Aclasta adalah obat baru yang terdaftar tahun 2006.
Informasi di bawah ini merupakan informasi update tahun 2010.

LEAFLET

ACLASTA®
(zoledronic acid)

5 mg/100 mL solution for infusion

Name of the medicinal product

ACLASTA® 5 mg/100 mL solution for infusion

Qualitative and quantitative composition

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

For a full list of excipients, see section List of excipients.

Pharmaceutical form

Solution for infusion.

The solution is sterile, clear and colourless.

Clinical particulars

Therapeutic indications

Treatment of osteoporosis in postmenopausal women at increased risk of fracture.

Treatment of Paget's disease of bone.

Posology and method of administration

General

The incidence of post-dose symptoms occurring within the first three days after administration of Aclasta® can be reduced with the administration of paracetamol 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 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 calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate (see section 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: Specific re-treatment data are not available. After a single treatment with Aclasta in Paget's disease an extended remission period is observed in responding patients (see section Pharmacodynamic properties). However, re-treatment with Aclasta may be considered in patients who have relapsed, based on increases in serum alkaline phosphatase, in patients who failed to achieve normalisation of serum alkaline phosphatase, or in patients with symptoms, as dictated by medical practice 12 months after the initial dose.

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

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 infusion of Aclasta, see section Instructions for use and handling.

Patients with renal impairment

The use of Aclasta in patients with creatinine clearance < 35 mL/min is not recommended due to lack of adequate clinical experience in this population (see section Special warnings and precautions for use).

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

Patients with hepatic impairment

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

Elderly (≥ 65 years)

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

Children and adolescents

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates.

Hypocalcaemia (see section Special warnings and special precautions for use).

Pregnancy and breast feeding women (see section Pregnancy and lactation).

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. 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; intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.

Renal impairment

Aclasta is not recommended for patients with renal impairment (creatinine clearance < 35 mL/min) due to lack of adequate clinical experience in this population. Patients should have serum creatinine measured before receiving Aclasta.

Calcium and Vitamin D Supplementation

Treatment of Postmenopausal Osteoporosis

Adequate calcium and vitamin D intake is important in 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 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, sometimes symptomatic, may develop and is ussually maximal within the first 10 days after infusion of Aclasta. 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, corticosteroids, poor oral hygiene). While on treatment, these patients should avoid invasive dental procedures if possible. For patients who develop osteonecrosis of the jaw while on bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgement of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Interaction with other medicinal products 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* (see section Pharmacokinetic properties). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely. Zoledronic acid is eliminated by renal excretion. Caution is indicated when Aclasta is administered in conjunction with drugs that can significantly impact renal function (e.g. aminoglycosides or diuretics that may cause dehydration).

Pregnancy and lactation

There are no data on the use of zoledronic acid in pregnant women. Studies in animals have shown reproductive toxicological effects including malformations (see section Preclinical safety data). The potential risk for humans is unknown. It is known wheter zoledronic acid is excreted into human breast milk. Aclasta is contraindicated during pregnancy and in breast-feeding women (see section Contraindications).

Effects on ability to drive and use machines

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

Undesirable effects

Post-menopausal osteoporosis and Paget's disease

The safety of zoledronic acid in the treatment of postmenopausal osteoporosis was assessed in a large, randomized, double-blind, placebocontrolled, multinational study of 7736 women aged 65-89 years with postmenoupausal osteoporosis. 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 Zoledronic acid group and 2.9% in placebo group.

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

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

Very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1,000) adverse drug reactions suspected (investigator assessment) to be associated with Aclasta are shown in Table 1. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1 Adverse drug reactions suspected* (at least 1%) to be associated with Aclasta in post-menopausal osteoporosis in HORIZON PFT study

Cardiovascular disoreder		
	Common:	Atrial fibrillation
Nervous system disorders		
	Common:	Headache, dizziness.
	Uncommon:	Lethargy† †,paraesthesia, somnolence, tremor, syncope, dysgeusia.
Eye disorders		
	Uncommon:	Conjunctivitis, eye pain, uveitis.
	Rare:	Episcleritis, iritis.
Ear and labyrinth disorders		
	Uncommon:	Vertigo.
Respiratory, thoracic and mediastinal disorders		
	Common:	Dyspnoea†
Gastrointestinal disorders		
	Common:	Nausea, vomiting, diarrhoea.
	Uncommon:	Dyspepsia† †, abdominal pain, dry mouth, oesophagitis.
Skin and subcutaneous tissue disorders		
	Uncommon:	Rash.
Musculoskeletal disorder		
	Common:	Myalgia, arthralgia, bone pain, back pain, pain in extremity.
	Uncommon:	Joint swelling, shoulder pain, muscle spasms, muscular weakness, joint stiffness.
Renal and urinary disorders		
	Uncommon:	Blood creatinine increased.

General disorders and administration site conditions		
-	Very common:	Fever
	Common:	Hypocalcaemia†, flu-like symptoms† † † , chills, fatigue, asthenia, pain, malaise, rigors† .
-	Uncommon:	Anorexia, peripheral odema, thirst

* Incidence based on investigator assesment of causality and includes those events with a greater frequency than placebo

Key deviations in the adverse events in the Paget's disease clinical trials compared to the post-menopausal HORIZON-PFT trial are summarised below:

† Common in Paget's disease only

† † Common in Paget's disease

† † † Very Common in Paget's disease

In one 3 year trial in women with postmenopausal osteoporosis (Horizon PFT), the overall incidence of all trial fibrillation adverse event was 2.5% (96 out of 3,862) in the Aclasta group vs. 1.9% (75 out of 3,852) in the placebo group.

In the postmenopausal osteoporosis trial, adjudicated serious adverse events of atrial fibrillation in the zoledronic acid treatment group occured 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 zoledronic acid group vs. 1.9% of patients (75 out of 3852) in the placebo group. Over 90% of these events in both treatment groups occured more than a month after the infusion. In an ECG sub-study, ECG measurements were performed on a subset 0f 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 infusions.

Class Effects

Renal dysfunction

Treatment with intravenous bisphosphonates, including zoledronic acid, has been associated with renal dysfunction manifested as deterioration in renal function (i.e. increased serum creatinine) and in rare cases acute renal failure. In the clinical trial for postmenopausal osteoporosis, patients with baseline creatinine clerance < 30 mL/min, urine dipstick =2+ protein or increase in serum creatinine of >0.5 mg/dL during the screening visits were excluded. Renal dysfuction has been observed following the administration of zoledronic acid, especially in patients with pre-existing renal compromise or additional risk factors (e.g. oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration), the majority of whom received a 4 mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In the HORIZON-PFT trial, the change in creatinine clearance (measured annually prior to dosing), and the incidence of renal failure and impairement was comparable for both the Aclasta and placebo treatment groups over 3 years, including patients with mild to moderate renal impairment (creatinine clearance between 30-60 mL/min) at baseline. 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.

Laboratory findings

In the HORIZON-PFT trial, approximately 0.2% of patients had notable declines of serum calcium

levels (less than 1.87 mmol/L) following Aclasta administration. No symptomatic cases of hypocalcaemia were observed.

In the 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 HORIZON-PFT trial, local reaction at the infusion site such as redness, itching, swelling and/or pain were reported (0,7%) following the administration of zoledronic acid.

Osteonecrosis of the jaw

Cases of osteonecrosis (primarily of the jaw) heve been reported predominantly in cancer patients treated with bisphosponates, including zoledronic acid (uncommon). Many of these patients had signs of local infection including osteomylitis, and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple well documented risk factors including a diagnosis of cancer, concomitant therapies (e.g. chemotherapy, radiotherapy, corticosteroids) and co-morbid conditions (e.g anemia, coagulophaties, 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 Special warnings and precautions for use). In the HORIZON-PFT trial in 7736 patients, ONJ has been reported in one patients treated with Aclasta and one patient treated with placebo. Both cases resolved.

Post-marketing experience

The following adverse reactions have been reported during post-approval use of zoledronic acid. Because these reports are from a population of uncertain size and are subject to confounding factors, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. The following adverse reactions have been identified during post approval use of Aclasta: hypocalcemia, arthalgia, myalgia, flu-like symptoms, fever, headache, and urticaria.

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

Overdose

There is no experience of acute intoxication with Aclasta. 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.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: Bisphosphonate (ATC code: M05B 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 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 in oestrogen-deficient animals, zoledronic acid inhibited bone resorption and increased bone mass at doses ranging from 0.03 to 8 times the equivalent human dose. A dose-dependent increase in bone strength and other bone mechanical properties was demonstrated. At doses 0.8 to 8 times the humans equivalent, bone mechanical properties were improved in ovariectomised animals relative to monovariectomised controls. Histomorphometric analyses showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclastis activity and activation frequency of new remodelling sites in both trabecular and Haversion bone. Continuing bone remodelling was observed in bone samples from all animals treated with clinically relevant doses of zoledronic acid. There was no eviedence of a mineralising defect, no aberrant accumulation of osteoid, and no woven bone in treated animals.

Clinical efficacy for the treatment of post-menopausal osteoporosis

The efficacy and safety of Aclasta was demonstrated in HORIZON-PFT, a randomised, double-blind, placebo controlled, multinational study of 7736 women aged 65-89 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). 85% of patients were bisphosponate-naive while 15% had receive prior bisphosponate treatment. Aclasta was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes for a total of there doses. The two primary efficacy variables were the incidence of morphometric vertebral fractures at 3 years, and the incidence of hip fractures over a median duration of 3 years. 7736 women were evaluated for the incidence of hip and clinical fracture. Of these, 5661 women were evaluated annually for incidence of vertebral fractures. Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and clinical fracture evaluations. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifene, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day.

Effect on Morphometric 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 2).

Table 2 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, 72)**
** $p < 0.0001$				

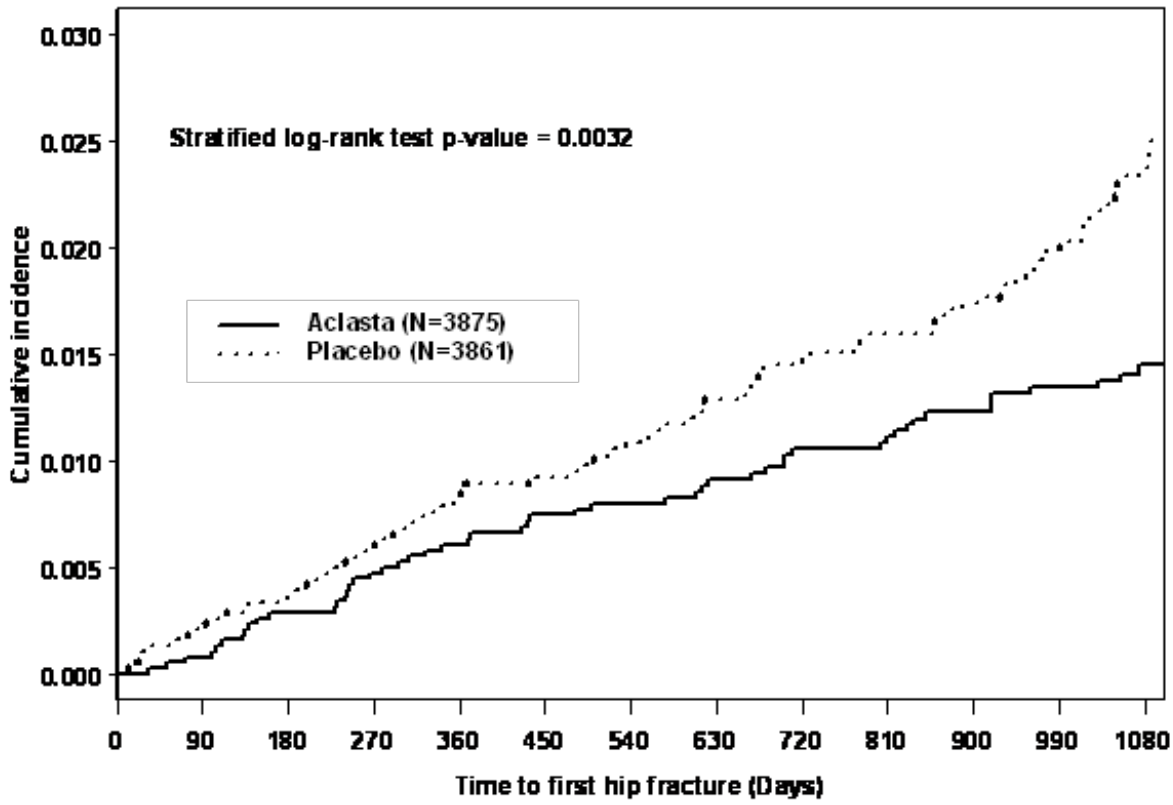
Aclasta significantly decreased the risk of at least one new moderate or severe vertebral fracture at 1 year (60%), 2 years (70%) and 3 years (70%) (all $p<0.0001$).

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 60% reduction in the risk of vertebral fractures compared to placebo patients ($p<0.0001$).

Effect on Hip Fracture

Aclasta demonstrated a 41% reduction in the risk of hip fractures over 3 years (95% CI, 17% to 58%). The hip fracture event rate was 1.44% for Aclasta-treated patients compared to 2.49% for placebo-treated patients. The effect over time is displayed in Figure 1.

Figure 1 Cumulative incidence of hip fracture over 3 years



In 6,084 women who did not take concomitant osteoporosis therapy Aclasta demonstrated a 41% reduction (95% CI, 13% to 59%) in the risk of hip fractures over this time period. In 1.652 women who were allowed to take concomitant osteoporosis therapy a comparable 42% reduction was observed (95% CI, -27% to 73%) in the risk of hip fractures.

The reductions in hip fractures over three years were greater than placebo regardless of age, geoghraphical 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 3.

Table 3 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	12.8	4.5	33**
Clinical vertebral fracture (2)	0.5	2.6	2.1	77**
Non-vertebral fracture (1)	8.0	10.7	2. 7	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 6.7% 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

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

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 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

Aclasta significantly reduced both 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 efficacy for the treatment of Paget's disesase 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 0f 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 a-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) respectetively 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 4.

Table 4 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**

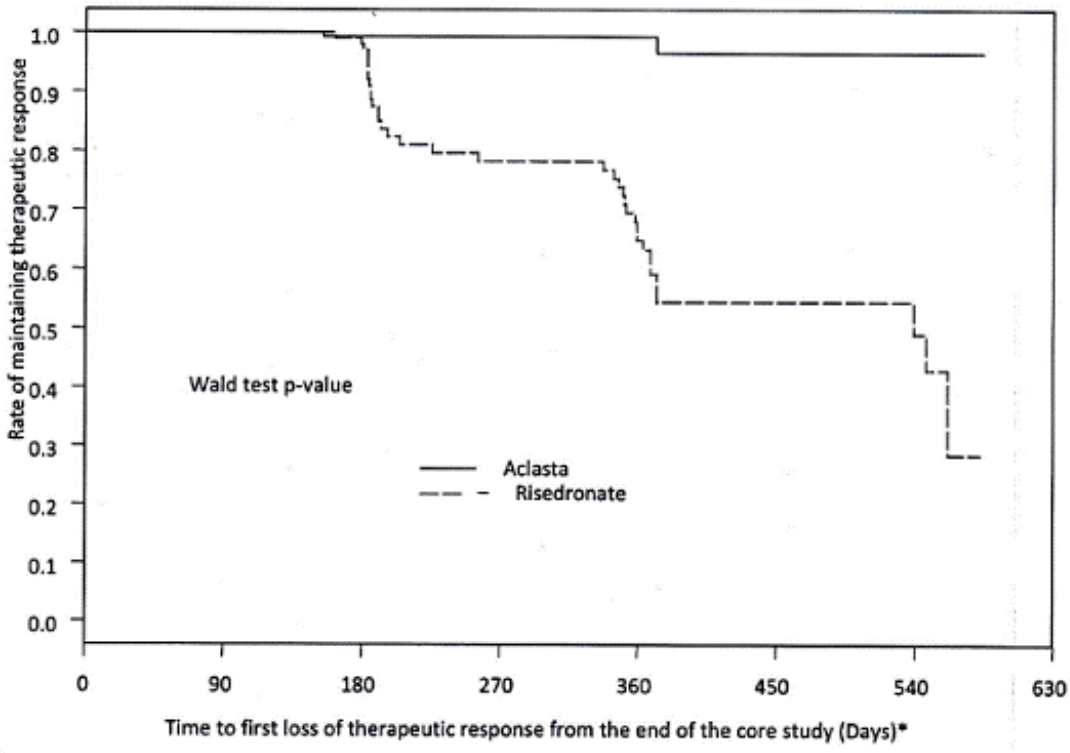
SAP = serum alkaline phosphatase. ULN = upper limit of normal. A therapeutic response is defined as normalisation of SAP or a reduction of ≥ 75% from baseline in SAP excess. N = number of patients with baseline and at least one post-baseline SAP measurements. n = number of patients with therapeutic response 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 143 Aclasta-treated patients and 107 risedronate-treated patients who entered an extended observation study, after a median duration of follow-up of 18 months from time of dosing, 141 Aclasta-treated patients maintained their therapeutic response compared to 71 risedronate-treated patients.

The cumulative rate of maintaining therapeutic response in the extended follow-up period is displayed in Figure 2.

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.

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 $t_{½a}$ 0.24 and $t_{½b}$ 1.87 hours, followed by a long elimination phase with a terminal elimination half-life of $t_{½g}$ 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.

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 Posology and method of administration)

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 due to lack of adequate clinical experience in this population (see section Special warnings and precautions for use). No dose adjustment is necessary in patients with creatinine clearance ≥35 mL/min.

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.

Pharmaceutical particulars

List of excipients

Mannitol, sodium citrate, water for injections.

Incompatibilities

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

Special precautions for storage

Do not store above 30ºC, after opening: 24 hours at 2-8ºC.
Aclasta must be kept out of the reach and sight of children.

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.

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. DKI0667505349A1

HARUS DENGAN RESEP DOKTER
To be dispensed only on the prescription of a physician

Manufactured by Novartis Pharma Stein AG, Stein, Switzerland for Novartis Pharma AG, Basel, Switzerland, imported by PT Novartis Indonesia, Citeureup, Bogor, Indonesia.