LEAFLET

ACLASTA®

(zoledronic acid)

5 mg/100 mL solution for infusion

DISETUJUI OLEH BPOM : 13/09/2022 EREG100005VR12200122

Trade name(s)

ACLASTA® 5 mg/100 mL solution for infusion

Description and composition

Pharmaceutical forms

Solution for infusion.

The solution is sterile, clear and colourless.

Active substance(s)

One bottle with 100 mL solution contains 5 mg zoledronic acid (anhydrous), corresponding to 5.330 mg zoledronic acid monohydrate.

Active moiety

Zoledronic acid (anhydrous)

Excipients

Mannitol, sodium citrate, water for injections

Indications

- Treatment of osteoporosis in postmenopausal women at increased risk of fracture. In patients at high risk of fracture, defined as a recent low-trauma hip fracture, Aclasta reduces the incidence of new clinical fractures.

- Osteoporosis in men.

  Aclasta is indicated for treatment to increase bone mineral density in men with osteoporosis.

- Glucocorticoid-induced osteoporosis.

  Aclasta is indicated for the treatment and prevention of glucocorticoid-induced osteoporosis in men and women who are either initiating or continuing systemic glucocorticoids in a daily dosage equivalent up to 7.5 mg or greater of prednisone and who are expected to remain on glucocorticoids for at least 12 months.

- Treatment of Paget's disease of bone.

Dosage and Administration

General

The incidence of post-dose symptoms (fever, myalgia, flu-like symptoms, arthralgia, and headache) 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 Warnings and Precautions).

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 warnings and Precautions).

Patients with a recent low-trauma hip fracture

In patients with a recent low-trauma hip fracture, it is recommended to give the 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 Pharmacodynamic properties).

Osteoporosis in men

For 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 Warnings and Precautions).

Treatment and prevention of glucocorticoid-induced osteoporosis

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

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

Treatment of Paget's disease of bone

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

Re-treatment of Paget's disease: After initial treatment with Aclasta in Paget's disease an extended remission period is observed in responding patients. Re-treatment consists of an additional intravenous infusion of 5 mg Aclasta after an interval of one year or longer from initial treatment in patients who have relapsed. Limited data on re-treatment of Paget's disease are available.

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 Warnings and Precautions).

Special populations

Patients with renal impairment

The use of Aclasta in patients with creatinine clearance < 35 mL/min contraindicated (see section Contraindications Warnings and Precautions)

Patients with hepatic impairment

No dose adjustment is required (see section Pharmacokinetic properties).

Geriatric patients (≥ 65 years or above)

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

Pediatric patients

Aclasta is not recommended for use in children and adolescents below 18 years of age due to 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 instruction for use and handing of Aclasta, see section Pharmaceutical information

Contraindication

- Hypocalcemia (see section Warnings and Precautions).
- Severe renal impairment with creatinine clearance <35 mL/min (see section Warnings and precautions)

- Pregnancy and breast feeding women (see section Pregnancy, lactation, females and males of reproductive potential).
- Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates

Warnings and Precautions

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. Caution is indicated when Aclasta is administered in conjunction with medicinal product that significantly impact renal function (e.g. amino glycosides or diuretics that may cause dehydration).

Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta (see section 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 Adverse drug reactions, 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 Interactions), 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 risk factors described above.

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

- Patients should have serum Creatinine clearance measured should be calculated (e.g. Cockcroft-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 Interactions).

- 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 Dosage and Administration).

Calcium and Vitamin D Supplementation

Treatment of osteoporosis

Adequate supplemental calcium and vitamin D intake is important in men and women with osteoporosis if dietary intake is inadequate.

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 Adverse drug reactions). 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 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 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 with such symptoms should be evaluated for possible femur fracture.

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 Pharmacokinetic properties). 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.

Pregnancy, lactation, females and males of reproductive potential

Pregnancy

Risk Summary

Aclasta is contraindicated during pregnancy (see section Contraindications). Studies in rats have shown reproductive toxicological effects. The potential risk in humans is unknown.

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 Contraindications and section Non-clinical safety data).

Data

Human Data

There are no data on the use of zoledronic acid in pregnant women.

Animal Data

Teratogenicity studies were performed in two species, both via subcutaneous administration of zoledronic acid. In rats, teratogenicity was observed at doses ≥ 0.2 mg/kg (2.4 fold, the anticipated human exposure, based on AUC comparison) and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg/day) tested in rats.

In rabbits, no teratogenic embryo/foetal effects were observed, although maternal toxicity was marked at 0.1 mg/kg/day. Adverse maternal effects were associated with, and may have been caused by, drug-induced hypocalcemia.

Lactation

Risk Summary

Aclasta is contraindicated during pregnancy and in breast-feeding women (see section Contraindications).

Females and males of reproductive potential

Women of child-bearing potential should be advised to avoid becoming pregnant while receiving Aclasta.

Infertility

The fertility was decreased in rats dosed subcutaneously with 0.1 mg/kg/day of zoledronic acid. There are no data available in humans.

Effects on ability to drive and use machines

There are no data to suggest that Aclasta affects the ability to drive or use machines.

Adverse drug reaction

Summary of the safety profile

The presented adverse reactions in this section have been derived from different studies in the clinical program (see section Clinical studies).

Aclasta was studied in:

- Postmenopausal osteoporosis in the pivotal fracture trial, a randomised, double-blind, placebo-controlled, multinational study (HORIZON-PFT) including 7,736 women.

- Paget's disease in two double blind, randomized safety and efficacy trials involving 357 patients.

- Prevention of clinical fractures in patients who suffered from a recent low-trauma hip fracture was demonstrated in a randomized, double-blind, placebo-controlled, multinational endpoint study of 2,127 men and women.

- Treatment and prevention of glucocorticoid-induced osteoporosis in a randomised, multicentre, double-blind, stratified, active-controlled study of 833 men and women.

- Men with osteoporosis or significant osteoporosis secondary to hypogonadism in a randomised, multicentre, double-blind, active-controlled study of 302 men.

Treatment of postmenopausal osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT), osteoporosis in men, 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 at increased risk of fracture after a recent 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.

The safety of zoledronic acid in the treatment of postmenopausal osteoporosis was assessed in a large, randomized, double-blind, placebo-controlled, multinational study (HORIZON – Pivotal Fracture

Trial [PFT]) of 7736 postmenopausal women aged 65-89 years with osteoporosis, diagnosed by bone mineral density or the presence of a prevalent vertebral fracture. The duration of the trial was three years with 3862 patients exposed to Aclasta and 3852 patients exposed to placebo administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes, for a total of three doses. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was similar between groups: 3.4% in the Aclasta group and 2.9% in the placebo group. The incidence of serious adverse events was 29.2% in the Aclasta group and 30.1% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 5.4% and 4.8% for the Aclasta and placebo group, respectively.

The safety of Aclasta in the treatment of osteoporosis patients with a recent (within 90 days) low-trauma hip fracture was assessed in a randomized, double-blind, placebo controlled, multinational endpoint-driven study (HORIZON – Recurrent Fracture Trial [RFT]) of 2127 men and women aged 50-95 years, 1065 patients were randomized to Aclasta and 1062 patients were randomized to placebo. Aclasta was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. The study continued until at least 211 patients had a confirmed clinical fracture in the study population who were followed for an average of approximately 2 years on the study drug. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000 to 125,000 IU orally of IM) was given to patients and they were started on 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day for at least 14 days prior to the study drug infusions.

The incidence of all-cause mortality was 9.6% in the Aclasta group and 13.3% in the placebo group. The incidence of serious adverse events was 38.3% in the Aclasta group and 41.3% in the placebo group. The percentage of patients who withdrew from study due to adverse events was 5.3% and 4.7% for Aclasta and placebo groups, respectively.

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

The incidence of serious adverse events was 5.1% in the Aclasta group and 6.4% in the risedronate group. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 1.2% for the Aclasta and risedronate groups, respectively.

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 at increased risk of fracture after a recent 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**:**	Anemia
Metabolism and nutrition disorders	
Uncommon**:**	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
Cardiac disorder	
Common	Atrial fibrillation
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, hyperhidrosis*, pruritus, erythema
Musculoskeletal disorders	
Common:	Myalgia*, arthralgia*, bone pain, back pain, pain in extremity.
Uncommon:	Neck pain, musculoskeletal stiffness*, joint swelling*, muscle spasms, 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
Immune system disorders		
	Not known**	Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reaction/shock

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

** Based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to exposure to the medicinal product.

Table 2 Additional adverse reactions which were reported in the individual studies but with lower frequency in the Aclasta group compared with that of the placebo group

Cardiac disorders
Atrial fibrillation*, palpitations
Eye disorders
Ocular hyperaemia
Gastrointestinal disorders:
Gastritis, toothache
General disorders and administration site conditions:
Infusion site reaction
Investigations:
C-reactive protein increased
Metabolism and nutrition disorders:
Hypocalcaemia
Nervous system disorders:
Dysgeusia
*see below ‘atrial fibrillation’ subsection in ‘description of selected adverse reactions’ section.

In HORIZON-PFT study, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.3% of patients (50 out of 3862) compared to 0.4% (17 out of 3852) in the placebo group. The overall incidence of all atrial fibrillation adverse events in the zoledronic acid treatment group was reported in 2.5% of patients (96 out of 3862) in the Aclasta group vs. 1.9% of patients (75 out of 3852) in the placebo group. Over 90% of these events in both treatment groups occurred more than a month after the infusion. In an ECG sub-study, ECG measurements were performed on a subset of 559 patients before and 9 to 11 days after treatment. There was no difference in the incidence of atrial fibrillation between treatment groups suggesting these events were not related to the acute infusion. In HORIZON-RFT study, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occurred in 1.0% of patients (11 out of 1054) compared to 1.2% (13 out of 1057) in the placebo group demonstrating no difference between treatment group.

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 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 indications treatment of osteoporosis in men and postmenopausal women at increased risk of fractures after a recent hip fractures and 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.

Hypocalcemia

In the HORIZON-PFT core trial, approximately 0.2% of patients had notable declines of serum calcium levels (less than 7.5 mg/dL) following Aclasta administration. No symptomatic cases of hypocalcaemia were observed.

In the HORIZON-RFT trial, following pre-treatment with vitamin D, no patients had treatment emergent serum calcium levels below 7.5 mg/dL.

In men with osteoporosis and treatment and prevention of glucocorticoid-induced osteoporosis trials, there were no patients who had treatment emergent serum calcium levels below 7.5 mg/dL.

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels were observed. Approximately, 21% of patients had serum calcium levels < 8.4 mg/dL 9-11 days following Aclasta administration.

Local reactions

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

In men with 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.

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 Warnings and Precautions).

In the HORIZON-PFT trial in 7736 patients, ONJ has been reported in one patient treated with Aclasta and one patient treated with placebo. Both cases resolved.

In the HORIZON-RFT, men with osteoporosis and treatment and prevention of glucocorticoid-induced osteoporosis trials there were no cases of osteonecrosis of the jaw.

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.

Table 3 Adverse drug reactions from spontaneous reports and literature (frequency not known)

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 Warnings & Precautions)
Renal and urinary disorders: Renal failure requiring dialysis or with fatal outcome*, renal impairment (see section Warnings & Precautions)
*especially in patients with pre-existing renal impairment or other risk factors such as advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy, or dehydration in the post infusion period.

Overdosage

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

Clinical Pharmacology

Pharmacotherapeutic group, ATC code:

Pharmacotherapeutic group: Bisphosphonate.

ATC code: M05B A08

Mechanism of action (MOA):

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, localizes 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 properties (PD)

Osteoporosis

Aclasta treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks.

Thereafter bone markers stabilized within the pre-menopausal 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, mineralization 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 remodeling sites in both trabecular and Haversian bone. Continuing bone remodeling was observed in bone samples from all animals treated with clinically relevant doses of zoledronic acid. There was no evidence of a mineralizing defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Pharmacokinetic properties (PK)

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 $t_{½\alpha}$ 0.24 and $t_{½\beta}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½\gamma}$ 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.

Drug-drug interactions

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. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Special populations (see section Dosage and 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 $AUC_{(0-24hr)}$, 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} = 30–50 mL/min) renal impairment are not necessary.

The use of Aclasta in patients with creatinine clearance < 35 mL/min is not recommended to ensure an adequate safety margin against renal impairment in patients administered the drug outside a trial environment (see section Warnings and Precautions). No dose adjustment is necessary in patients with creatinine clearance ≥35 mL/min.

Clinical studies

Clinical trial results for the treatment of post-menopausal osteoporosis (PMO)

The efficacy and safety of Aclasta 5 mg once a year for 3 consecutive years were demonstrated in post-menopausal women (7,736 women aged 65-89 years) with either: a femoral neck bone mineral density (BMD) with a T-score ≤ -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score ≤ -2.5 with or without evidence of existing vertebral fracture(s). 85% of patients were bisphosphonate-naïve. 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 and 400 to 1200 IU of vitamin D supplements daily.

Effect on morphometric vertebral fracture in the treatment of PMO

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 4).

Table 4 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 (4.4, 6.6)	71 (62, 78)**
At least one new vertebral fracture (0-3 year)	3.3	10.9	7.6 (6.3, 9.0)	70 (62, 76)**

** $p < 0.0001$

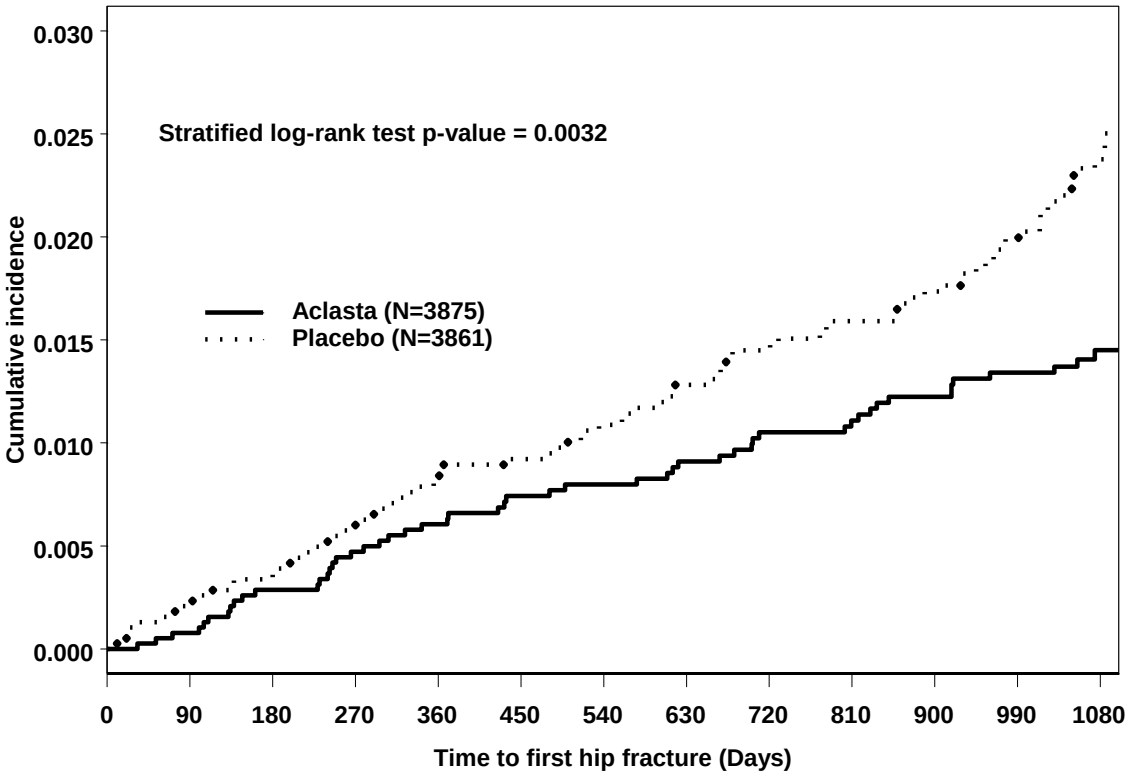
The reductions in vertebral fractures over three years were consistent and significantly greater than placebo regardless of age, geographical region, race, baseline body mass index, number of baseline

vertebral fractures, femoral neck BMD T-score or prior bisphosphonate use. Specifically for patients aged 75 years and older, Aclasta patients had a 60% reduction in the risk of vertebral fractures compared to placebo patients (p<0.0001).

Effect on hip fracture in the treatment of PMO

Aclasta demonstrated a 1.1% absolute reduction and 41% relative reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The hip fracture event rate was 1.4% 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



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

Effect on all clinical fractures in the treatment of PMO

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 5.

Table 5 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)	**308 (8.4)**	**456 (12.8)**	**4.4 (3.0, 5.8)**	**33 (23, 42)****
Clinical vertebral fracture (2)	**19 (0.5)**	**84 (2.6)**	**2.1 (1.5, 2.7)**	**77 (63, 86)****
Non-vertebral fracture (1)	**292 (8.0)**	**388 (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) in the treatment of PMO

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 6.7% increase in BMD at the lumbar spine, 6.0 % at the total hip, and 5.1% at the femoral neck, and 3.2% at the distal radius over 3 years as compared to placebo.

Bone Histology in the treatment of PMO

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 mineralization defects. Microcomputed tomography analysis demonstrated preservation of trabecular bone architecture in patients treated with Aclasta compared to placebo.

Bone turnover markers in the treatment of PMO

Bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP) and serum beta-C-telopeptides (b-CTx) were evaluated in subsets ranging from 517 to 1246 patients at periodic intervals throughout the study. Treatment with a 5 mg annual dose of Aclasta significantly reduced BSAP by 30% relative to baseline at 12 months which was sustained at 28% below baseline levels at 36 months. P1NP was significantly reduced by 61% below baseline levels at 12 months and was sustained at 52% below baseline levels at 36 months. B-CTx was significantly reduced by 61% below baseline levels at 12 months and was sustained at 55% below baseline levels at 36 months. During this entire time period bone turnover markers were within the pre-menopausal range at the end of each year. Repeat dosing did not lead to further reduction of bone turnover markers.

Effect on Height in the treatment of PMO

In the 3-year osteoporosis study standing height was measured annually using a stadiometer. The Aclasta group revealed approximately 2.5 mm less height loss compared to placebo (95%CI: 1.6 mm, 3.5 mm) [p<0.0001].

Days of disability in the treatment of PMO

Aclasta significantly reduced the mean days of limited activity and the days of bed rest due to back pain by 17.9 days and 11.3 days respectively compared to placebo and significantly reduced the mean days of limited activity and the days of bed rest due to fractures by 2.9 days and 0.5 days respectively compared to placebo (all p <0.01).

Clinical in the treatment of osteoporosis in patients at increased risk of fracture after a recent hip fracture (RFT)

The incidence of clinical fractures, including vertebral, non-vertebral and hip fractures, was evaluated in 2,127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study medication. Approximately 42% of patients had a femoral neck BMD T-score below -2.5 and approximately 45% of the patients had a femoral neck BMD T-score above -2.5. Aclasta was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. 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. Ninety-five percent of the patients received their infusion two or more weeks after the hip fracture repair and the median timing of infusion was approximately six weeks after the hip fracture repair. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on all clinical fractures in the prevention of clinical fractures after hip fracture

All causes 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). The incidence of delayed hip fracture healing was comparable between Aclasta (34 [3.2%]) and placebo (29 [2.7%]).

Table 6 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	Aclasta (N=1065) event rate (%)	Placebo (N=1062) event rate (%)	Absolute reduction in fracture event rate (%) (CI)	Relative risk reduction in fracture incidence (%) (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 (1)	7.6	10.7	3.1 (0.3, 5.9)	27 (2, 45)*

*p-value <0.05, **p-value <0.01

(1) Excluding finger, toe and facial fractures

(2) Including clinical thoracic and clinical lumbar vertebral fractures

Effect on bone mineral density (BMD) in the prevention of clinical fractures after hip fracture

In the HORIZON-RFT study Aclasta treatment significantly increased BMD at the total hip and femoral neck relative to treatment with placebo at all timepoints. Treatment with Aclasta resulted in an increase in BMD of 5.4 % at the total hip and 4.3% at the femoral neck over 24 months as compared to placebo.

Clinical trial results for the treatment of male osteoporosis (MO)

The efficacy and safety of Aclasta in men with osteoporosis or significant osteoporosis secondary to hypogonadism were assessed in a randomized, multicentre, double-blind, active-controlled study of 302 men aged 25-86 years (mean age of 64 years). The duration of the trial was two years. Patients were randomized to either Aclasta, which was administered once annually as a single 5 mg dose in 100 ml infused over 15 minutes for a total of two doses, or to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day. Efficacy was demonstrated if non-inferiority to alendronate was shown with respect to the percentage change in lumbar spine BMD at 24 months relative to baseline.

Effect on bone mineral density (BMD) in the treatment of MO

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.

Clinical trial results in the 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 18-85 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 Aclasta, which was administered once as a single 5 mg dose in 100 mL infused over 15 minutes, or to oral risedronate 5 mg daily for one year. All participants received 1000 mg elemental calcium plus 400 to 1000 IU vitamin D supplementation per day. The study was designed to show non-inferiority of a single infusion of Aclasta relative to risedronate in these two subpopulations. Efficacy was demonstrated if non-inferiority to risedronate was shown sequentially with respect to the percentage change in lumbar spine BMD at 12 months relative to baseline in the treatment and prevention subpopulations, respectively.

Effect on bone mineral density (BMD) in the treatment and prevention of glucocorticoid-induced osteoporosis

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 7.

Table 7 **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) [1]**
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 in the treatment and prevention of glucocorticoid-induced osteoporosis

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.

Clinical trial results 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 2.6-3.0 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 α-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 8.

Table 8 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**
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.

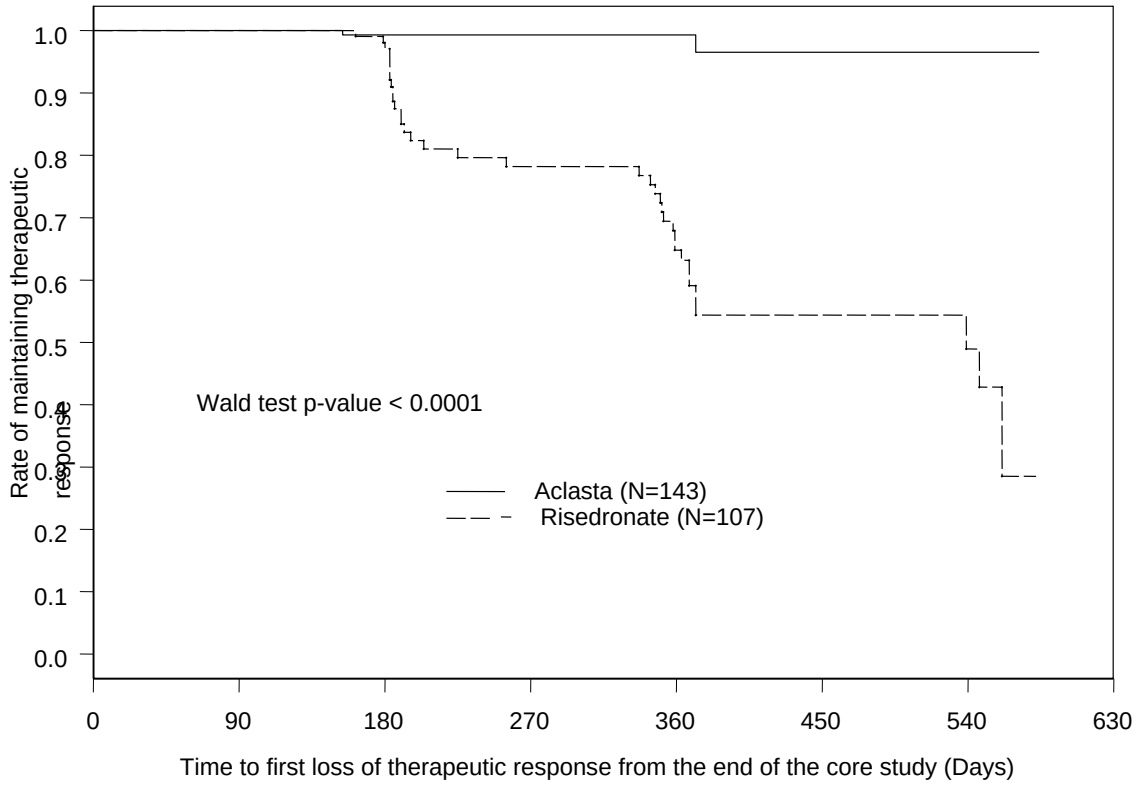
*Including previous treatment with risedronate

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 from the end of the core study (Days)*

* 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 (0.8–500 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.

Non-clinical 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.

The kidney was identified as a target organ for toxicity in parenteral studies with zoledronic acid. In intravenous infusion studies, renal tolerability was observed in rats at doses of up to 0.6 mg/kg given as six infusions at 3-day intervals and in dogs up to 0.5 mg/kg given 3 times at aproximately 119 - day interval.

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.

Mutagenicity

Zoledronic acid was not mutagenic *in vitro* and *in vivo* in the mutagenicity tests performed.

Carcinogenicity

In oral carcinogenicity studies in rodents, zoledronic acid revealed no carcinogenic potential.

Pharmaceutical information

Incompatibilities

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

Aclasta is compatible with the typical infusion line materials polyvinylchloride (PVC), polyurethane (PUR) and polyethylene (PE).

Special precautions for storage

Do not store above 30ºC, after opening, the solution is chemically and physically stable for at least 24 hours at 2-8ºC.

Aclasta must be kept out of the reach and sight of children.

Special precautions for disposal

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.

Instructions for use and handling

Aclasta must not be mixed or given intravenously with any other medication and must be given through a separate vented infusion line at a constant infusion rate**.** If refrigerated, allow the refrigerated

solution to reach room temperature before administration. Aseptic techniques must be followed during the preparation of the infusion.

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

Package

Box, One bottle with 100 mL solution contain 5 mg zoledronic acid (anhydrous)

Reg. No.

Shelf life : The expiry date is indicated on the packaging.

HARUS DENGAN RESEP DOKTER

To be dispensed only on the prescription of a physician

Manufactured by Fresenius Kabi Austria GmbH, Graz, Austria for Novartis Pharma AG, Basel, Switzerland

Released by Lek Pharmaceuticals d.d., Ljubljana, Slovenia

Imported by PT Novartis Indonesia, Jakarta, Indonesia.

Leaflet by CDS 04-Nov-2016 (safety)