AUSTRALIAN PRODUCT INFORMATION - OSTEOVAN® (zoledronic acid) Solution for Injection

1. NAME OF THE MEDICINE

Zoledronic acid

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Contains sodium and sulfites.

For the full list of excipients, section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for intravenous infusion

Osteovan 5 mg/100 mL solution for infusion is sterile, clear and colourless.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC 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.

4.2 DOSE AND METHOD OF 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 section 4.4 Special warnings and precautions for use). 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 section 5.1 Pharmacodynamic properties, 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 section 5.1 Pharmacodynamic properties, 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 section 5.1 Pharmacodynamic properties, Clinical trials).

Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a low trauma hip fracture (see section 4.4 Special warnings and precautions for use 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 section 4.4 Special warnings and precautions for use).

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 section 4.4 Special warnings and precautions for use).

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: After the initial treatment with Osteovan in Paget's disease, an extended remission period of 7.7 years as a mean was observed in responding patients. As Paget's disease of bone is a lifelong disease, re-treatment is likely to be needed. Re-treatment of Paget's disease of bone consists of an additional intravenous infusion of 5 mg Osteovan after an interval of one year or longer from initial treatment. Periodic assessment of the patient's serum alkaline phosphatase levels, e.g., every 6 to 12 months and clinical responses to treatment should guide the decision of when re-treatment should occur on an individual basis. In the absence of worsening of clinical symptoms (e.g. bone pain or compression symptoms) and/or bone scan consistent with relapse of Paget's disease of bone, a second intravenous infusion of Osteovan should not be administered earlier than 12 months following the initial treatment. No experience of retreatment more than once is available (see section 5.1 Pharmacodynamic properties, Clinical trials).

In patients with Paget's disease, adequate vitamin D intake is recommended in association with Osteovan administration (see section 4.4 Special warnings and precautions for use 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 section 4.4 Special warnings and precautions for use).

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 section 4.2 Dose and method of administration, 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 section 4.3 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 section 4.4 Special warnings and precautions for use). 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.

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates; hypocalcaemia; renal impairment with creatinine clearance < 35 mL/min (see section 4.4 Special warnings and precautions for use); current or recent uveitis, or a history of bisphosphonate-associated uveitis; pregnancy and lactation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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 section 4.8 Adverse effects (Undesirable effects) and section 4.2 Dose and method of 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 section 4.3 Contraindications). Physicians should consider clinical monitoring after treatment in patients with pre-existing disturbances of mineral metabolism.

Use in Renal Impairment

The use of Osteovan in patients with severe renal impairment (creatinine clearance <35 mL/min) is contraindicated due to an increased risk of renal failure in this population.

Renal impairment has been observed following the administration of Osteovan (see section 4.8 Adverse effects (Undesirable effects), Post-marketing Experience), especially in patients with pre-existing renal impairment or other risk factors including advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy (see section 4.5 Interactions with other medicines and other forms of interactions), 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:

- Creatinine clearance should be calculated (e.g. Cockroft-Gault formula) before each Osteovan dose (see section 4.3 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.

- Osteovan should be used with caution when concomitantly used with other medicinal products that could impact renal function (see section 4.5 Interactions with other medicines and other forms of interactions).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Osteovan (see section 4.4 Special warnings and precautions for use Hydration).
- A single dose of Osteovan should not exceed 5 mg and the duration of infusion should not be less than 15 minutes (see section 4.2 Dose and method of 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 section 4.8 Adverse effects (Undesirable effects)). Adequate vitamin D intake is recommended in association with Osteovan administration (see section 4.4 Special warnings and precautions for use 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, anti-angiogenic drugs, corticosteroids, poor oral hygiene). During treatment with zoledronic acid, it is prudent to maintain good oral hygiene, undergo routine dental check-ups, and immediately report any oral symptoms. 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 section 5.1 Pharmacodynamic properties, Clinical trials)

Osteonecrosis of other bones

Cases of osteonecrosis of other bones (including femur, hip, knee and humerus) have also been reported.

Osteonecrosis of the external auditory canal

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

Atypical Fractures of the Femur

Atypical subtrochanteric and diaphyseal femoral fractures have been reported in association with bisphosphonate therapy, primarily in patients receiving long-term treatment for osteoporosis. These transverse or short oblique fractures can occur anywhere along the femur from just below the lesser trochanter to just above the supracondylar flare. These fractures occur after minimal or no trauma and some patients experience thigh or groin pain weeks to months before presenting with a completed femoral fracture. Fractures are often bilateral; therefore the contralateral femur should be examined in bisphosphonate-treated patients who have sustained a femoral shaft fracture. Poor healing of these fractures has also been reported. Discontinuation of bisphosphonate therapy in patients suspected to have an atypical femur fracture should be considered pending evaluation of the patient, based on an individual benefit risk assessment. Causality has not been established as these fractures also occur in osteoporotic patients who have not been treated with bisphosphonates.

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

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.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 section 5.2 Pharmacokinetic properties). 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.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Fertility was decreased in rats dosed subcutaneously (SC) with zoledronic acid 0.01 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).

Women of child-bearing potential

Women of child-bearing potential should be advised to avoid becoming pregnant while receiving Osteovan. There is a theoretical risk of fetal harm (e.g. skeletal and other abnormalities) if a woman becomes pregnant while receiving bisphosphonate therapy. The impact of variables such as time between cessation of bisphosphonate therapy to conception, the particular bisphosphonate used, and the route of administration on this risk have not been established (See section 4.6 Fertility, pregnancy and lactation, Use in Pregnancy, section 4.3 Contraindications and Carcinogenicity).

Use in Pregnancy

Category B3. Osteovan is contraindicated during pregnancy (see section 4.3 Contraindications). 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

Osteovan is contraindicated in breast-feeding women (see section 4.3 Contraindications). 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.

4.7 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 of ACLASTA include dizziness which could affect the ability to drive or use machines (see Section 4.8 ADVERSE EFFECT (UNDESIRABLE EFFECTS))

4.8 ADVERSE EFFECTS (UNDESIRABLE 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 section 5.1 Pharmacodynamic properties, 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 61.

Table 1 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	
System Organ Class	5 mg IV Osteovan once per year % (N=3862)	Placebo once per year % (N=3852)	5 mg IV Osteovan 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 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 ≥ 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 2.

Table 2 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 3.

Table 3 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 4.

Table 4 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 5 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 5 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 and connective tissue 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:	Pyrexia
Common:	Influenza-like illness, chills, fatigue*, asthenia, pain*, malaise
Uncommon:	Peripheral oedema, thirst*, acute phase reaction*, non-cardiac chest pain

* Adverse reactions reported most 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 10 (due to a lower frequency in the Osteovan group compared with that of the placebo group when the data were pooled) include:

Cardiac disorders: Atrial fibrillation*, palpitations

Eye disorders: Ocular hyperemia

Gastrointestinal disorders: Gastritis, toothache

General disorders and administration site conditions: Infusion site reaction

Investigations: C-reactive protein increased

Metabolism and nutrition disorders: Hypocalcemia

Nervous system disorders: Dysgeusia

*see below 'atrial fibrillation' subsection in 'description of selected adverse reactions' section

Description of selected adverse reactions

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 impairment or additional risk factors (e.g. advanced age, oncology patients with chemotherapy, concomitant nephrotoxic medications, concomitant diuretic therapy, severe dehydration with the majority of them receiving a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In the treatment of postmenopausal osteoporosis core 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.

Hypocalcamia

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 hypocalcemia 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 hypocalcemia was observed in approximately 1% of patients, all of which resolved.

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.

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, anti-angiogenic drugs, 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 core trial in 7736 intention-to-treated (ITT) 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.

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.

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 drug reactions have been derived from post-marketing experience with Osteovan via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorized as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Eye disorders: scleritis, parophthalmia

Immune system disorders: hypersensitivity reactions including anaphylactic reaction, anaphylactic shock, angioedema, bronchospasm, urticaria

Metabolism and nutrition disorders: dehydration secondary to post-dose symptoms such as pyrexia, vomiting and diarrhea; hypotension in patients with underlying risk factors; hypophosphataemia.

Musculoskeletal and connective tissue disorders: osteonecrosis of jaw (see section 4.4 Special warnings and precautions for use)

Renal and urinary disorders: renal failure requiring dialysis or with fatal outcome*, renal impairment (see section 4.4 Special warnings and precautions for use)

*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.

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."

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

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.

For information on the management of overdose, contact the Poison Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

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.

Mechanism of action

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.

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 section 5.1 Pharmacodynamic properties, 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.

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 6).

Table 6 Summary of vertebral fracture efficacy at 12 months, 24 months and 36 months

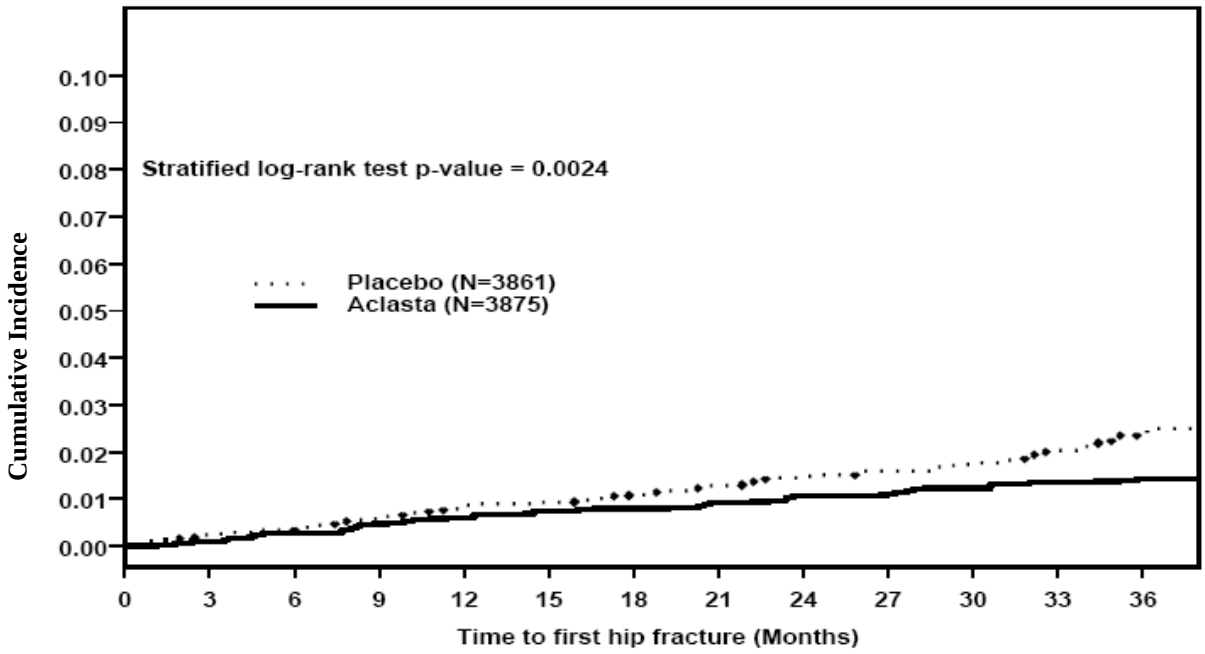
Outcome	Osteovan Event rate (%)	Placebo Event rate (%)	Absolute reduction in fracture incidence (%) (95% CI)	Relative reduction in fracture incidence (%) (95% CI)
At least one new vertebral fracture (0-1 year)	1.5	3.7	2.2 (1.4, 3.1)	60 (43, 72)**
At least one new vertebral fracture (0-2 year)	2.2	7.7	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 7.

Table 7 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.

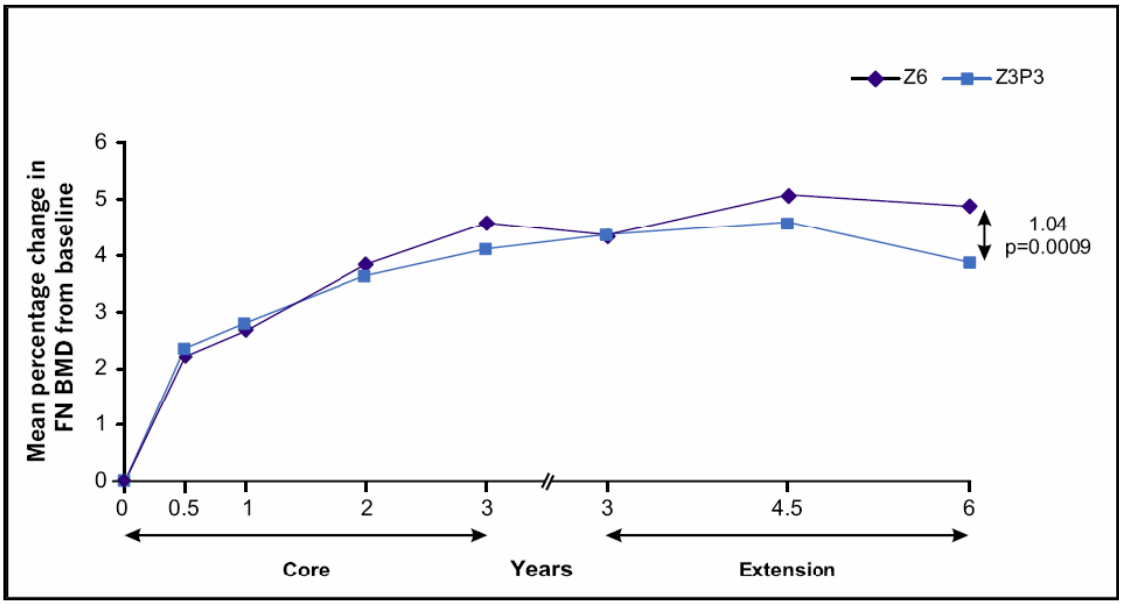
The extension study demonstrated that the therapeutic benefit of continued annual zoledronic acid therapy on maintaining or increasing BMD in women with postmenopausal osteoporosis is sustained long-term, while the discontinuation of therapy results in a gradual loss of bone mass.

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 8).

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 8.

Table 8 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Osteovan (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, 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 9.

Table 9 Effects of Osteovan and risedronate on bone mineral density of the lumbar spine, total hip and femoral neck (modified ITT population)

		Osteovan	Risedronate

Population	Location	n LS Mean* (SE)	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 therapeutic response by subgroup is presented in Table 10.

Table 10 Proportion of patients who achieved therapeutic response at 6 months by disease factors

Subgroup	Zoledronic acid n/N (Proportion)	Risedronate n/N (Proportion)
Baseline SAP		
< 3xULN	**87/90 (0.97)**	**74/99 (0.75)**
⩾ 3xULN	**82/86 (0.95)**	**53/72 (0.74)**
Last Paget's therapy		
Oral bisphos.*	**53/55 (0.96)**	**33/60 (0.55)**
IV bisphos.	**22/25 (0.88)**	**21/26 (0.81)**
Clodronate	**6/6 (1.00)**	**2/2 (1.00)**
Others	**8/8 (1.00)**	**6/7 (0.86)**
No previous therapy	**80/82 (0.98)**	**65/76 (0.86)**

SAP = serum alkaline phosphatase. ULN = upper limit of normal. A therapeutic response is defined as normalisation of SAP or a reduction of ≥75% from baseline in SAP excess. N = number of patients with baseline and at least one post-baseline SAP measurements. n = number of patients with therapeutic response at visit.

*Including previous treatment with risedronate

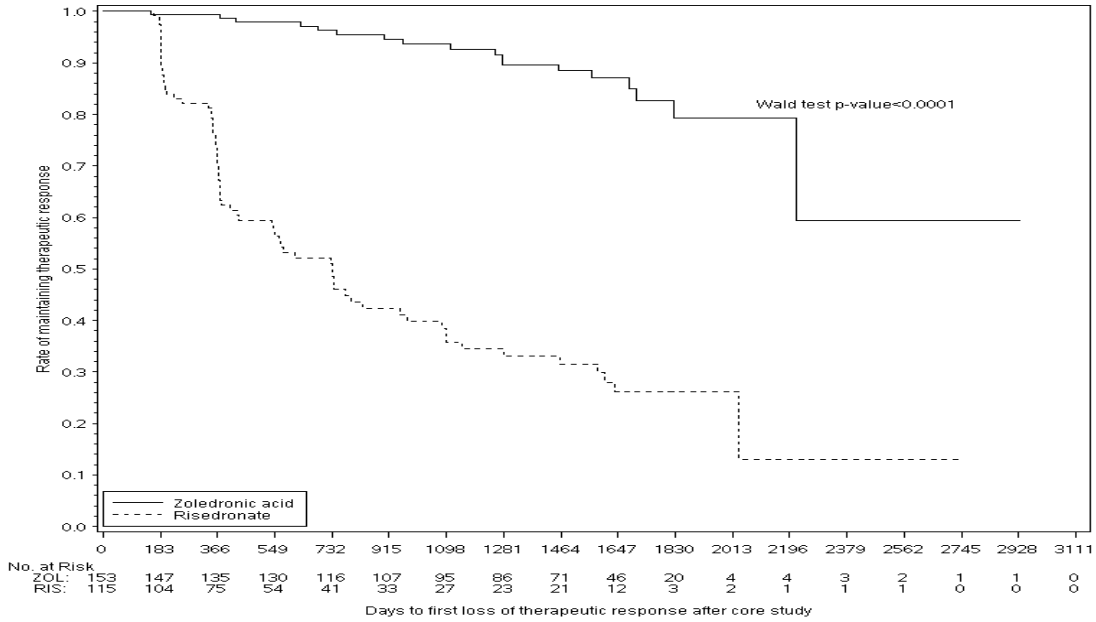
The adverse reaction profile reflects a very common incidence of acute phase reactions in the zoledronic acid group (influenza-like illness, pyrexia, myalgia, arthralgia and bone pain).

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 3.8 years from time of dosing, the proportion of patients ending the Extended Observation Period due to the need for retreatment (clinical judgment) was higher for risedronate (48 patients, or 41.7%) compared with zoledronic acid (11 patients, or 7.2%). The mean time of ending the Extended Observation Period due to the need for Paget's retreatment from the initial dose was longer for zoledronic acid (7.7 years) than for risedronate (5.1 years). 135 Osteovan-treated patients maintained their therapeutic response compared to 44 risedronate-treated patients.

The cumulative rate of maintaining therapeutic response in the extended follow-up period is displayed in Figure 3.

Figure 3Cumulative rate of maintaining therapeutic response over time



Time to first loss of therapeutic response: the occurrence of an SAP level that no longer meets the criteria of a therapeutic response (less than 75% reduction in SAP excess and/or SAP above the upper limit of the normal range).

Six patients who achieved therapeutic response 6 months after treatment with Osteovan and later experienced disease relapse during the extended follow-up period were retreated with Osteovan after a mean time of 6.5 years from initial treatment to re-treatment. Five of the 6 patients had Serum Alkaline Phosphatase within the normal range at Month 6.

5.2 PHARMACOKINETIC PROPERTIES

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 t½ 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.

Excretion

Intravenously administered zoledronic acid is eliminated by a triphasic process: rapid biphasic disappearance from the systemic circulation, with half-lives of $t½_{alpha}$ 0.24 and $t½_{beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t½_{gamma}$ 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 contraindicated due to an increased risk of renal failure in this population (see section 4.3 Contraindications). No dose adjustment is necessary in patients with creatinine clearance ≥ 35 mL/min.

5.3 PRECLINICAL SAFETY DATA

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.

Long term studies

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.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Mannitol, sodium citrate dihydrate, water for injections.

6.2 INCOMPATIBILITIES

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

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30ºC. Osteovan must be kept out of the reach and sight of children. After opening, the solution is chemically and pysically stable for at least 24 hours.

6.5 NATURE AND CONTENTS OF CONTAINER

Osteovan 5 mg/100 mL solution for infusion 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.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

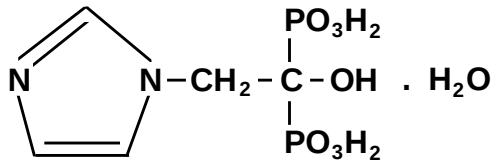
6.7 PHYSIOCHEMICAL PROPERTIES

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.

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.

Chemical structure:

The chemical structure of zoledronic acid monohydrate is:



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)

118072-93-8 (zoledronic acid anhydrous)

7. MEDICINE SCHEDULE (POISON STANDARD)

Prescription Medicine (Schedule 4).

8. SPONSOR

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Macquarie Park NSW 2113

9. DATE OF FIRST APPROVAL

23 June 2008

10. DATE OF REVISION

7 November 2022

® = Registered Trademark

Summary table of changes

Section changed	Summary of new information
4.6	Revise: "Fertility was decreased in rats dosed subcutaneously (SC) with zoledronic acid 0.1 mg/kg/day..." to "Fertility was decreased in rats dosed subcutaneously (SC) with zoledronic acid 0.01 mg/kg/day..."

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