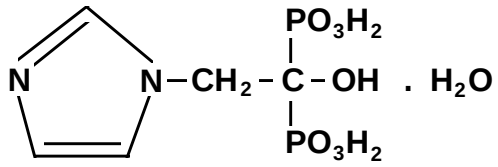
Tracking No: 2010-PSB/GLC-0310-s; based on ACPM resolution 9533

# OSTEOVAN®
**zoledronic acid**

## NAME OF THE MEDICINE

The active ingredient of Osteovan® is a bisphosphonate, zoledronic acid, or 1-hydroxy-2-(1H-imidazol-1-yl)ethane-1,1-diphosphonic acid. Although zoledronic acid is marketed by Novartis as a monohydrate, doses refer to the anhydrous substance.

The chemical structure of zoledronic acid monohydrate is:




## DESCRIPTION

Zoledronic acid monohydrate is a white, crystalline powder. It is soluble in water, most soluble at neutral pH (>290 mg/mL; pH=6.8) and practically insoluble in organic solvents.

| | |
|---|---|
| Empirical formula: | $C_5H_{10}N_2O_7P_2 \cdot H_2O$ |
| Relative molecular mass: | 290.11 |
| CAS number: | 165800-06-6 (zoledronic acid monohydrate)<br>118072-93-8 (zoledronic acid anhydrous) |

Osteovan 5 mg/100 mL solution for infusion contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

Osteovan contains the following excipients: mannitol, sodium citrate, water for injections.

Zoledronic acid is also marketed as a 4 mg/5 mL concentrated injection for infusion and as a powder for injection containing 4 mg of zoledronic acid for use in patients with malignancies under the trade-name Zometa®.

# PHARMACOLOGY

## Pharmacodynamics

**Pharmacotherapeutic group:** Bisphosphonate (ATC code: M05B A08).

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

The action of bisphosphonates on bone is based on their high affinity for mineralised bone. Intravenously administered zoledronic acid is rapidly distributed to bone. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms.

### Osteoporosis

Osteovan treatment rapidly reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralisation or the mechanical properties of bone. Histomorphometric data from long-term rat and monkey experiments showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclast activity and activation frequency of new remodelling sites in both trabecular and Haversian bone. Continuing bone remodelling was observed in bone samples from all animals treated with zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid and no woven bone in treated animals.

**Bone Histology:** In the postmenopausal osteoporosis treatment trial, bone biopsy specimens were obtained between months 33 and 36 from 82 postmenopausal patients with osteoporosis treated with 3 annual doses of Osteovan. Of the biopsies obtained, 81 were adequate for qualitative histomorphometry assessment, 59 were adequate for partial quantitative histomorphometry assessment, and 38 were adequate for full quantitative histomorphometry assessment. Micro CT analysis was performed on 76 specimens. Qualitative, quantitative and micro CT assessments showed bone of normal architecture and quality without mineralisation defects.

In the treatment and prevention of glucocorticoid-induced osteoporosis trial, bone biopsy specimens were obtained at month 12 from 23 patients treated with either an annual dose of Osteovan or daily oral risedronate (12 in the Osteovan treatment group and 11 in the risedronate treatment group). All biopsies were adequate for qualitative histomorphometry assessment. Qualitative assessments showed bone of normal architecture and quality without mineralisation defects. Apparent reductions in activation frequency and remodelling rates were seen when compared with the histomorphometry results seen with Osteovan in the postmenopausal osteoporosis population. The long term consequences of this degree of suppression of bone remodelling in glucocorticoid-treated patients is unknown.

**Paget's Disease of Bone**

Paget's disease of bone is a chronic, focal skeletal disorder characterised by greatly increased and disorderly bone remodelling. Excessive osteoclastic bone resorption is followed by irregular osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganised, enlarged and weakened bone structure. Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

In two 6-month randomised comparative, controlled clinical trials in patients with Paget's disease, biochemical markers of bone formation and resorption demonstrated normalisation of bone turnover in more Osteovan treated patients compared to risedronate treated patients (see **CLINICAL TRIALS**).

**Bone Histology:** In the two trials in patients with Paget's disease, bone histology was evaluated in 7 patients 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

**Pharmacokinetics**

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

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, achieving their peak at the end of the infusion period, followed by a rapid decline to < 10% of peak after 4 hours and < 1% of peak after

24 hours, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak levels.

**Distribution**

There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (alpha and beta, with $t_{½}$ values below) presumably represent rapid uptake into bone and excretion via the kidneys.

Zoledronic acid is not highly bound to plasma proteins (approximately 30-60% bound) and binding is concentration and divalent cation ion dependent. Interactions resulting from displacement of highly protein-bound drugs are unlikely.

**Metabolism**

Zoledronic acid is not metabolised in humans. The substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, therefore zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P450 enzyme systems.

**Elimination**

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{½alpha}$ 0.24 and $t_{½beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½gamma}$ 146 hours.

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 ± 2.5 L/h, independent of dose, and unaffected by gender, age, race or body weight. The inter- and intra-subject variation for plasma clearance of zoledronic acid was shown to be 36% and 34%, respectively. Increasing the infusion time from 5 to 15 minutes caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

No specific drug-drug interaction studies have been conducted with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes, zoledronic acid is unlikely to reduce the metabolic

clearance of substances which are metabolised via the cytochrome P450 enzyme systems.

**Pharmacokinetics in special patient groups**

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 patients studied. Small observed increases in $AUC_{(0\text{-}24hr)}$, by about 30% to 40% in mild to moderate renal impairment, compared to a patient with normal renal function, and lack of accumulation of drug with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild ($Cl_{cr}$ = 50-80 mL/min) and moderate ($Cl_{cr}$ = 35-50 mL/min) renal impairment are not necessary. The use of Osteovan in patients with creatinine clearance < 35 mL/min is not recommended due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**). No dose adjustment is necessary in patients with creatinine clearance≥ 35 mL/min.

# CLINICAL TRIALS

**Clinical Efficacy for the Treatment of Postmenopausal Osteoporosis**

The efficacy and safety of Osteovan were demonstrated in a randomised, double-blind, placebo-controlled, multinational study of 7736 ambulant women aged 65 to 89 years with either: a femoral neck BMD T-score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). Clinical experience in postmenopausal women without a history of low trauma hip fracture is limited to women aged over 63 years. Patients pretreated with other bisphosphonates were excluded except if they complied with a washout schedule of between two months and two years, determined by the duration of pretreatment; for instance, patients who had used oral bisphosphonates for more than 8 weeks but less than 48 weeks were eligible after a washout period of at least one year; more extensively pretreated patients were eligible after a washout period of at least 2 years. There are limited 12 month evaluated clinical data on the use of Osteovan in patients who had been extensively treated with bisphosphonates but without a washout period. In the pivotal studies, extensively pretreated patients were enrolled after a washout period of two years. This experience should be considered when selecting patients for Osteovan treatment.

Osteovan was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes for a total of three doses. The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years, and the incidence of hip fractures over a median duration of 3

years. 7736 women were evaluated for the incidence of hip and all clinical fractures. Of these, 5661 women were evaluated annually for incidence of vertebral fractures. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day.

**Primary Efficacy Variables**

**Effect on Vertebral Fracture:** Osteovan significantly decreased the incidence of one or more new vertebral fractures over three years and as early as the one year time point (see Table 1).

**Table 1 Summary of vertebral fracture efficacy at 12 months, 24 months and 36 months**

| **Outcome** | **Osteovan**<br><br>**Event rate (%)** | **Placebo**<br><br>**Event rate (%)** | **Absolute reduction in fracture incidence (%) (95% CI)** | **Relative reduction in fracture incidence (%) (95% CI)** |
|---|---|---|---|---|
| At least one new vertebral fracture (0-1 year) | 1.5 | 3.7 | 2.2 (1.4, 3.1) | 60 (43, 72)** |
| At least one new vertebral fracture (0-2 year) | 2.2 | 7.7 | 5.5 (4.3, 6.6) | 71 (61, 78)** |
| At least one new vertebral fracture (0-3 year) | 3.9 | 10.9 | 7.6 (6.3, 9.0) | 70 (62, 76)** |

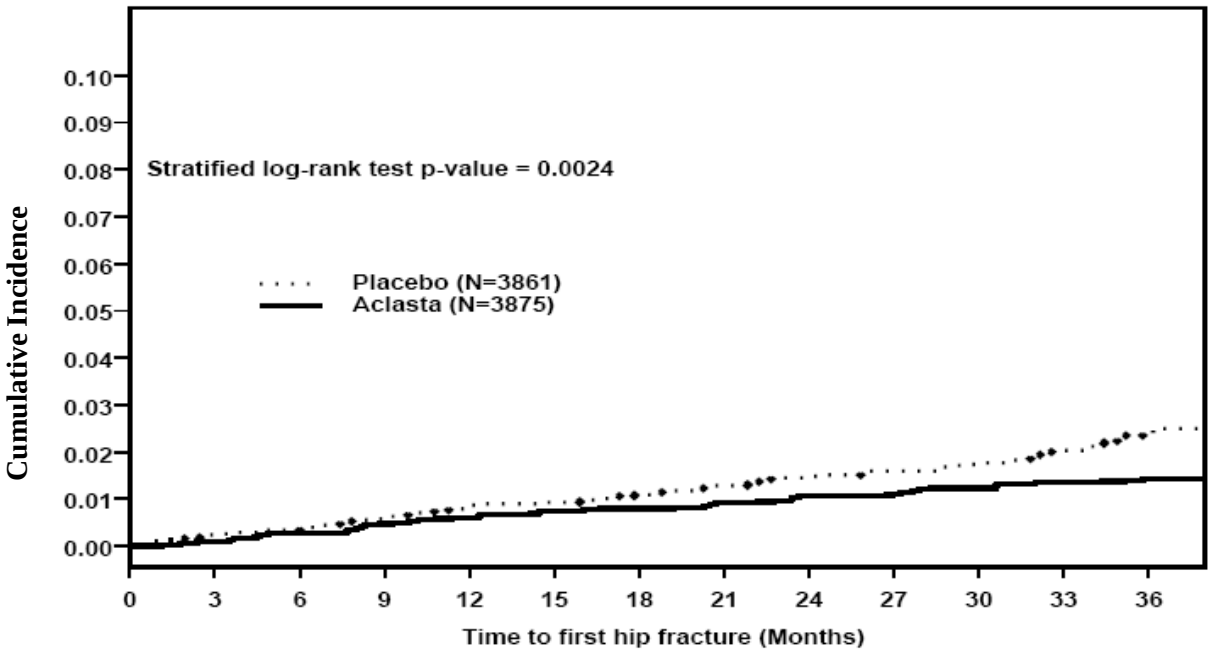
** $p < 0.0001$

The reductions in vertebral fractures over three years were consistent and significantly greater than placebo regardless of age, geographical region, race, baseline body mass index, number of baseline vertebral fractures, femoral neck BMD T-score or prior bisphosphonate use. Specifically for patients aged 75 years and older, Osteovan patients had a 61% reduction in the risk of vertebral fractures compared to placebo patients ($p<0.0001$).

**Effect on Hip Fracture:** Osteovan demonstrated a 41% reduction in the risk of hip fractures over 3 years. The hip fracture event rate was 1.4% for Osteovan-treated

patients compared to 2.5% for placebo-treated patients. The effect over time is displayed in Figure 1.

**Figure 1 Cumulative incidence of hip fracture over 3 years**




The reduction in the risk of hip fractures was similar in women who did not take concomitant osteoporosis therapy to women who were allowed to take concomitant therapy. In 6084 women who did not take concomitant osteoporosis therapy, Osteovan demonstrated a 41% reduction (95% CI, 13% to 59%) in the risk of hip fractures over this time period. In 1652 women who were allowed to take concomitant osteoporosis therapy, a comparable 42% reduction in the risk of hip fractures was observed (95% CI, -2.7% to 73%). The study was not powered to determine if this difference was statistically significant.

The reductions in hip fractures over three years were greater than placebo regardless of femoral neck BMD T-score.

**Secondary Efficacy Variables**

**Effect on Vertebral Fractures:** Osteovan significantly decreased the risk of one or more new/worsening vertebral fractures at 1 year (58%), 2 years (68%) and 3 years (67%) (all $p<0.0001$). Osteovan significantly decreased the risk of at least one new moderate or severe vertebral fracture at 1 year (60%), 2 years (71%) and 3 years (70%) (all $p<0.0001$).

**Effect on All Clinical Fractures:** Osteovan demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical vertebral and non-vertebral

fractures. All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 2.

**Table 2 Between-treatment comparisons of the incidence of key clinical fracture variables over 3 years**

| Outcome | Osteovan (N = 3875) Event rate (%) | Placebo (N = 3861) Event rate (%) | Absolute reduction in fracture incidence (%) (95% CI) | Relative reduction in fracture incidence (%) (95% CI) |
|---|---|---|---|---|
| Any clinical fracture (1) | 8.4 | 12.8 | 4.4 (3.0, 5.8) | 33 (23, 42)** |
| Clinical vertebral fracture (2) | 0.5 | 2.6 | 2.1 (1.5, 2.7) | 77 (63, 86)** |
| Non-vertebral fracture (1) | 8.0 | 10.7 | 2.7 (1.4, 4.0) | 25 (13, 36)* |

*p-value < 0.001, **p-value <0.0001

(1) Excluding finger, toe and facial fractures

(2) Includes clinical thoracic and clinical lumbar vertebral fractures

**Effect on Bone Mineral Density (BMD):** Osteovan significantly increased BMD at the lumbar spine, hip and distal radius relative to treatment with placebo at all time points (6, 12, 24 and 36 months). Treatment with Osteovan resulted in a 6.7% increase in BMD at the lumbar spine, 6.0 % at the total hip, 5.1% at the femoral neck and 3.2% at the distal radius over 3 years as compared to placebo.

**Bone Turnover Markers:** Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (beta-CTx) were evaluated in subsets ranging from 517 to 1246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of Osteovan reduces bone turnover markers to the premenopausal range. Repeat dosing does not lead to further reduction of bone turnover markers.

**Effect on Height:** In the 3-year osteoporosis study, standing height was measured annually using a stadiometer. The Osteovan group revealed less height loss compared to placebo (4.2 mm vs. 7.0 mm, respectively ($p<0.001$)).

**Days of Disability:** Osteovan significantly reduced both the days of limited activity and the days of bed rest due to fractures compared to placebo (both $p<0.01$). Osteovan also significantly reduced both the days of limited activity and the days of bed rest due to back pain compared to placebo (both $p\leq0.008$).

**Effects of Prolonged Therapy and its Discontinuation:** The effects of prolonged zoledronic acid therapy as well as its discontinuation were assessed in a 3 year extension to the treatment of postmenopausal osteoporosis trial. The extension was a

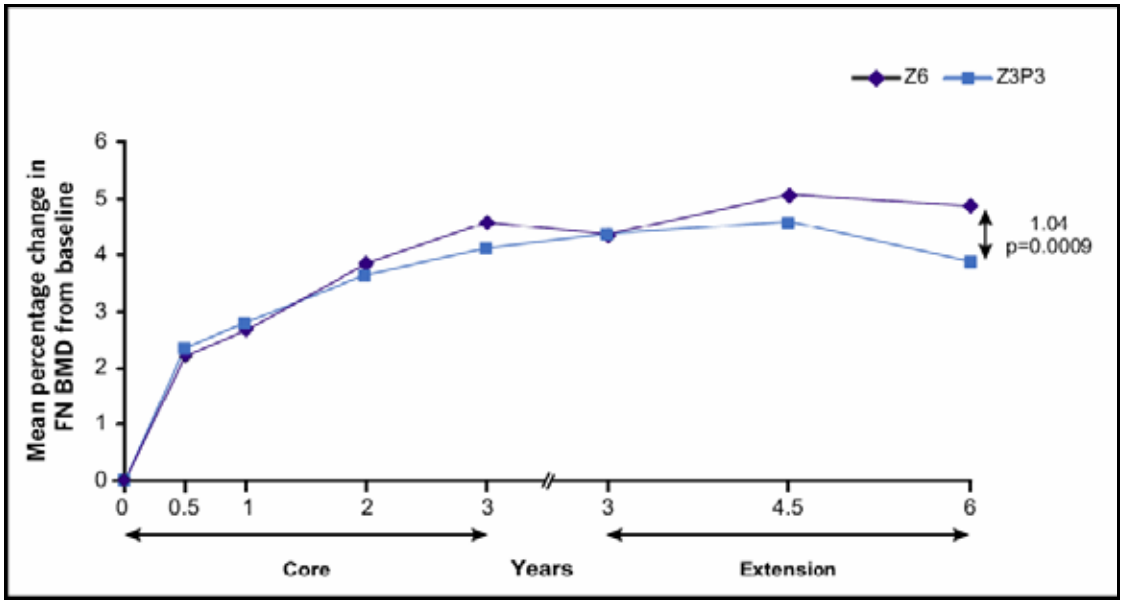
randomised, double-blind, multinational study in 2456 ambulatory postmenopausal women who had completed participation in the core study. The same dosing regimen of zoledronic acid was used in the extension study as in the core study (5 mg intravenous infusion once yearly). The trial design did not allow identification of the specific subset of patients likely to benefit.

The extension study demonstrated that the therapeutic benefit of continued annual zoledronic acid therapy on maintaining or increasing BMD in women with postmenopausal osteoporosis is sustained long-term, while the discontinuation of therapy results in a gradual loss of bone mass.

Compared to treatment with zoledronic acid for 3 years followed by 3 years of placebo, treatment with zoledronic acid for 6 years significantly reduced the risk of new morphometric vertebral fractures by 52% ($p<0.05$) and significantly reduced the risk of new or worsening morphometric fractures by 51% ($p<0.05$). No significant differences were observed between the two groups in the risk of clinical, non-vertebral, hip and clinical vertebral fractures. There is no statistically significant difference in clinical fractures between the group who received zoledronic acid for 6 years compared to the group who received zoledronic acid for 3 years followed by 3 years of placebo.

Bone marker levels remained below pre-treatment levels 6 years earlier and mean values remained within the pre-menopausal reference range for all 3 biomarkers.

**Figure 2 Femoral neck BMD percentage change over time**




There were no cases of atypical femoral fractures in the extension study.

**Clinical Efficacy in the Prevention of Clinical Fractures after Hip Fracture**

The efficacy and safety of Osteovan in the prevention of clinical fractures in patients who suffered a recent low trauma hip fracture were demonstrated in a randomised, double-blind, placebo-controlled, multinational endpoint study of 2127 ambulant men and women aged 50-95 years (mean age of 74.5). The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2127 men and women with a recent (within 90 days) low trauma hip fracture (pertrochanteric or femoral neck) but not malignant fractures and fractures associated with previously implanted orthopedic devices. The washout periods for patients who had been pretreated with other bisphosphonates were the same as those in the postmenopausal osteoporosis study described above. Patients were followed for an average of 2 years on study drug. The following concomitant osteoporosis therapies were allowed: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone, DHEA(s), ipriflavone, and testosterone, as hormone replacement in the case of hypogonadal men; but excluded other bisphosphonates and parathyroid hormone.

Osteovan was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes, until at least 211 patients had confirmed clinical fractures in the study population. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally or via the intramuscular route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

**Primary Efficacy Variable**

**Effect on All Clinical Fractures:** In the prevention of clinical fractures after hip fracture trial, treatment with Osteovan significantly reduced the incidence of any clinical fracture by 35% (see Table 3).

**Secondary Efficacy Variables**

**Other Clinical Fracture Endpoints:** There was also a 46% reduction in the risk of a clinical vertebral fracture; a 27% reduction in the risk for non-vertebral fractures with Osteovan. There was a 30% reduced risk for a subsequent hip fracture that was observed for the Osteovan group that did not meet statistical significance. See Table 3.

**Table 3 Between treatment comparisons of the incidence of key clinical fracture variables**

| Outcome | Osteovan (N=1064) | Placebo (N=1063) | Absolute reduction in | Relative risk reduction in |
|---|---|---|---|---|

| | Event rate (%) | Event rate (%) | fracture incidence(%) (95% CI) | fracture incidence (%) (95% CI) |
|---|---|---|---|---|
| Any clinical fracture (1) | 8.6 | 13.9 | 5.3 (2.3, 8.3) | 35 (16, 50)** |
| Clinical vertebral fracture (2) | 1.7 | 3.8 | 2.1 (0.5, 3.7) | 46 (8, 68)* |
| Non-vertebral fracture (3) | 7.6 | 10.7 | 3.1 (0.3, 5.9) | 27 (2, 45)* |
| Hip fracture | 2.0 | 3.5 | 1.5 (-0.1, 3.1) | 30 (-19, 59) |

*p-value <0.05, **p-value <0.005

(1) Excluding finger, toe and facial fractures

(2) Including clinical thoracic and clinical lumbar vertebral fractures

(3) Excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures

**Effect on Bone Mineral Density (BMD):** In the prevention of clinical fractures after hip fracture trial, Osteovan treatment significantly increased BMD relative to placebo at the hip and femoral neck at all time points (12, 24 and 36 months). Treatment with Osteovan resulted in a 5.4 % increase at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo. Similar significant results were observed for femoral neck BMD measures.

**Treatment of Male Osteoporosis**

The efficacy and safety of Osteovan in men with osteoporosis were assessed in a randomised, multicentre, double-blind, active-controlled study of 302 men aged 25 to 86 years (mean age of 64 years) with either: a femoral neck BMD T-score less than or equal to -2.0 and a lumbar spine BMD T-score less than or equal to -1.0 or a femoral neck BMD T-score less than or equal to -1.0 and at least one vertebral deformity or a history of an osteoporotic fracture. The duration of the trial was two years. Patients were randomised to either Osteovan, which was administered once annually as a single 5 mg dose in 100 mL infused over 15 minutes for a total of two doses, or to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to alendronate was shown with respect to the percentage change in lumbar spine BMD at 24 months relative to baseline.

Osteovan has not been studied in hypogonadal men. Fracture data are not available from the study.

**Effect on Bone Mineral Density (BMD):** An annual infusion of Osteovan was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline (Osteovan 6.1% compared to alendronate 6.2%). The percentage increases in lumbar spine BMD at month 12 were also similar between treatment groups. The criterion for non-inferiority of zoledronic acid by comparison with alendronate was met as the lower bound of the 95% CI (-1.12 for the ITT

population, -1.27 per protocol) exceeded the pre-specified non-inferiority margin of -1.5%.

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

The efficacy and safety of Osteovan in the treatment and prevention of glucocorticoid-induced osteoporosis were assessed in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women aged 18 to 85 years (mean age of 54.4 years) treated with ≥ 7.5 mg/day oral prednisone (or equivalent). Patients in the prevention subpopulation were treated with glucocorticoids ≤ 3 months prior to randomisation, and the treatment subpopulation was treated with glucocorticoids ≥ 3 months prior to randomisation. The duration of the trial was one year. Patients were randomised to either Osteovan, which was administered once as a single 5 mg dose in 100 mL infused over 15 minutes, or to oral risedronate 5 mg daily for one year. All participants received 1000 mg elemental calcium plus 400 to 1000 IU vitamin D supplementation per day.

The study was designed to show non-inferiority of a single infusion of Osteovan relative to risedronate in these two subpopulations. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively.

This was not a fracture study and limited data only are available: over the 12 months of the study, new vertebral fractures detected by x-ray morphometry occurred in 5/379 (1.3%) of Osteovan-treated patients and assessed, compared to 3/381 (0.8%) in the risedronate treated group. An analysis of the time to first clinical fracture during the study period showed no difference between the treatment groups. During the 12 month study, 8 Osteovan-treated patients and 7 risedronate treated patients had at least one clinical fracture.

**Effect on Bone Mineral Density (BMD):** Non-inferiority to risedronate was shown. There was a trend to greater increase in BMD in the Osteovan-treated group in both the treatment and prevention sub-populations at all sites, which included the lumbar spine, femoral neck, total hip, trochanter and distal radius at 12 months compared to risedronate. A summary of the key results appears in Table 4.

**Table 4 Effects of Osteovan and risedronate on bone mineral density of the lumbar spine, total hip and femoral neck (modified ITT population)**

| Population | Location | Osteovan n LS Mean* (SE) | Risedronate n LS Mean* (SE) |
|---|---|---|---|
| Treatment | Lumbar spine | 249 4.06 (0.28) | 245 2.71 (0.28) |
| | Total hip | 247 1.65 (0.21) | 239 0.45 (0.20) |

| | | | |
|---|---|---|---|
| | Femoral neck | 247 1.45 (0.31) | 239 0.39 (0.30) |
| Prevention | Lumbar spine | 129 2.60 (0.45) | 136 0.64 (0.46) |
| | Total hip | 126 1.54 (0.36) | 135 0.03 (0.36) |
| | Femoral neck | 126 1.30 (0.45) | 135 -0.03 (0.46) |

* LS Mean – Least Square Mean

**Clinical Efficacy for the Treatment of Paget's Disease of Bone**

Osteovan was studied in male and female patients aged above 30 years with mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6-3.0 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of one infusion of 5 mg Osteovan versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month controlled comparative trials. The primary objective of these trials was to show non-inferiority of zoledronic acid compared to risedronate with respect to the proportion of patients who achieved a therapeutic response at 6 months. Non-inferiority was defined as: zoledronic acid is non-inferior to risedronate if the lower bound of a two-sided 95% confidence interval for the difference between zoledronic acid and risedronate in the proportion of therapeutic responders exceeded -0.16. If non-inferiority was shown and the pre-defined non-inferiority margin was exceeded, testing for superiority would be performed.

The primary outcome variable was the proportion of patients achieving a therapeutic response defined as either normalisation of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of 6 months. SAP excess was defined as the difference between the measured level and midpoint of the normal range.

At 6 months, combined data from both trials showed that 96.0% (169/176) Osteovan-treated patients achieved a therapeutic response as compared with 74.3% (127 of 171) of patients treated with risedronate ($p<0.001$). In addition, at 6 months, 88.6% (156/176) of Osteovan-treated patients achieved remission (normalisation of SAP levels) compared to 57.9% (99/171) of patients treated with risedronate ($p<0.0001$). Non-inferiority was found (the difference between combined groups was 0.22 (0.14, 0.30)).

In combined data from both trials, after 2 months, the therapeutic response rate was 90% (158/176) and the SAP normalisation rate was 63% (111/176) compared to 47% (81/171) and 26% (45/171) respectively for risedronate (all $p<0.001$).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Osteovan and risedronate.

The adverse reaction profile reflects a very common incidence of acute phase reactions in the zoledronic acid group (influenza-like illness, pyrexia, myalgia, arthralgia and bone pain).

**Extended Observation Period**

Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended follow-up period. Of the 152 Osteovan-treated patients and 115 risedronate-treated patients who entered an extended observation study, after a median duration of follow-up of 32 months from time of dosing, 142 Osteovan-treated patients maintained their therapeutic response compared to 50 risedronate-treated patients ($p<0.0001$).

# INDICATIONS

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures.
- Treatment of osteoporosis in patients over 50 years of age with a history of at least one low trauma hip fracture, to reduce the incidence of further fractures.
- To increase bone mineral density in men with osteoporosis.
- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use.
- To prevent glucocorticoid-induced bone mineral density loss.
- Treatment of Paget's disease of bone.

# CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates; hypocalcaemia; renal impairment (creatinine clearance < 35 mL/min); current or recent uveitis, or a history of bisphosphonate-associated uveitis; pregnancy and lactation.

# PRECAUTIONS

## General

The dose of 5 mg zoledronic acid must be administered intravenously over at least 15 minutes.

Osteovan contains the same active ingredient found in Zometa® (zoledronic acid), used for oncology indications, and a patient being treated with Zometa should not be treated with Osteovan.

Consider carefully before using Osteovan in patients who have been extensively pretreated with other bisphosphonates. Consider discontinuing Osteovan on the occurrence of atypical fractures such as subtrochanteric fractures or atypical stress fractures. The Optimum duration of bisphosphonate treatment is currently unknown. The risk: benefit ratio of prolonged therapy should be estimated in each patient. No data are available on recommencing therapy after cessation of treatment.

**Acute Phase Reaction**

Post-dose symptoms commonly occur within the first three days following Osteovan administration and may include fever, flu-like symptoms, myalgia, arthralgia and headache (see **ADVERSE REACTIONS** and **DOSAGE AND ADMINISTRATION**). The incidence of these symptoms can be reduced by approximately 50% with the administration of paracetamol shortly following Osteovan administration. Non-steroidal anti-inflammatory agents are not recommended first line to manage the acute phase reaction.

**Hydration**

Patients must be appropriately hydrated prior to administration of Osteovan. This is especially important in the elderly and for patients receiving diuretic therapy. Adequate hydration can be achieved by the patient drinking two glasses of fluid (such as water) before and two glasses of fluid after the infusion.

**Pre-existing Hypocalcaemia or Vitamin D Deficiency**

If there are clinical reasons to suspect hypocalcaemia, vitamin D deficiency or other disturbances of mineral metabolism (e.g. thyroid surgery, parathyroid surgery, calcium malabsorption), the appropriate tests should be performed and, if abnormalities are discovered, these should be corrected before initiating therapy with Osteovan (see **CONTRAINDICATIONS**). Physicians should consider clinical monitoring after treatment in patients with pre-existing disturbances of mineral metabolism.

**Renal Impairment**

Renal impairment has been observed following the administration of Osteovan (see **ADVERSE REACTIONS, Post-marketing Experience**), especially in patients with pre-existing renal compromise or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see

**PRECAUTIONS Interactions with Other Medicines**), or dehydration occurring after Osteovan administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the risk factors described above.

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

- Osteovan should not be used in patients with severe renal impairment (creatinine clearance < 35 mL/min) due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**).
- Osteovan should be used with caution when concomitantly used with other medicinal products that could impact renal function (see **PRECAUTIONS Interactions with Other Medicines**).
- Creatinine clearance should be calculated (e.g. Cockroft-Gault formula) before each Osteovan dose (see **CONTRAINDICATIONS**). Transient increase in serum creatinine may be greater in patients with underlying impaired renal function; interim monitoring of serum creatinine should be considered in at-risk patients.
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Osteovan (see **PRECAUTIONS Hydration**).
- A single dose of Osteovan should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see **DOSAGE AND ADMINISTRATION**).

**Calcium and Vitamin D Supplementation**

**Treatment of Osteoporosis:** Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis if dietary intake is inadequate.

**Prevention of Clinical Fractures after a Hip Fracture:** Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a hip fracture.

**Treatment of Paget's Disease of Bone:** Elevated bone turnover is a characteristic of Paget's disease of bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Osteovan (see **ADVERSE REACTIONS**). Adequate vitamin D intake is recommended in association with Osteovan administration (see **PRECAUTIONS Pre-existing Hypocalcaemia or Vitamin D Deficiency**). In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Osteovan administration.

Patients should be informed about symptoms of hypocalcaemia. Physicians should consider clinical monitoring for patients at risk.

**Musculoskeletal Pain**

Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates including Osteovan.

**Osteonecrosis of the Jaw (ONJ)**

Osteonecrosis of the jaw has been reported predominantly in cancer patients treated with bisphosphonates, including 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. Symptoms include persistent pain and/or non-healing sores of the mouth or jaw. Many had signs of local infection including osteomyelitis.

Discuss with the patient the need to have dental work completed before commencing Osteovan treatment. 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. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

In the treatment of postmenopausal osteoporosis trial in 7714 patients who received Osteovan or placebo, ONJ has been reported in one patient with Osteovan and one patient treated with placebo. Both cases resolved. In the prevention of clinical fractures after hip fracture trial, in 2111 patients who received Osteovan or placebo there were no reports of ONJ. (See **CLINICAL TRIALS.**)

**Effects on Fertility**

Fertility was decreased in rats dosed subcutaneously (SC) with zoledronic acid 0.1 mg/kg/day for 71 days (males) or 15 days (females), with animal/human exposure margins 2-8 (based on cumulative AUC for unbound drug), and preimplantation loss was increased at 0.01 mg/kg/day. Reversible testicular atrophy occurred in rats at 0.003 mg/kg/day SC for 12 months (exposure margin 1). In dogs, testicular and

prostatic atrophy and oligospermia were observed at 0.2 mg/kg/day intravenously (IV) for 3 months (exposure margin 160). Testicular atrophy and/or mineralisation were additionally observed in the dog at 0.03 mg/kg IV dosed every 2 to 3 days for 6 months (exposure margin 56), although no such changes were seen at 0.1 mg/kg for 12 months (exposure margin 269). Female dogs had decreased weights of ovaries and uterus, correlated with anoestrus and, in some animals, with vaginal epithelial degeneration at 0.01 mg/kg IV daily for 3 months (exposure margin 14). There were no effects on reproductive organs in dogs dosed with up to 1 mg/kg zoledronic acid by IV infusion once every 3 weeks for 26 weeks (exposure margin 60).

**Use in Pregnancy**

Category B3. There are no data on the use of zoledronic acid in pregnant women. Teratology studies were performed in rats and rabbits, both via subcutaneous administration. Teratogenicity was observed in rats at doses≥ 0.2 mg/kg (0.2 times clinical exposure based on unbound AUC) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological effects were observed in rabbits, but maternal toxicity and increased embryo/foetal resorption occurred at ≥ 0.03 mg/kg (0.14 times clinical exposure based on dose adjusted for body surface area). In the absence of adequate data in pregnant women, Osteovan is contraindicated during pregnancy. Women who might become pregnant at some time in the future should be warned about the long half-life of bisphosphonates.

**Use in Lactation**

Studies have not been performed in lactating animals, and the transfer of zoledronic acid into milk is unknown. Because many drugs are excreted in human milk, breast-feeding should be discontinued before Osteovan administration.

**Paediatric Use**

Osteovan is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.

**Use in the Elderly**

The postmenopausal osteoporosis trial included 3868 Osteovan-treated patients who were at least 65 years of age, while 1497 patients were at least 75 years old. No overall differences in efficacy or safety were observed between patients under 75 years of age with those at least 75 years of age, except that the acute phase reactions occurred less frequently in the older patients.

The prevention of clinical fractures after hip fracture trial included 893 Osteovan-treated patients who were at least 65 years of age, while 586 patients were at least 75 years old. Those who were 65 years and older had the same reduction in clinical fractures (35%) as those less than 65 years of age. Those 75 years and older had a 42% reduction in clinical fractures. No overall differences in safety were observed between these patients and younger patients.

However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

**Carcinogenicity**

In carcinogenicity studies, zoledronic acid was administered orally by gavage to rats and mice at daily doses of 0.1, 0.5 and 2.0 mg/kg and 0.1, 0.3 and 1.0 mg/kg, respectively, for at least 104 weeks without evidence of carcinogenic potential. Pharmacological bone changes typically observed following long-term bisphosphonate administration to young animals with growing skeletons were observed in these studies, suggesting systemic exposure to zoledronic acid in both species.

**Genotoxicity**

Zoledronic acid was not mutagenic in bacterial reverse mutation tests in *Salmonella typhimurium* and *Escherischia coli* or in cultured V79 Chinese hamster lung cells. Zoledronic acid did not induce chromosome aberrations in an *in vitro* test in Chinese hamster ovary cells or in an *in vivo* micronucleus test in rats.

**Interactions with Other Medicines**

Specific drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P450 enzymes *in vitro* (see **PHARMACOLOGY Pharmacokinetics**). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely. Zoledronic acid is eliminated by renal excretion.

**Drugs that Could Impact Renal Function:** Caution is indicated when Osteovan is administered in conjunction with drugs that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

**Drugs Primarily Excreted by the Kidney:** In patients with renal impairment, the systemic exposure to concomitant medicinal products that are primarily excreted via the kidneys may increase.

**Effects on Ability to Drive and Use Machines**

There are no data to suggest that Osteovan affects the ability to drive or use machines. However, patients should be warned about post-infusion hypocalcaemia which is usually asymptomatic but occasionally causes tetany.

# ADVERSE EFFECTS

## Adverse Events in Clinical Trials

### Postmenopausal Osteoporosis

In the Phase III randomised, double-blind, placebo-controlled, multinational study of 7736 postmenopausal women aged 65-89 years (see **CLINICAL TRIALS**), there were no significant differences in the overall incidence of serious adverse events compared to placebo and most adverse events were mild to moderate. The incidence of all-cause mortality was similar between groups: 3.4% in the Osteovan group and 2.9% in the placebo group. Osteovan was administered once yearly for three consecutive years for a total of three doses.

Consistent with the intravenous administration of bisphosphonates, Osteovan has been most commonly associated with the following post-dose symptoms: fever (18.1%), myalgia (9.4%), flu-like symptoms (7.8%), arthralgia (6.8%) and headache (6.5%), the majority of which occur within the first 3 days following Osteovan administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased markedly with subsequent annual doses of Osteovan.

The incidence of post-dose symptoms occurring within the first 3 days after administration of Osteovan can be reduced by approximately 50% with the administration of paracetamol shortly following Osteovan administration.

Adverse events occurring in ≥ 2.0% of postmenopausal women with osteoporosis are shown in Table 5.

**Table 5 Adverse events occurring in ≥ 2.0% of postmenopausal women with osteoporosis and in ≥ 2.0% of men and women following hip fracture receiving Osteovan (5 mg IV infusion once yearly) and more frequently than in placebo-treated patients over 3 years**

| | **Postmenopausal osteoporosis trial** | | **Prevention of clinical fracture after hip fracture trial** | |
|---|---|---|---|---|
| | **5 mg IV** | **Placebo** | **5 mg IV** | **Placebo** |

| System Organ Class | Osteovan once per year % (N=3862) | once per year % (N=3852) | Osteovan once per year % (N=1054) | once per year % (N=1057) |
|---|---|---|---|---|
| **Infections and infestations** | | | | |
| Urinary tract infection | 12.1 | 11.7 | 10.6 | 9.6 |
| Nasopharyngitis | 11.3 | 11.0 | 4.7 | 4.3 |
| Bronchitis | 5.3 | 6.1 | 3.9 | 3.1 |
| **Blood and the Lymphatic System Disorders** | | | | |
| Anaemia | 4.4 | 3.6 | 5.3 | 5.2 |
| **Metabolism and Nutrition Disorders** | | | | |
| Hypercholesterolaemia | 4.0 | 3.9 | 2.9 | 2.1 |
| Dehydration | 0.6 | 0.6 | 2.5 | 2.3 |
| Anorexia | 2.0 | 1.1 | 1.0 | 1.0 |
| **Nervous System Disorders** | | | | |
| Headache | 12.4 | 8.1 | 3.9 | 2.5 |
| Dizziness | 7.6 | 6.7 | 2.0 | 4.0 |
| **Eye Disorders** | | | | |
| Cataract | 6.3 | 5.8 | 3.0 | 2.3 |
| **Ear and Labyrinth Disorders** | | | | |
| Vertigo | 4.3 | 4.0 | 1.3 | 1.7 |
| **Cardiac Disorders** | | | | |
| Atrial fibrillation | 2.5 | 1.9 | 3.0 | 2.8 |
| Cardiac failure congestive | 3.0 | 2.8 | 2.8 | 2.6 |
| **Vascular Disorders** | | | | |
| Hypertension | 12.7 | 12.4 | 6.8 | 5.4 |
| **Gastrointestinal Disorders** | | | | |
| Nausea | 8.5 | 5.2 | 4.5 | 4.5 |
| Diarrhoea | 6.0 | 5.6 | 5.2 | 4.7 |
| Vomiting | 4.6 | 3.2 | 3.4 | 3.4 |

| | | | | |
|---|---|---|---|---|
| Abdominal pain upper | 4.6 | 3.1 | 0.9 | 1.5 |
| Dyspepsia | 4.3 | 4.0 | 1.7 | 1.6 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | | | |
| Arthralgia | 23.8 | 20.4 | 17.9 | 18.3 |
| Myalgia | 11.7 | 3.7 | 4.9 | 2.7 |
| Pain in extremity | 11.3 | 9.9 | 5.9 | 4.8 |
| Shoulder pain | 6.9 | 5.6 | 0.0 | 0.0 |
| Bone pain | 5.8 | 2.3 | 3.2 | 1.0 |
| Neck pain | 4.4 | 3.8 | 1.4 | 1.1 |
| Muscle spasms | 3.7 | 3.4 | 1.5 | 1.7 |
| Osteoarthritis | 9.1 | 9.7 | 5.7 | 4.5 |
| Musculoskeletal pain | 0.4 | 0.3 | 3.1 | 1.2 |
| **General Disorders and Administrative Site Conditions** | | | | |
| Pyrexia | 17.9 | 4.6 | 8.7 | 3.1 |
| Influenza-like illness | 8.8 | 2.7 | 0.8 | 0.4 |
| Fatigue | 5.4 | 3.5 | 2.1 | 1.2 |
| Chills | 5.4 | 1.0 | 1.5 | 0.5 |
| Asthenia | 5.3 | 2.9 | 3.2 | 3.0 |
| Peripheral oedema | 4.6 | 4.2 | 5.5 | 5.3 |
| Pain | 3.3 | 1.3 | 1.5 | 0.5 |
| Malaise | 2.0 | 1.0 | 1.1 | 0.5 |
| Hyperthermia | 0.3 | <0.1 | 2.3 | 0.3 |
| Chest pain | 1.3 | 1.1 | 2.4 | 1.8 |
| **Investigations** | | | | |
| Weight decreased | 1.8 | 1.2 | 2.4 | 2.1 |
| Creatinine renal clearance decreased | 2.0 | 2.4 | 2.1 | 1.7 |
| **Injury, Poisoning and Procedural Complications** | | | | |
| Post procedure complication | 0.0 | 0.0 | 3.8 | 3.3 |
| Contusion | 2.9 | 2.6 | 2.9 | 2.6 |

The safety results in the three year extension to the treatment of postmenopausal osteoporosis trial suggest that the overall safety profile for zoledronic acid 5 mg yearly is similar in patients who continued therapy for 6 years to patients who stopped treatment after 3 years.

**Prevention of Clinical Fractures after Hip Fracture**

In a randomised, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50-95 years with a recent (within 90 days) low trauma hip fracture, 1065 patients were exposed to Osteovan (zoledronic acid) and 1062 patients exposed to placebo. Osteovan was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of 2 years on study drug. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day.

Most adverse events were of mild to moderate severity and did not lead to discontinuation. The incidence of serious adverse events was 38% in the Osteovan group and 41% in the placebo group. All cause mortality was 9.6% in the Osteovan-treated group compared to 13.3% in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality (p=0.01).

Osteovan was associated with the following post-dose symptoms: fever (7%) and arthralgia (3%), which occur within the first 3 days following Osteovan administration. The majority of these symptoms were mild to moderate in nature and resolved within 3 days of the event onset. The incidence of these symptoms decreased with subsequent doses of Osteovan. The main reason for the lower rate of post-dose symptoms in this trial compared to the rate of post-dose symptoms in the treatment of postmenopausal osteoporosis trial was that, in this prevention of clinical fractures after hip fracture trial, paracetamol was provided to patients and its use encouraged to manage post-dose symptoms.

Adverse events occurring in $\geq$ 2.0% of men and women following hip fracture (prevention of clinical fractures after hip fracture) are shown above in Table 5.

**Treatment of Male Osteoporosis**

The safety of Osteovan in men with osteoporosis or significant osteoporosis secondary to hypogonadism was assessed in a two-year randomised, multicentre, double-blind, active-controlled group study of 302 men aged 25-86 years. One hundred and fifty-three patients were exposed to Osteovan administered once annually as a single 5 mg dose in 100 mL infused over 15 minutes for a total of two

doses and 148 patients were exposed to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar between the Osteovan and alendronate treatment groups. The percentage of patients experiencing at least one adverse event was comparable between the Osteovan and alendronate treatment groups, with the exception of a higher incidence of post-dose symptoms in the Osteovan group that occurred within 3 days after infusion. The overall safety and tolerability profile of Osteovan in male osteoporosis was similar to that reported in the Osteovan postmenopausal osteoporosis trial.

Adverse events reported in at least 2% of men with osteoporosis and more frequently in the Osteovan treatment group than the alendronate group and either not reported in the postmenopausal osteoporosis trial or reported more frequently in the osteoporosis trial in men are presented in Table 6.

**Table 6 Adverse events occurring in ≥ 2% of men with osteoporosis and more frequently in the Osteovan-treated patients than the alendronate-treated patients and either not reported in the postmenopausal osteoporosis trial or reported more frequently in this trial**

| System Organ Class | 5 mg IV Osteovan once per year % (N=153) | Alendronate 70 mg once weekly % (N=148) |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 4.6 | 3.4 |
| Tooth abscess | 2.6 | 0.7 |
| Cellulitis | 2.0 | 1.4 |
| **Neoplasma Benign, Malignant and Unspecified (including cysts and polyps)** | | |
| Basal cell carcinoma | 3.3 | 0.7 |
| **Psychiatric disorders** | | |
| Anxiety | 2.6 | 2.0 |
| **Nervous System Disorders** | | |
| Headache | 15.0 | 6.1 |
| Lethargy | 3.3 | 1.4 |
| Paraesthesia | 2.6 | 0.7 |
| Syncope | 2.6 | 1.4 |
| Hypoaesthesia | 2.0 | 1.4 |
| **Eye Disorders** | | |
| Eye pain | 2.0 | 0.0 |
| **Cardiac Disorders** | | |

| | | |
|---|---|---|
| Atrial fibrillation | 3.3 | 2.0 |
| Palpitations | 2.6 | 0.0 |
| **Vascular Disorders** | | |
| Hypotension | 2.0 | 1.4 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnoea | 6.5 | 4.7 |
| Chronic obstructive pulmonary disease | 2.6 | 0.7 |
| Pulmonary oedema | 2.0 | 0.7 |
| **Gastrointestinal Disorders** | | |
| Dental caries | 4.6 | 0.0 |
| Abdominal pain* | 7.9 | 4.1 |
| Colonic polyp | 2.0 | 1.4 |
| Haemorrhoids | 2.0 | 1.4 |
| Toothache | 2.0 | 0.7 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Skin lesion | 3.3 | 0.0 |
| Actinic keratosis | 2.6 | 0.7 |
| Hyperhidrosis | 2.6 | 2.0 |
| Alopecia | 2.0 | 0.0 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Myalgia | 19.6 | 6.8 |
| Musculoskeletal pain** | 12.4 | 10.8 |
| Musculoskeletal stiffness | 4.6 | 0.0 |
| Muscular weakness | 2.0 | 1.4 |
| **Renal and Urinary Disorders** | | |
| Urinary retention | 2.0 | 0.7 |
| Blood creatinine increased | 2.0 | 0.7 |
| **General Disorders and Administrative Site Conditions** | | |
| Fatigue | 17.6 | 6.1 |
| Pain | 11.8 | 4.1 |
| Chills | 9.8 | 2.7 |
| Influenza like illness | 9.2 | 2.0 |
| Malaise | 7.2 | 0.7 |
| Acute phase reaction | 3.9 | 0.0 |
| Chest pain | 2.0 | 1.4 |
| **Investigations** | | |
| C-reactive protein increased | 4.6 | 1.4 |
| Weight decreased | 3.3 | 1.4 |
| **Injury, Poisoning and Procedural Complications** | | |
| Rib fracture | 3.3 | 0.7 |

* Combined abdominal pain, abdominal pain upper and abdominal pain lower as one AE.

** Combined musculoskeletal pain and musculoskeletal chest pain as one AE.

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

The safety of Osteovan in men and women in the treatment and prevention of glucocorticoid-induced osteoporosis was assessed in a randomised, multicentre, double-blind, active-controlled, stratified study of 833 men and women aged 18-85 years treated with ≥ 7.5 mg/day oral prednisione (or equivalent). Patients in the prevention subpopulation were treated with glucocorticoids ≤ 3 months prior to randomisation, and the treatment subpopulation was treated with glucocorticoids > 3 months prior to randomisation.

The duration of the trial was one year, with 416 patients exposed to Osteovan administered once as a single 5 mg dose in 100 mL infused over 15 minutes and 417 patients exposed to oral risedronate 5 mg daily for one year. All participants received 1000 mg elemental calcium plus 400 to 1000 IU vitamin D supplementation per day.

The incidence of serious adverse events was similar between the Osteovan and risedronate treatment groups. Overall safety and tolerability were similar between the Osteovan and risedronate groups, with the exception of a higher incidence of post-dose symptoms in the Osteovan group that occurred within 3 days after infusion. The overall safety and tolerability profile of Osteovan in glucocorticoid-induced osteoporosis was similar to that reported in the Osteovan postmenopausal osteoporosis clinical trial.

Adverse events reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis trial or reported more frequently in the treatment and prevention of glucocorticoid induced osteoporosis trial are presented in Table 7.

**Table 7 Adverse events occurring in ≥ 2% of patients receiving at least 7.5 mg/day or equivalent for the treatment or prevention of glucocorticoid-induced osteoporosis patients and either not reported in the postmenopausal osteoporosis trial or reported more frequently in this trial**

| System Organ Class | 5 mg IV Osteovan once per year % (N=416) | Risedronate 5 mg/day % (N=417) |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 3.4 | 1.9 |
| Upper respiratory tract infection | 2.4 | 1.9 |
| **Nervous System Disorders** | | |
| Sciatica | 2.4 | 0.2 |

| | | |
|---|---|---|
| **Gastrointestinal Disorders** | | |
| Nausea | 9.6 | 8.4 |
| Dyspepsia | 5.5 | 4.3 |
| Abdominal pain* | 7.5 | 5.0 |
| Constipation | 2.2 | 1.7 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Rheumatoid arthritis | 6.3 | 5.0 |
| Musculoskeletal pain** | 3.1 | 1.7 |
| **General Disorders and Administrative Site Conditions** | | |
| Oedema peripheral | 2.9 | 2.2 |

* Combined abdominal pain, abdominal pain upper and abdominal pain lower as one AE.

** Combined musculoskeletal pain and musculoskeletal chest pain as one AE.

**Paget's Disease of Bone**

In the Paget's disease trials, two 6-month, double-blind, comparative, multinational studies of 349 men and women aged > 30 years with moderate to severe disease and with confirmed Paget's disease of bone, 177 patients were exposed to Osteovan and 172 patients exposed to risedronate. Osteovan was administered once as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. Risedronate was given as an oral daily dose of 30 mg for 2 months.

The signs and symptoms of acute phase reaction (influenza-like illness, pyrexia, myalgia, arthralgia and bone pain) were reported in 25% of patients in the Osteovan-treated group compared to 8% in the risedronate-treated group. Symptoms usually occur within the first 3 days following Osteovan administration. The majority of these symptoms resolved within 4 days of onset.

Adverse events occurring in at least 2% of the Paget's patients receiving Osteovan (single 5 mg IV infusion) or risedronate (30 mg oral daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 8.

**Table 8 Adverse events reported in ≥ 2% of Paget's patients receiving Osteovan (single 5 mg IV infusion) or risedronate (oral 30 mg daily for 2 months) over a 6-month follow-up period**

| **System Organ Class** | **5 mg IV Osteovan %** **(N = 177)** | **Risedronate 30 mg/day x 2 months %** **(N = 172)** |
|---|---|---|
| **Infections and Infestations** | | |
| Influenza | 7 | 5 |
| **Metabolism and Nutrition Disorders** | | |

| | | |
|---|---|---|
| Hypocalcaemia | 3 | 1 |
| Anorexia | 2 | 2 |
| **Nervous System Disorders** | | |
| Headache | 11 | 10 |
| Dizziness | 9 | 4 |
| Lethargy | 5 | 1 |
| Paraesthesia | 2 | 0 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | |
| Dyspnoea | 5 | 1 |
| **Gastrointestinal Disorders** | | |
| Nausea | 9 | 6 |
| Diarrhoea | 6 | 6 |
| Constipation | 6 | 5 |
| Dyspepsia | 5 | 4 |
| Abdominal distension | 2 | 1 |
| Abdominal pain | 2 | 2 |
| Vomiting | 2 | 2 |
| Abdominal pain upper | 1 | 2 |
| **Skin and Subcutaneous Tissue Disorders** | | |
| Rash | 3 | 2 |
| **Musculoskeletal, Connective Tissue and Bone Disorders** | | |
| Arthralgia | 9 | 11 |
| Bone pain | 9 | 5 |
| Myalgia | 7 | 4 |
| Back pain | 4 | 7 |
| Musculoskeletal stiffness | 2 | 1 |
| **General Disorders and Administrative Site Conditions** | | |
| Influenza-like illness | 11 | 6 |
| Pyrexia | 9 | 2 |
| Fatigue | 8 | 4 |
| Rigors | 8 | 1 |
| Pain | 5 | 4 |
| Peripheral oedema | 3 | 1 |
| Asthenia | 2 | 1 |

**Adverse Reactions with Suspected Relationship to Product**

Table 9 lists the adverse reactions suspected (investigator assessment) to be associated with Osteovan in the pooled studies supporting the indications: treatment of osteoporosis in men and postmenopausal women, prevention of clinical fractures after low trauma hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone by system organ class and by frequency

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) adverse drug reactions.

**Table 9 Adverse reactions suspected to be associated with Osteovan treatment**

| | |
|---|---|
| **Infections and Infestations** | |
| Uncommon: | Influenza, nasopharyngitis |
| **Blood and Lymphatic System Disorders** | |
| Uncommon: | Anaemia |
| **Metabolism and Nutrition Disorders** | |
| Uncommon: | Anorexia*, decreased appetite |
| **Psychiatric Disorders** | |
| Uncommon: | Insomnia |
| **Nervous System Disorders** | |
| Common: | Headache, dizziness |
| Uncommon: | Lethargy*, paraesthesia, somnolence, tremor, syncope |
| **Eye Disorders** | |
| Uncommon: | Conjunctivitis, eye pain |
| Rare: | Uveitis*, episcleritis, iritis |
| **Ear and Labyrinth Disorders** | |
| Uncommon: | Vertigo |
| **Vascular Disorders** | |
| Uncommon: | Hypertension, flushing |
| **Respiratory, Thoracic and Mediastinal Disorders** | |
| Uncommon: | Cough, dyspnoea* |
| **Gastrointestinal Disorders** | |
| Common: | Nausea, vomiting, diarrhoea |
| Uncommon: | Dyspepsia*, abdominal pain upper, abdominal pain*, gastroesophageal reflux disease, constipation, dry mouth, oesophagitis* |
| **Skin and Subcutaneous Tissue Disorders** | |
| Uncommon: | Rash, hyperhydrosis*, pruritus, erythema |
| **Musculoskeletal Disorders** | |
| Common: | Myalgia*, arthralgia*, bone pain, back pain, pain in extremity |
| Uncommon: | Neck pain, musculoskeletal stiffness*, joint swelling*, muscle spasms, shoulder pain, musculoskeletal chest pain*, musculoskeletal pain, joint stiffness*, arthritis, muscular weakness |
| **Renal and Urinary Disorders** | |
| Uncommon: | Blood creatinine increased, pollakiuria, proteinuria |
| **General Disorders and Administration Site Conditions** | |
| Very common: | Fever |
| Common: | Flu-like symptoms, chills, fatigue*, asthenia, pain*, malaise |

| | |
|---|---|
| Uncommon: | Peripheral oedema, thirst*, acute phase reaction*, non-cardiac chest pain |

* Adverse reactions reported more frequently in the individual studies are: *Very common:* myalgia, arthralgia, fatigue, pain *Common:* lethargy, dyspnoea, dyspepsia, oesophagitis, abdominal pain, hyperhydrosis, musculoskeletal (muscle) stiffness, joint swelling, musculoskeletal chest pain, joint stiffness, anorexia, thirst, acute phase reaction *Uncommon:* uveitis.

Additional adverse reactions which were reported in the individual studies but are not included in the Table 9 (due to a lower frequency in the Osteovan group compared with that of the placebo group when the data were pooled) include: ocular hyperaemia, C-reactive protein increased, hypocalcaemia, dysgeusia, toothache, gastritis, palpitation, infusion site reaction.

**Atrial Fibrillation**

In one clinical trial, the overall incidence of atrial fibrillation was 2.5% (96 out of 3862) and 1.9% (75 out of 3852) in patients receiving Osteovan and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving Osteovan (1.3%) (51 out of 3862) compared with patients receiving placebo (0.6%) (22 out of 3852). The mechanism behind the increased incidence of atrial fibrillation is unknown. These imbalances were not observed in other trials; the overall pooled atrial fibrillation incidences were 2.6% for Osteovan and 2.1% for placebo and for serious adverse events, the pooled incidences were 1.3% for Osteovan and 0.8% for placebo.

**Local Reactions**

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

In the prevention of clinical fractures after hip fracture trial, the event rate was comparable for both Osteovan and placebo treatment groups.

**Laboratory Test Abnormalities**

In the treatment of postmenopausal osteoporosis trial, approximately 0.2% of patients had notable declines of serum calcium levels (less than 1.87 mmol/L) following Osteovan administration. No symptomatic cases of hypocalcaemia were observed.

In the prevention of clinical fractures after hip fracture trial, there were no patients who had treatment emergent serum calcium levels below 1.87 mmol/L.

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

**Class Effects**

**Renal impairment**

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal impairment manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. Renal impairment has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medications, concomitant diuretic therapy, severe dehydration), the majority of whom received a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In the treatment of postmenopausal osteoporosis trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment were comparable for both the Osteovan and placebo treatment groups over 3 years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of Osteovan-treated patients versus 0.8% of placebo-treated patients.

In the prevention of clinical fractures after hip fracture trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment were comparable for both the Osteovan and placebo treatment groups over 3 years.

In clinical trials in Paget's disease, there were no cases of renal deterioration following a single 5 mg 15-minute infusion.

**Osteonecrosis of the jaw (ONJ)**

Cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid (uncommon). 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 jaw has multiple documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g. anaemia, coagulopathies, infection, pre-existing dental disease). Although causality has not been determined, it is prudent to avoid dental surgery as recovery may be prolonged.

In the treatment of postmenopausal osteoporosis trial in 7736 patients, ONJ has been reported in one patient treated with Osteovan and one patient treated with placebo. Both cases resolved.

In the prevention of clinical fractures after hip fracture trial, there were no reports of osteonecrosis of the jaw.

**Eye disorders**

Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates. In the treatment of postmenopausal osteoporosis trial, 9 (0.2%) patients treated with Osteovan and 1 (<0.1%) patient treated with placebo developed iritis/uveitis/episcleritis. Patients who develop ocular symptoms after a zoledronic acid infusion should seek medical help.

**Post-marketing Experience**

The following adverse reactions have been reported during post-approval use of zoledronic acid. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock have been reported.

Rare cases of renal impairment including renal failure requiring dialysis or with fatal outcome, especially in patients with pre-existing renal compromise or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period have been reported.

In very rare cases, the following events have been reported: dehydration secondary to post-dose symptoms such as fever, vomiting and diarrhoea; hypotension in patients with underlying risk factors; osteonecrosis of the jaw; scleritis and orbital inflammation. In 2010, the Atypical Femoral Fractures Task Force Report identified that “Subtrochanteric and diaphyseal fractures, with or without atypical features have been estimated as 1 to 3 reports per 1,000,000 patient years of exposure to bisphosphonates.”

# DOSAGE AND ADMINISTRATION

**General**

The incidence of post-dose symptoms occurring within the first three days after administration of Osteovan can be reduced with the administration of paracetamol shortly following Osteovan administration.

Patients must be appropriately hydrated prior to administration of Osteovan. This is especially important in the elderly and for patients receiving diuretic therapy (see **PRECAUTIONS**). Adequate hydration can be achieved by the patient drinking two glasses of fluid (such as water) before and after the infusion.

The inclusion and exclusion criteria of the clinical trials should be used as a basis for patient selection (see **CLINICAL TRIALS**).

**Treatment of Postmenopausal Osteoporosis**

For the treatment of postmenopausal osteoporosis the recommended dose is a single intravenous infusion of 5 mg of Osteovan administered once a year.

Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate. In the treatment of postmenopausal osteoporosis trial, all women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day (see **CLINICAL TRIALS**).

**Prevention of Clinical Fractures After a Hip Fracture**

For the prevention of clinical fractures after a low trauma hip fracture, the recommended dose is a single intravenous infusion of 5 mg Osteovan administered once a year.

In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Osteovan infusion (see **CLINICAL TRIALS**).

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a low trauma hip fracture (see **PRECAUTIONS Calcium and Vitamin D Supplementation**).

**Treatment of Osteoporosis in Men**

For the treatment of osteoporosis in men, the recommended dose is a single intravenous infusion of 5 mg Osteovan administered once a year.

Adequate supplemental calcium and vitamin D intake is important in men with osteoporosis if dietary intake is inadequate (see **PRECAUTIONS**).

**Treatment and Prevention of Glucocorticoid-induced Osteoporosis**

For the treatment and prevention of glucocorticoid-induced osteoporosis, the recommended dose is a single intravenous infusion of 5 mg Osteovan administered once a year.

Adequate supplemental calcium and vitamin D intake is important in patients with osteoporosis if dietary intake is inadequate (see **PRECAUTIONS**).

**Treatment of Paget's Disease of Bone**

For the treatment of Paget's disease, Osteovan should be prescribed only by physicians with experience in treatment of Paget's disease of the bone The recommended dose is a single intravenous infusion of 5 mg Osteovan.

**Re-treatment of Paget's disease:** Specific re-treatment data are not available. After a single treatment with Osteovan in Paget's disease, an extended remission period is observed in responding patients. Of the 152 Osteovan -treated patients who entered the extended observation study of the pivotal studies, after a median duration of follow-up of 32 months from time of dosing, 142 Osteovan -treated patients maintained their therapeutic response (see **CLINICAL TRIALS**).

However, re-treatment with Osteovan may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, in patients who failed to achieve normalisation of serum alkaline phosphatase, or in patients with symptoms, as dictated by medical practice 12 months after the initial dose.

In patients with Paget's disease, adequate vitamin D intake is recommended in association with Osteovan administration (see **PRECAUTIONS Pre-existing Hypocalcaemia or Vitamin D Deficiency)**. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Osteovan administration (see **PRECAUTIONS**).

**Method of Administration**

Osteovan (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line, given at a constant infusion rate. The infusion time must not be less than 15 minutes (see **Instructions for Use and Handling**).

**Patients with Renal Impairment**

The use of Osteovan in patients with creatinine clearance < 35 mL/min is not recommended due to limited clinical safety data in such patients (see **CONTRAINDICATIONS**).

No dose adjustment is necessary in patients with creatinine clearance≥ 35 mL/min.

**Patients with Hepatic Impairment**

No dose adjustment is required for patients with hepatic impairment.

**Elderly Patients**

No dose adjustment is necessary (see **PRECAUTIONS**). However, because decreased renal function occurs more commonly in the elderly, special care should be taken to monitor renal function.

**Instructions for Use and Handling**

Osteovan must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate. If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

Use in one patient on one occasion only. Any unused solution should be discarded. Only clear solution free from particles and discolouration should be used.

After opening, the solution is chemically and physically stable for at least 24 hours at 2°C to 8°C.

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

**Incompatibilities**

Osteovan solution for infusion must not be allowed to come into contact with any calcium- or other divalent cation-containing solutions.

# OVERDOSAGE

Clinical experience with acute overdosage is limited. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an infusion of calcium gluconate.

Contact the Poisons Information Centre on 13 11 26 for advice on management.

## PRESENTATION AND STORAGE CONDITIONS

Osteovan 5 mg/100 mL solution for infusion is sterile, clear and colourless. It is supplied in a 100 mL transparent plastic vial closed with a fluoro-polymer-coated bromobutyl rubber stopper and an aluminium/polypropylene cap with a flip component.

Osteovan is supplied as packs containing one vial and multipacks comprising three or six packs, each containing one vial. Not all pack sizes may be marketed.

**Storage:** The unopened vial does not require any special storage conditions. Osteovan must be kept out of the reach and sight of children.

## POISON SCHEDULE OF THE MEDICINE

Prescription Medicine (Schedule 4).

## NAME AND ADDRESS OF SPONSOR

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Reference/Publication #