NEW ZEALAND DATA SHEET

1 PRODUCT NAME

ACLASTA® zoledronic acid 5 mg/100 mL solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Single-use sterile solution containing 5 mg/100 mL zoledronic acid (anhydrous), corresponding to 5.330 mg/100 mL zoledronic acid monohydrate.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for infusion.

The solution 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 and to increase bone mineral density.
- Treatment of osteoporosis in men.
- Treatment of Paget's disease of bone.
- Treatment and prevention of glucocorticoid-induced osteoporosis.
- Prevention of clinical fractures in patients after hip fracture.
- Prevention of postmenopausal osteoporosis.

4.2 Dose and method of administration

Dose

The incidence of post-dose symptoms occurring within the first three days after administration of Aclasta® can be reduced with the administration of paracetamol or ibuprofen 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 Section 4.4 Special warnings and precautions for use).

Treatment of Postmenopausal Osteoporosis

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

Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate (see Section 4.4 Special warnings and precautions for use).

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, it is recommended to give the first Aclasta

infusion two or more weeks after hip fracture repair.

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 Section 5.1 Pharmacodynamic properties).

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).

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 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 Aclasta 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).

Prevention of Postmenopausal Osteoporosis

For the prevention of postmenopausal osteoporosis, the recommended regimen is a single intravenous infusion of 5 mg Aclasta. An annual assessment of the patient's risk of fracture and clinical response to treatment should guide the decision of when re-treatment should occur.

For the prevention of postmenopausal osteoporosis it is important that patients be adequately supplemented with calcium and vitamin D 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, 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: After the initial treatment with Aclasta 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 Aclasta 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 Aclasta should not be administered earlier than 12 months following the initial treatment (see Section 5.2 Pharmacodynamic properties - Clinical efficacy and safety).

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

Special Populations

Elderly (≥65 years):

No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.

Renal impairment:

The use of Aclasta in patients with creatinine clearance <35 mL/min is contraindicated (see Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use). No dose adjustment is necessary in patients with creatinine clearance ≥35 mL/min.

Hepatic impairment:

No dose adjustment is required (see Section 5.2 Pharmacokinetic properties).

Paediatric population:

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

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.

For information on the instructions for use and handling of Aclasta, see Section 6 Pharmaceutical particulars.

4.3 Contraindications

- Severe renal impairment with creatinine clearance <35 mL/min (see Section 4.4 Special warnings and precautions for use).
- Hypocalcaemia (see Section 4.4 Special warnings and precautions for use).
- Pregnancy and breast feeding women (see Section 4.6 Fertility, pregnancy and lactation).
- Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates (see Section 6.1 List of excipients).

4.4 Special warnings and precautions for use

General

The dose of 5 mg zoledronic acid must be administered 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.

Patients must be appropriately hydrated prior to administration of Aclasta. This is

especially important in the elderly and for patients receiving diuretic therapy.

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta (see Section 4.3 Contraindications). Other disturbances of mineral metabolism must also be effectively treated (e.g. diminished parathyroid reserve; thyroid surgery, parathyroid surgery, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.

Renal Impairment

The use of Aclasta 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 Aclasta (see Section 4.8 Undesirable effects from post marketing spontaneous reports), 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 interaction), or dehydration occurring after Aclasta administration. Renal impairment has been observed in patients after a single administration. Renal failure requiring dialysis or with a fatal outcome has rarely occurred in patients with underlying renal impairment or with any of the other 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 Aclasta dose. 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.
- Aclasta 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 interaction).
- Patients, especially elderly patients and those receiving diuretic therapy, should be appropriately hydrated prior to administration of Aclasta.
- A single dose of Aclasta 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 and prevention of osteoporosis:

Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis or treated to prevent postmenopausal 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 Section 4.8 Undesirable effects). Adequate vitamin D intake is recommended in association with Aclasta administration. 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

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. Many had signs of local infection including osteomyelitis. A dental examination with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates in patients with concomitant risk factors (e.g. cancer, chemotherapy, 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 judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Osteonecrosis of other bones

Cases of osteonecrosis of other bones (including femur, hip, knee and humerus) have also been reported; however, causality has not been determined in the population treated with Aclasta.

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 Aclasta, 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.

4.5 Interaction with other medicines and other forms of interaction

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. 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. Zoledronic acid is not highly bound to plasma proteins (approximately 43 to 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 medicinal products 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

Women of child-bearing potential

Women of child-bearing potential should be advised to avoid becoming pregnant while receiving Aclasta. 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, Section 4.3 Contraindications and Section 5.3 Preclinical safety data).

Pregnancy – Category B3

Aclasta is contraindicated during pregnancy (see Section 4.3 Contraindications). There are no data on the use of zoledronic acid in pregnant women. Studies in rats have shown reproductive toxicological effects (see Section 5.3 Preclinical safety data). The potential risk in humans is unknown.

Breastfeeding

Aclasta is contraindicated in breast-feeding women (see Section 4.3 Contraindications).

Fertility

There are no data available in humans.

4.7 Effects on ability to drive and use machines

Adverse reactions, such as dizziness, may affect the ability to drive or use machine.

4.8 Undesirable effects

Summary of the Safety Profile

The presented adverse reactions in this section have been derived from different studies in the clinical program. Aclasta was studied in postmenopausal osteoporosis in the pivotal fracture trial, a randomised, double-blind, placebo-controlled, multinational study including 7,736 women and in Paget's disease in two double blind, randomised safety and efficacy trials involving 357 patients; the prevention of clinical fractures in patients who suffered from a recent low-trauma hip fracture was demonstrated in a randomised, double-blind, placebo-controlled, multinational endpoint study of 2,127 men and women. Aclasta was studied in the treatment and prevention of glucocorticoid-induced osteoporosis in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women. Aclasta was studied in men with osteoporosis or significant osteoporosis secondary to hypogonadism in a randomised, multicentre, double-blind, active-controlled study of 302 men. Finally, Aclasta was studied in the prevention of bone loss in postmenopausal women with osteopenia in a 2-year randomised, multi-centre, double-blind, placebo-controlled study of 581 postmenopausal women.

Treatment of postmenopausal osteoporosis, osteoporosis in men, prevention of clinical fractures after hip fracture, treatment and prevention of glucocorticoid-induced osteoporosis and Paget's disease of the bone:

In the studies to support 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, there were no significant differences in the overall incidence of serious adverse events compared to placebo or comparator and most adverse events were mild to moderate. Aclasta was administered once a year in all aforementioned studies.

Consistent with the intravenous administration of bisphosphonates, Aclasta has been most commonly associated with the following post-dose symptoms (frequencies derived from the study in treatment of postmenopausal osteoporosis: 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 or ibuprofen shortly following Aclasta administration as needed.

Tabulated summary of adverse drug reactions from clinical trials:

Adverse drug reactions from clinical trials (Table 1) are listed according to system organ classes in MedDRA. These are suspected adverse reactions to Aclasta (investigator assessment) 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. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency using the following convention (CIOMS III) is also provided for each adverse drug reaction: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000), very rare (<1/10,000), including isolated

reports.

Table 1 Suspected adverse reactions to Aclasta (investigator assessment) in clinical trials

Infections and infestations	
Uncommon:	Influenza, nasopharyngitis
Blood and lymphatic system disorders	
Uncommon:	Anaemia
Metabolism and nutrition disorders	
Uncommon:	Anorexia*, decreased appetite
Psychatric 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 1 (due to a lower frequency in the Aclasta group compared with that of the placebo group when the data was 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.

Prevention of postmenopausal osteoporosis:

The overall safety and tolerability profile of Aclasta in the prevention of osteoporosis was comparable to the adverse reaction profile reported in the Aclasta postmenopausal osteoporosis treatment trial, however there was a higher incidence of post-dose symptoms in the Aclasta treated osteopenic patients that occurred within 3 days after infusion: pain, fever, chills, myalgia, nausea, headache, fatigue, dizziness, and arthralgia. The majority of these symptoms were mild to moderate and resolved within 3 days of the reaction onset. The incidence of these symptoms decreased with a subsequent dose of Aclasta. Suspected adverse reactions to Aclasta (investigator assessment) in prevention of postmenopausal osteoporosis which occurred more than once and which are either not included in Table 1 or reported with a higher frequency in the prevention of postmenopausal osteoporosis trial are summarised in Table 2 using

the following convention: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100).

Table 2 Suspected adverse reactions to Aclasta (investigator assessment) in prevention of postmenopausal osteoporosis. The adverse reactions listed are either in addition to or reported with a higher frequency than those in Table 1

Metabolism and nutrition disorders		
	Common:	Anorexia
Psychiatric disorders		
	Uncommon:	Anxiety
Nervous system disorders		
	Very Common:	Headache
	Common:	Tremor, lethargy
	Uncommon:	Hypoaesthesia, dysgeusia
Eye disorders		
	Common:	Conjunctivitis, eye pain, iritis
	Uncommon:	Vision blurred
Gastrointestinal disorders		
	Very Common:	Nausea
	Common:	Abdominal pain, abdominal pain upper, constipation
Skin and subcutaneous tissue disorders		
	Common:	Night sweats
Musculoskeletal and connective tissue disorders		
	Very common:	Myalgia
	Common:	Musculoskeletal pain, muscle spasms, musculoskeletal chest pain, pain in jaw, neck pain
	Uncommon:	Flank pain
General disorders and administration site conditions		
	Very common:	Pain, chills
	Common:	Oedema peripheral, infusion related reaction, non cardiac chest pain

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 medicinal products, concomitant diuretic therapy, severe dehydration), with the majority of them receiving a 4 mg dose every 3 to 4 weeks, but it has also been observed in patients after a single administration.

In the HORIZON-PFT core trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment was 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 studies to support the indications prevention of clinical fractures after hip fracture in men and women, treatment of osteoporosis in men, treatment and prevention of glucocorticoid-induced osteoporosis, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairment was comparable for both the Aclasta and placebo or comparator treatment groups.

In the prevention of postmenopausal osteoporosis trial, the change in creatinine clearance (measured annually prior to dosing and at one month after the first dose) and the incidence of renal failure and impairment were comparable in the Aclasta and placebo groups.

Hypocalcemia:

In the HORIZON-PFT core 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 hypocalcemia were observed.

In the HORIZON-RFT, treatment of male osteoporosis and treatment and prevention of glucocorticoid-induced osteoporosis trials, there were no patients who had treatment emergent serum calcium levels below 1.87 mmol/L.

In the prevention of postmenopausal osteoporosis trial there was one patient who had treatment emergent serum calcium levels below 1.87 mmol/L.

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

Local reactions:

In the HORIZON-PFT 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 HORIZON-RFT trial, the event rate was comparable for both the Aclasta and placebo treatment groups.

In the treatment of male osteoporosis trial, the event rate was 2.6% in the zoledronic

acid treatment group and 1.4% in the alendronate treatment group.

In the treatment and prevention of glucocorticoid-induced osteoporosis trial, no local reactions were reported.

In the prevention of postmenopausal osteoporosis trial, the event rate was 1.1% in Aclasta treated patients compared to 2.0% in placebo treated patients.

Osteonecrosis of the jaw:

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 (ONJ) has multiple well 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 (see Section 4.4 Special warnings and precautions for use).

In the HORIZON-PFT core trial in 7,736 intention-to-treated (ITT) patients, ONJ has been reported in one patient treated with Aclasta and one patient treated with placebo. Both cases resolved. In the HORIZON-RFT, treatment of male osteoporosis, treatment and prevention of glucocorticoid-induced osteoporosis and prevention of postmenopausal osteoporosis trials there were no cases of osteonecrosis of the jaw.

Atrial fibrillation

In one 3 year trial in postmenopausal women with osteoporosis (Horizon PFT), the overall incidence of all atrial fibrillation adverse events was 2.5% (96 out of 3,862) in the Aclasta group vs. 1.9% (75 out of 3,852) in the placebo group. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) in patients receiving Aclasta compared with 0.6% (22 out of 3,852) in patients receiving placebo. The mechanism behind the increased incidence of atrial fibrillation is unknown. The imbalance observed in this trial has not been observed in other clinical trials with zoledronic acid.

Adverse Drug Reactions from Post-marketing Spontaneous Reports

The following adverse drug reactions have been derived from post-marketing experience with Aclasta 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, urticarial.

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.

Reporting of suspected adverse reactions - Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs

Clinical experience with acute overdosage is limited. Patients who have received doses higher than those recommended should be carefully monitored.

Treatment

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 advice on the management of the overdose please contact the National Poison Centre 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonate, ATC code: M05 B-A08.

Mechanism of action

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 selective action of bisphosphonates on bone is based on their high affinity for mineralised bone. Intravenously administered zoledronic acid is rapidly distributed to bone and, like other bisphosphonates, localises preferentially at sites of high bone turnover. The main molecular target of zoledronic acid in the osteoclast is the enzyme farnesyl pyrophosphate synthase, but this does not exclude other mechanisms. The relatively long duration of action of zoledronic acid is attributable to its high binding affinity for the active site of farnesyl pyrophosphate (FPP) synthase and its strong binding affinity to bone mineral.

Pharmacodynamic effects

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 osteoclastic 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 clinically relevant doses of zoledronic acid. There was no evidence of a mineralising defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Clinical efficacy and safety

A. Clinical Efficacy for the Treatment of Postmenopausal Osteoporosis

The efficacy and safety of Aclasta was demonstrated in HORIZON-PFT, a randomised, double-blind, placebo-controlled, multinational study of 7,736 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). 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. 7,736 women were evaluated for the incidence of hip and all clinical fractures. Of these, 5,661 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 1,000 to 1,500 mg of elemental calcium plus 400 to 1,200 IU of vitamin D supplements per day.

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 timepoint (see Table 3).

Table 3 Summary of vertebral fracture efficacy at 12 months, 24 months, and 36 months

Outcome	Aclasta (%)	Placebo (%)	Absolute reduction in fracture incidence % (CI)	Relative reduction in fracture incidence % (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	12.8	8.9 (7.3, 10.5)	70 (62, 76)**
*** p < 0.0001*				

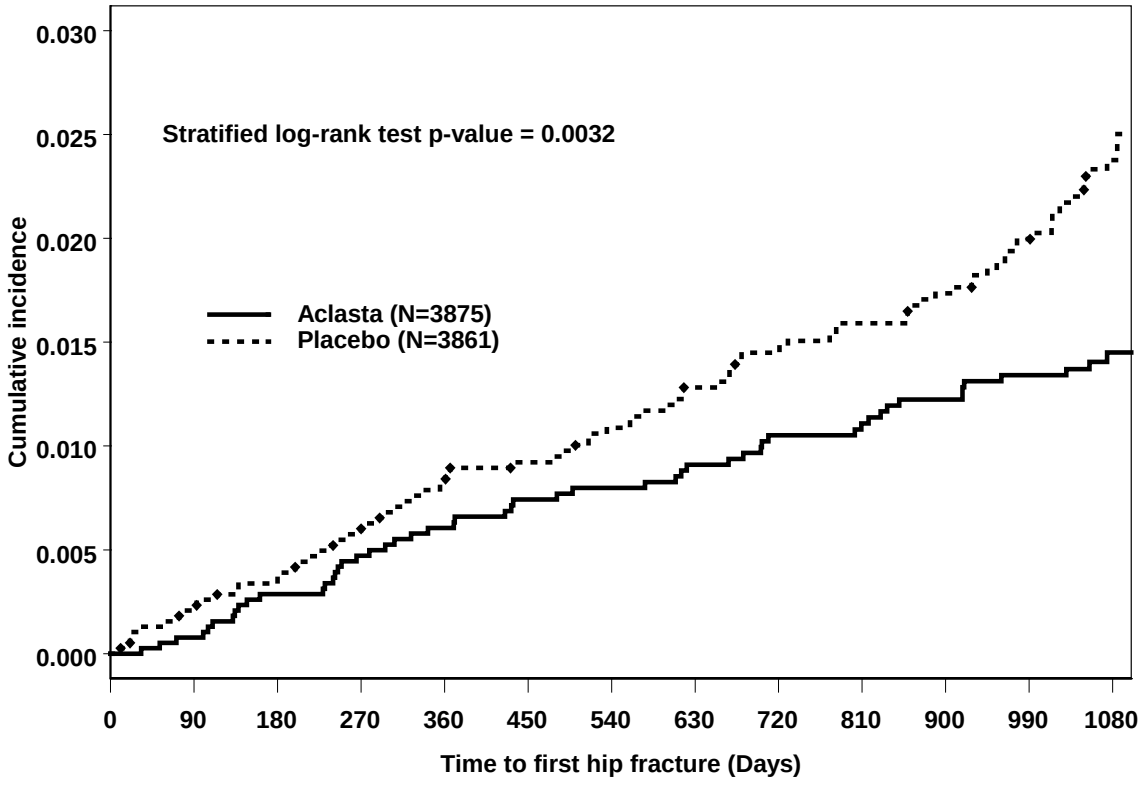
Aclasta significantly decreased the risk of one or more new/worsening vertebral fractures at 1 year (58%), 2 years (68%) and 3 years (67%) (all p<0.0001). Aclasta significantly decreased the risk of at least one new moderate or severe vertebral fracture at 1 year (60%), 2 years (71%) and 3 years (70%)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

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 40% reduction in the risk of hip fractures over 3 years. The hip fracture event rate was 1.45% for Aclasta-treated patients compared to 2.50% for placebo-treated patients. The effect over time is displayed in Figure 1.

Figure 1 Cumulative incidence of hip fracture over 3 years



In women who did not take concomitant osteoporosis therapy Aclasta demonstrated a 40% reduction (p=0.0089) in the risk of hip fractures over this time period. In women who were allowed to take concomitant osteoporosis therapy Aclasta demonstrated a 42% reduction (p=0.1707) in the risk of hip fractures over this time period.

The reductions in hip fractures over three years were greater than placebo regardless of age, geographical region, race, baseline body mass index, number of baseline vertebral fractures, or femoral neck BMD T-score.

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 4.

Table 4 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 event rate (%)	Relative risk reduction in fracture incidence (%)
Any clinical fracture (1)	8.4	12.9	4.5	33**
Clinical vertebral fracture (2)	0.6	2.6	2.0	75**
Non-vertebral fracture (1)	7.9	10.7	2. 8	25*

*- *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 timepoints (6, 12, 24, and 36 months). Treatment with Aclasta resulted in a 6.9% increase in BMD at the lumbar spine, 6.0% at the total hip, and 5.0% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone histology:

Dynamic bone histomorphometry in 36 postmenopausal patients with osteoporosis treated with 3 annual doses of Aclasta showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. Microcomputed tomography analysis demonstrated preservation of trabecular bone architecture in patients treated with Aclasta 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 1,246 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. 6.7 mm, respectively ($p<0.0001$).

Days of disability:

Aclasta significantly reduced both the days of limited activity and the days of bed rest due to back pain and due to fractures compared to placebo (all $p<0.01$).

B. 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 was demonstrated in **HORIZON-RFT**, a randomised, double-blind, placebo-controlled, multinational endpoint study of 2127 men and women aged 50 to 95 years (mean age of 74.5). The incidence of clinical fractures, including vertebral, non-vertebral, and hip fractures, was evaluated in 2,127 men and women with a recent (within 90 days) low-trauma hip fracture who 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 1,000 to 1,500 mg of elemental calcium plus 800 to 1,200 IU of vitamin D supplementation per day. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on all clinical fractures:

In the HORIZON-RFT trial, treatment with Aclasta significantly reduced the incidence of any clinical fracture by 35%. 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.

All cause mortality was 10% (101 patients) in the Aclasta-treated group compared to 13% (141 patients) in the placebo group. This corresponds to a 28% reduction in the risk of all cause mortality ($p=0.01$).

Table 5 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Aclasta	Placebo (N=1063)	Absolute reduction in	Relative risk reduction in

	(N=1064) event rate (%)	event rate (%)	fracture event rate (%)	fracture incidence (%)
Any clinical fracture (1)	8.6	13.9	5.3	35**
Clinical vertebral fracture (2)	1.7	3.8	2.1	46*
Non-vertebral fracture (1)	7.6	10.7	3.1	27*
Hip fracture	2.0	3.5	1.5	30

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

Effect on bone mineral density (BMD):

In the HORIZON-RFT trial, Aclasta treatment significantly increased BMD relative to placebo at the hip and femoral neck at all timepoints (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.

C. Treatment of Male Osteoporosis

The efficacy and safety of Aclasta in men with osteoporosis or significant osteoporosis secondary to hypogonadism were assessed in a randomised, multicentre, double-blind, active-controlled study of 302 men aged 25 to 86 years (mean age of 64 years). 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 1,000 mg elemental calcium plus 800 to 1,000 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.

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.

D. 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 > 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 1,000 mg elemental calcium plus 400 to 1,000 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.

Effect on bone mineral density (BMD):

The increases in BMD were significantly greater in the Aclasta treated group at all sites, which included the lumbar spine, femoral neck, total hip, trochanter, and distal radius at 12 months compared to risedronate (all p <0.03). A summary of the key results appear in Table 6.

Table 6 Effects of Aclasta and risedronate on bone mineral density of the lumbar spine, total hip and femoral neck (modified ITT population)

		Aclasta		Risedronate		LS Mean difference
Population	**Location**	**n**	**LS Mean (SE)**	**n**	**LS Mean (SE)**	**(95% CI)**
Treatment	Lumbar spine	249	4.06 (0.28)	245	2.71 (0.28)	1.36 (0.67, 2.05)**
	Total hip	247	1.65 (0.21)	239	0.45 (0.20)	1.21 (0.71, 1.79)**
	Femoral neck	247	1.45 (0.31)	239	0.39 (0.30)	1.06 (0.32, 1.79)*
Prevention	Lumbar spine	129	2.60 (0.45)	136	0.64 (0.46)	1.96 (1.04, 2.88)**
	Total hip	126	1.54 (0.36)	135	0.03 (0.36)	1.51 (0.78, 2.23)**
	Femoral neck	126	1.30 (0.45)	135	-0.03 (0.46)	1.33 (0.41, 2.25)*

** p < 0.01, ** p < 0.001*

Bone histology:

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, quantitative assessments showed bone of normal architecture and quality without mineralization defects.

E. Prevention of Postmenopausal Osteoporosis

The efficacy and safety of Aclasta in the prevention of osteoporosis in postmenopausal women was assessed in a 2-year randomised, multi-centre, double-blind, placebo-controlled study of 581 postmenopausal women aged ≥45 years, who were stratified by years since menopause: Stratum I women <5 years from menopause (n = 224); Stratum II women ≥5 years from menopause (n= 357). Patients within Stratum I and II were randomised to one of three treatment groups: Aclasta was given annually: at randomisation and Month 12 (n= 77) in Stratum I and (n=121) in Stratum II. Aclasta given at randomisation and placebo at Month 12 (n=70) in Stratum I and (n=111) in Stratum II. Placebo was given at randomisation and Month 12 (n=202). Aclasta was administered as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1,200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline.

Effect on bone mineral density:

Aclasta significantly increased lumbar spine BMD relative to placebo at Month 24. Treatment with Aclasta given annually resulted in 6.9% increase in BMD in Stratum I patients and 6.2% in Stratum II patients (both $p<0.0001$). Also, Aclasta given at randomisation resulted in 6.3% increase in BMD in Stratum I patients and 5.4% in Stratum II patients (both $p<0.0001$).

Aclasta administered annually and as a single dose significantly increased total hip BMD relative to placebo at Month 24 across both strata (all $p <0.0001$). Treatment with Aclasta given annually resulted in 4.8% increase in BMD in Stratum I patients and 4.1% in Stratum II patients relative to placebo. Treatment with a single dose of Aclasta resulted in 4.7% increase in BMD in Stratum I patients and 3.2% in Stratum II patients relative to placebo.

Bone turnover markers:

The effect of Aclasta treatment on markers of bone resorption b-CTx and bone formation BSAP, P1NP was evaluated in 571 patients stratified by duration from menopause at periodic intervals. Treatment with Aclasta results in a significantly greater reduction in bone turnover markers compared to placebo, and with the two annual Aclasta doses there was a significantly greater reduction compared to the single Aclasta dose. The two annual doses of Aclasta and the single Aclasta dose were associated with reductions in bone turnover markers to the premenopausal range with an approximate 55% and 44% reductions in b-CTx in postmenopausal women within 5 years of menopause, respectively, and approximately 59% and 46% reduction in b-CTx in postmenopausal women 5 years or more from menopause, respectively, over 24 months. The two annual doses of Aclasta and the single Aclasta dose were both associated with approximately 55% and 40% reductions in P1NP, in postmenopausal women within 5 years and 5 years or more from menopause, over 24 months.

F. Paget's Disease of Bone

Paget's disease of bone is a chronic, focal skeletal disorder characterised by greatly increased and disorderly bone remodeling. 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, well-controlled clinical trials, in patients with Paget's disease, Aclasta demonstrated a superior and more rapid response compared with risedronate. In addition, biochemical markers of bone formation and resorption demonstrated normalization of bone turnover in more Aclasta treated patients compared to risedronate treated patients (see Pharmacodynamic properties).

Clinical efficacy for the treatment of Paget's disease of the bone:

Aclasta was studied in male and female patients aged above 30 years with primary mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6 to 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 zoledronic acid versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month comparative trials. Therapeutic response was 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.

In both trials zoledronic acid demonstrated a superior and more rapid therapeutic response compared with risedronate as evidenced by biochemical markers of formation (SAP), serum N-terminal propeptide of type I collagen (P1NP) and resorption (serum CTx 1 (cross-linked C-telopeptides of type I collagen) and urine alpha-CTx).

In combined data from both trials, after 2 months, Aclasta showed a superior therapeutic response of 90% (158/176) and SAP normalisation rate of 63% (111/176) compared to 47% (81/171) and 26% (45/171) respectively for risedronate (all p<0.001). After 6 months, Aclasta showed 96% (169/176) and 89% (156/176) response and normalisation rates compared to 74% (127/171) and 58% (99/171) 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 therapeutic response by subgroup is presented in Table 7.

Table 7 Proportion of patients who achieved therapeutic response at 6 months by disease factors

Subgroup	**Aclasta n/N (Proportion)**	**Risedronate n/N (Proportion)**	**p-value for treatment difference**
Baseline SAP			
< 3xULN	87/90 (0.97)	74/99 (0.75)	<0.0001
≥ 3xULN	82/86 (0.95)	53/72 (0.74)	<0.0001

Subgroup	Aclasta n/N (Proportion)	Risedronate n/N (Proportion)	p-value for treatment difference
Last Paget's therapy			
Oral bisphos.*	53/55 (0.96)	33/60 (0.55)	<0.0001
IV bisphos.	22/25 (0.88)	21/26 (0.81)	0.4590
Clodronate	6/6 (1.00)	2/2 (1.00)	NA
Others	8/8 (1.00)	6/7 (0.86)	0.2733
No previous therapy	80/82 (0.98)	65/76 (0.86)	0.0075

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.

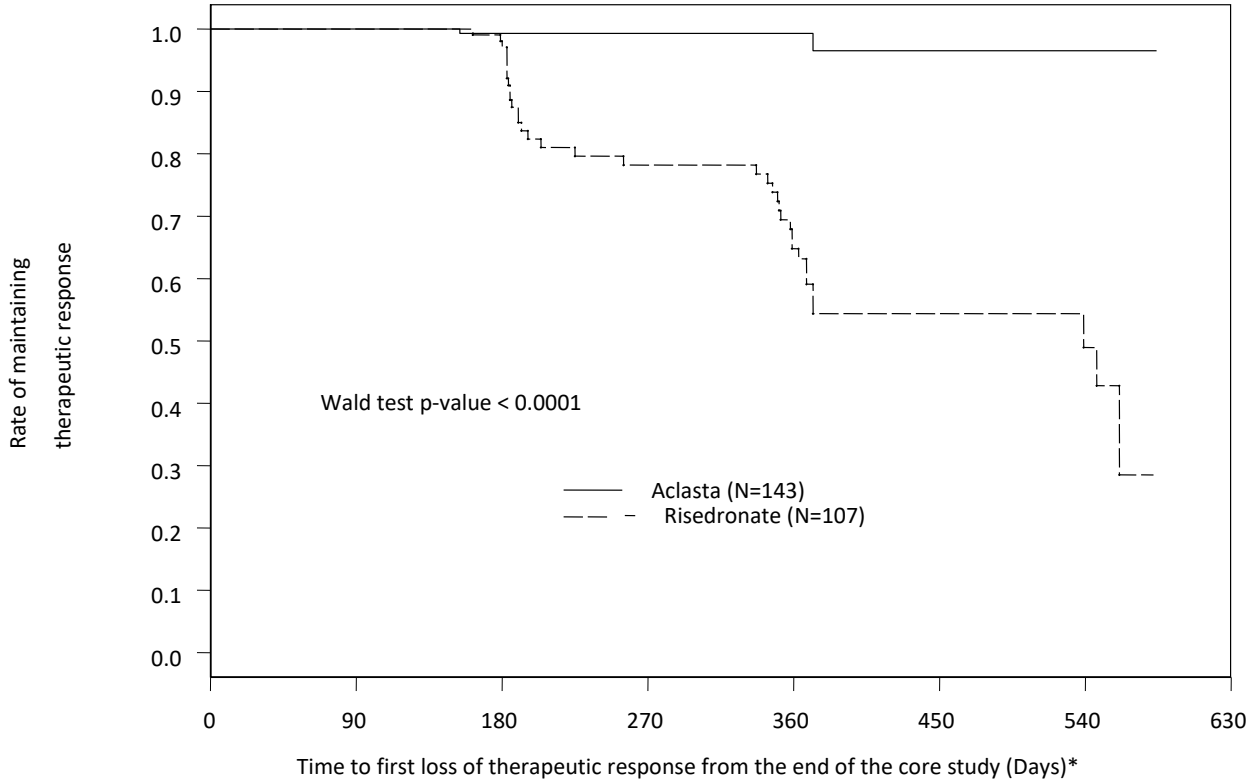
**Including previous treatment with risedronate*

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 153 Aclasta-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 Aclasta-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 2.

Six patients who achieved therapeutic response 6 months after treatment with Aclasta and later experienced disease relapse during the extended follow-up period were retreated with Aclasta after a mean time of 6.5 years from initial treatment to re-treatment. Five of the 6 patients had SAP within the normal range at Month 6 (LOCF) (83.3%, 95% CI: 35.9%, 99.6%).

Figure 2 Cumulative 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).*

Bone histology was evaluated in 7 patients with Paget's disease 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.

Bone safety studies:

Dose-response and duration of action of a single intravenous injection of zoledronic acid (0.8 to 500 micrograms/kg) were investigated in ovariectomised adult rats for 8 months after dosing, which corresponds to approximately 8 remodelling cycles over 2.7 years in humans. A single dose of zoledronic acid protected against ovariectomy-induced bone loss; both the magnitude and duration of the effect were dose-dependent. The two highest doses of 100 and 500 micrograms/kg significantly increased total bone mineral density, trabecular bone volume, trabecular number and connectivity density to levels above those of the sham-operated controls. Lower doses produced a weaker and less prolonged effect. Mechanical testing at study termination showed a dose-dependent increase in bone strength to values above those of the sham-operated controls at the higher dose. Histomorphometric analysis and measurement of plasma osteocalcin levels confirmed that bone formation was present at 32 weeks post-injection even at the highest dose of 500 micrograms/kg. This dose

in rats is approximately 3.4 fold higher than the 5 mg dose administered to a 50 kg patient. Similar results showing a dose-dependent improvement in bone mass and strength were obtained when weekly subcutaneous injections of zoledronic acid were given to ovariectomised rats (0.3 to 7.5 micrograms/kg for 52 weeks) and ovariectomised monkeys (0.5 to 12.5 micrograms/kg for 69 weeks). Overall, the results provide preclinical evidence for the efficacy and bone safety of zoledronic acid at clinically-relevant doses.

In addition, two studies were performed in ovariectomised (OVX) rats (12-month treatment with 0.3, 1.5 and 7.5 micrograms/kg) and OVX rhesus monkeys (16-month treatment with 0.5, 2.5 and 12.5 micrograms/kg) using once-a-week subcutaneous injections. Zoledronic acid treatment dose-dependently prevented all the OVX-induced changes in bone mineral density, bone mechanics and biochemical markers of bone metabolism in serum and urine. Often full efficacy was achieved with the intermediate dose, whereas the low dose had either no or only a slight effect. Drug treatment was well tolerated and there were no clinically meaningful adverse events in either species. Static and dynamic histomorphometric analysis of bones from both of these experiments indicated that zoledronic acid dose-dependently prevented the changes induced by OVX in both trabecular and Haversian bone. Moreover, there was no indication of any abnormality in bone or marrow tissue, no evidence of a mineralising defect, no accumulation of osteoid, and no woven bone. Except for its high anti-resorptive potency, the effect of zoledronic acid on bone was qualitatively similar to that published for other bisphosphonates. These results demonstrate bone safety in a laboratory rodent and a non-human primate species with a more frequent dosing regimen, and a 5- to 8-fold higher total yearly dose (based on 5 mg human dose), than the planned once-a-year dosing in humans.

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.

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. 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 above) presumably represent rapid uptake into bone and excretion via the kidneys.

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.

Special Populations (also see Section 4.2 Dose and method of administration)

Renal impairment

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 to 80 mL/min) and moderate (Cl_{cr} = 30 to 50 mL/min) renal impairment are not necessary. The use of Aclasta 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

Acute Toxicity

The highest non-lethal single intravenous dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats. In the single-dose dog infusion studies, 1.0 mg/kg (6 fold the recommended human therapeutic exposure based on AUC) administered over 15 minutes was well tolerated with no renal effects.

Subchronic and Chronic Toxicity

In the bolus parenteral studies, zoledronic acid was well tolerated when administered subcutaneously to rats and intravenously to dogs at doses of up to 0.02 mg/kg daily for 4 weeks. Administration of 0.001 mg/kg/day subcutaneously in rats and 0.005 mg/kg intravenously once every 2 to 3 days in dogs for up to 52 weeks was also well tolerated. In intravenous infusion studies, renal tolerability occurred in rats at doses of up to 0.6 mg/kg given as six infusions at 3-day intervals (6-fold the clinical dose), while five infusions of 0.25 mg/kg administered at 2 to 3-week intervals (7-fold the clinical dose) were well tolerated in dogs.

Longer-term repeat administration at cumulative exposures sufficiently exceeding the maximum intended human exposure produced toxicological effects in other organs, including the gastrointestinal tract and liver, and at the site of intravenous administration. The clinical relevance of these findings is unknown. The most frequent finding in the repeat-dose studies consisted of increased primary spongiosa in the metaphyses of long bones in growing animals at nearly all doses, a finding that reflected the compound's pharmacological antiresorptive activity.

Reproduction Toxicity

Teratology studies were performed in two species, both via subcutaneous

administration. Teratogenicity was observed in the rat at doses ≥0.2 mg/kg 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 or embryo/foetal effects were observed in the rabbit, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels.

Mutagenicity and Carcinogenic Potential

Zoledronic acid was not mutagenic in the mutagenicity tests performed and carcinogenicity testing did not provide any evidence of carcinogenic potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, sodium citrate and water for injections.

6.2 Incompatibilities

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

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store below 30°C prior to opening.

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

Information might differ in some countries.

6.5 Nature and contents of container

Aclasta 5 mg/100 mL solution for infusion is supplied in a 100 mL transparent plastic bottle 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 bottle.

For single use only. Only clear solution, free from particles and discoloration, should be used. Any unused solution should be discarded.

6.6 Special precautions for 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.

7 MEDICINE SCHEDULE

Prescription Only Medicine

8 SPONSOR

Novartis New Zealand Limited

PO Box 99102

Newmarket,

Auckland 1149

Telephone: 0800 354 335

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9 DATE OF FIRST APPROVAL

Date of publication in the New Zealand Gazette of consent to first distribute the medicine: 30 August 2007

10 DATE OF REVISION OF THE TEXT

11 August 2020

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information
Section 8 Sponsor	Removed Sponsor's old address.

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