PRESCRIBING INFORMATION

Pr ACLASTA*

(zoledronic acid injection)

5 mg/100 mL solution for intravenous infusion

Bone Metabolism Regulator

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Dorval, Quebec, H9S 1A9

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Non-medicinal Ingredients
Intravenous infusion	5 mg/100 mL[a]	• mannitol • sodium citrate • water for injection

[a] One bottle with 100 mL solution contains 5.330 mg of zoledronic acid monohydrate, equivalent to 5 mg zoledronic acid on an anhydrous basis.

INDICATIONS AND CLINICAL USE

ACLASTA* (zoledronic acid 5 mg/100 mL) is indicated for:

- The treatment of osteoporosis in postmenopausal women, as a once-yearly intravenous infusion, to reduce the incidence of hip, vertebral and non-vertebral fractures.
- The treatment to increase bone mineral density in men with osteoporosis, as a once-yearly intravenous infusion.
- The treatment and prevention of glucocorticoid-induced osteoporosis, to increase bone mineral density, as a once-yearly intravenous infusion.
- The prevention of postmenopausal osteoporosis in women with osteopenia as a single intravenous infusion.
- The treatment of Paget's disease of the bone in men and women, as a single-dose intravenous infusion. Treatment is indicated in patients with Paget's disease of bone with elevations in serum alkaline phosphatase (SAP) of at least two times the upper limit of the age-specific normal reference range, or those who are symptomatic, or those at risk for complications from their disease to induce remission (normalization of serum alkaline phosphatase). The effectiveness of ACLASTA* is based on serum alkaline phosphatase (SAP) levels.

Geriatrics (> 65 years of age):

No overall differences in safety and efficacy were observed according to age (see **WARNINGS AND PRECAUTIONS – Special Populations**).-

Pediatrics (<18 years of age):

Safety and efficacy in children and growing adolescents have not been established. ACLASTA* should not be given to this patient population.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation, or to any bisphosphonates or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING SECTION** of the Product Monograph.
- Pregnancy and nursing mothers.
- Non-corrected hypocalcemia at the time of infusion.

WARNINGS AND PRECAUTIONS

General

ACLASTA* contains the same active ingredient that is found in ZOMETA* (zoledronic acid). Patients being treated with ZOMETA* should not be treated with ACLASTA*.

Patients being treated with ACLASTA* should not be treated with other bisphosphonates concomitantly.

Infusion duration

The 5 mg single dose of ACLASTA* (zoledronic acid 5 mg/100 mL) should be infused in **no less than 15 minutes**.

Cardiovascular

Overall incidence of atrial fibrillation in the 3-year postmenopausal osteoporosis trial (HORIZON-PFT) using ACLASTA* (zoledronic acid) 5 mg dose yearly, was 2.5% (96 out of 3,862) and 1.9% (75 out of 3,852) in patients receiving zoledronic acid and placebo, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving zoledronic acid and placebo, respectively. The overall incidence of atrial fibrillation in the 2-year male osteoporosis trial was 3.3 % (5 out of 153) for zoledronic acid-treated patients compared to 2% (3 out of 148) for alendronate-treated patients. The rate of atrial fibrillation serious adverse events was 0% for zoledronic acid-treated patients compared to 0.7% (1/148) for alendronate-treated patients. The overall incidence of atrial fibrillation in the 1-year glucocorticoid induced-osteoporosis trial was 0.7 % (3 out of 416) for zoledronic acid-treated patients compared to 0.0% (0 out of 417) for risedronate-treated patients. The rate of atrial fibrillation serious adverse events was 0% for zoledronic acid-treated

patients and 0% for risedronate-treated patients. This increased incidence of atrial fibrillation was not observed in clinical trials conducted in Paget's disease, in the HORIZON-RFT trial in post-hip fracture patients, or in the trial for the prevention of postmenopausal osteoporosis. The mechanism behind the increased incidence of atrial fibrillation is unknown.

Endocrine and Metabolism

Hypocalcemia

It is recommended that all patients should have their serum calcium levels and vitamin D levels assessed before treatment with ACLASTA* (e.g., as part of their annual examination). Pre-existing hypocalcemia must be treated by adequate administration of calcium and vitamin D before initiating ACLASTA* (see **CONTRAINDICATIONS**). Other disturbances of mineral metabolism (e.g., diminished parathyroid reserve; thyroid surgery, parathyroid surgery, intestinal calcium malabsorption) must also be effectively treated.

It is strongly advised that patients receive adequate calcium and vitamin D supplementation. All patients should be counseled regarding the importance of calcium and vitamin D supplementation in maintaining serum calcium levels and on the symptoms of hypocalcemia. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs. In the postmenopausal osteoporosis trial (HORIZON-PFT), patients received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day.

Renal

Patients must be appropriately hydrated prior to administration of ACLASTA*, and this is especially important for patients receiving diuretic therapy (see **DOSAGE AND ADMINISTRATION**). On the day of infusion, it is recommended that patients eat and drink normally, which includes drinking at least 2 glasses of fluids (500 mL or 2 cups), such as water, before and after the administration of ACLASTA* (see "**Information to be provided to the Patients**").

It is recommended that all patients have their renal function assessed before treatment with ACLASTA* (e.g., as part of their annual examination).

Renal dysfunction:

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. Renal deterioration, progression to renal failure (some with fatal outcome) and dialysis have been reported very rarely in oncology patients (e.g., those with hypercalcemia of malignancy and/or pre-existing renal disease), after the initial dose or a single dose of zoledronic acid (4 mg dose, every 3-4 weeks) (see **ADVERSE REACTIONS**).

Renal Insufficiency:

ACLASTA* is not recommended for use in patients with severe renal impairment (creatinine clearance <30 mL/min) due to lack of adequate clinical experience in this population (see **DOSAGE AND ADMINISTRATION**). It is recommended that all patients have their serum creatinine measured before treatment with ACLASTA* (e.g., as

part of their annual examination).

Osteonecrosis of the Jaw

Osteonecrosis of the jaw (ONJ) has been reported rarely in the treatment of postmenopausal osteoporosis with zoledronic acid as well as with other oral and intravenous bisphosphonates. The condition currently termed Osteonecrosis of the jaw has unknown etiology and pathogenesis, and may or may not originate in the bone. ONJ has been reported in patients with cancer receiving treatment regimens that include bisphosphonates such as zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with invasive dental procedures, such as root canal or dental extraction. Many had signs of local infection including osteomyelitis. A causal relationship between bisphosphonate use and ONJ has not been established.

A routine dental examination with appropriate preventive dentistry should be performed prior to treatment with bisphosphonates, such as ACLASTA*, in patients with possible risk factors (e.g., cancer, chemotherapy, head and neck radiotherapy, corticosteroids, poor oral hygiene). While receiving treatment, these patients should avoid invasive dental procedures, if possible, but should continue with regular dental cleaning and oral hygiene. For patients requiring oral surgery, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of ONJ. In patients who develop ONJ while on bisphosphonate therapy, surgery at the affected area may exacerbate the condition. Clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.

Musculoskeletal Pain

In post-marketing experience with multiple dose regimen bisphosphonates, including ACLASTA*, severe and occasionally incapacitating bone, joint, and/or muscle pain has been reported in patients. The time to onset of symptoms varied from one day to several months after starting the drug. A subset of patients had recurrence of symptoms when rechallenged with the same drug or another bisphosphonate.

Respiratory

While not observed in clinical trials with ACLASTA*, there have been reports of bronchoconstriction in ASA (acetylsalicylic acid) sensitive patients receiving bisphosphonates. ACLASTA* must be used with caution in ASA-sensitive patients.

Special Populations

Pregnant Women: ACLASTA* should not be used during pregnancy as zoledronic acid may cause fetal harm when administered to a pregnant woman. In reproductive studies in the pregnant rat, subcutaneous doses equivalent to 2.0 or 4.5 times the human systemic exposure (an i.v. dose of 5 mg based on an AUC comparison) resulted in pre- and post-implantation losses, decreases in viable fetuses and fetal skeletal, visceral and external malformations.

There are no studies in pregnant women using zoledronic acid. If the patient becomes pregnant while taking this drug, the patient should be apprised of the potential harm to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Nursing Women: It is not known whether ACLASTA* is excreted in human milk. Because many drugs are excreted in human milk, it should not be administered to a nursing woman.

***Pediatrics* (*<18 years of age*)**: The safety and effectiveness of ACLASTA* in pediatric patients have not been established.

***Geriatrics* (*>65 years of age*)**: The combined osteoporosis trials (HORIZON-PFT and HORIZON-RFT) included 4,761 ACLASTA*-treated patients who were at least 65 years of age, while 2,083 patients were at least 75 years old. No overall differences in safety and efficacy were observed according to age.

The osteoporosis study in men included 59 (38.3%) ACLASTA*-treated patients who were at least 65 years of age, while 24 (15.6%) patients were at least 75 years old. No overall differences in safety and efficacy were observed according to age.

The glucocorticoid-induced osteoporosis trial included 116 (27.9%) ACLASTA*-treated patients who were at least 65 years of age, while 29 (7.0%) patients were at least 75 years old. No overall differences in safety and efficacy were observed according to age.

Phase 3 studies of ACLASTA* in the treatment of Paget's disease of bone included 132 (75.5%) ACLASTA*-treated patients who were at least 65 years of age, while 68 (37.4%) ACLASTA*-treated patients were at least 75 years old. No overall differences in efficacy or safety were observed between these patients and younger patients.

Information to be Provided to the Patient

Physicians should instruct their patients to read the Patient Information before starting therapy with ACLASTA* (zoledronic acid 5 mg/100 mL).

- ACLASTA* is given as one single infusion into a vein by a nurse or a doctor, and the infusion time must **not be less than 15 minutes**.
- Before being given ACLASTA* patients should tell their doctor if they have kidney problems and what medications they are taking (see **ADVERSE REACTIONS**-*Renal dysfunction*).
- ACLASTA* should not be given if the patient is taking ZOMETA*, which contains the same active ingredient as in ACLASTA*.
- ACLASTA* should not be given if the patient is pregnant or plans to become pregnant, or if they are breast-feeding (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS**).
- If the patient had surgery to remove some or all of the parathyroid glands or thyroid gland in their neck, or had sections of their intestine removed, or are unable to take calcium supplements, they should tell the doctor.
- It is strongly advised that patients receive adequate calcium and vitamin D supplementation in order to maintain normal blood calcium levels. Supplementation of both calcium and vitamin D is especially important in the days before and following ACLASTA* administration. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.

- On the day of infusion, it is recommended that patients eat and drink normally, which includes drinking at least 2 glasses of fluids (500 mL or 2 cups) such as water, before and after the administration of ACLASTA*.
- Patients should also be aware of the most common side effects. Patients may experience one or more side effects that could include: fever and chills; muscle, bone or joint pain; nausea; fatigue; and headache. Most of these side effects are mild to moderate and occur within 3 days after taking ACLASTA*. They usually go away within 3 days after they start, but may last for up to 7-14 days. The incidence of post-dose symptoms occurring within the first 3 days after administration of ACLASTA*, can be reduced with the administration of acetaminophen or ibuprofen shortly following ACLASTA* administration.
- Some patients experienced hypocalcemia. Hypocalcemia is usually asymptomatic, but symptoms may include numbness or tingling sensations, especially in the area around the mouth, muscle cramps or muscle spasms. Patients should consult their physician immediately if they develop these symptoms of hypocalcemia after ACLASTA* treatment (see **ADVERSE REACTIONS**).
- Redness, swelling and or pain at the infusion site may occur. Redness, itching, or pain to the eyes may occur.
- There have been some reports of persistent pain and/or a non-healing sore of the mouth or jaw, if you experience these symptoms tell your doctor or dentist.

Monitoring and Laboratory Tests

Hypocalcemia: Serum calcium levels and vitamin D levels should be assessed for all patients before treatment with ACLASTA* (e.g., as part of their annual examination). The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs.

Renal: Renal function should be assessed and serum creatinine should be measured before every treatment with ACLASTA* (e.g., as part of their annual examination).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

- *Postmenopausal osteoporosis*

In the postmenopausal osteoporosis trial (HORIZON-PFT), Phase III randomized, double-blind, placebo-controlled, multinational study of 7,736 women aged 65-89 years (see **CLINICAL TRIALS**), there were no significant differences in the overall incidence of serious adverse events compared to placebo and most adverse events were mild to moderate. The duration of the trial was three years with 3,862 patients exposed to ACLASTA* and 3,852 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: 3.4% in the ACLASTA* group and 2.9% in the placebo group. The incidence of serious adverse events was similar between treatment groups 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 2.1% and 1.8% for the ACLASTA* and placebo groups, respectively. The rate of atrial fibrillation serious adverse events was 1.3% (51 out of 3,862) and 0.6% (22 out of 3,852) in patients receiving ACLASTA* (zoledronic acid) and placebo, respectively.

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 3 days after administration of ACLASTA*, can be reduced with the administration of acetaminophen or ibuprofen shortly following ACLASTA* administration.

In the HORIZON-RFT trial (see **CLINICAL TRIALS**), a randomized, double-blind, placebo-controlled, multinational endpoint study of 2,127 osteoporotic patients aged 50-95 years with a recent (within 90 days) low-trauma hip fracture, 1,054 patients were exposed to ACLASTA* (zoledronic acid) and 1,057 patients were exposed to placebo. ACLASTA* was administered once annually as a single 5 mg dose in 100 mL solution infused over at least 15 minutes. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day.

The incidence of all-cause mortality was 9.6% in the ACLASTA*-treated group compared to 13.3% in the placebo group. The incidence of serious adverse events was 38% in the ACLASTA* group and 41% in the placebo group. The percentage of patients who withdrew from the study due to adverse events was 2.0% and 1.7% for the ACLASTA* and placebo groups, respectively.

- *Osteoporosis in men*

In general, ACLASTA* was well tolerated in the male osteoporosis trial as assessed in a two-year randomized, multicentre, double-blind, active-controlled group study of 302 men aged 25-86 years. 153 patients were exposed to ACLASTA* administered once annually as a single 5 mg dose in 100 mL solution infused over 15 minutes for a total of two doses and 148 patients were exposed to oral alendronate 70 mg weekly for two years. All participants received 1000 mg elemental calcium plus 800 to 1000 IU vitamin D supplementation per day (see **CLINICAL TRIALS**).

The incidence of serious adverse events was similar between the ACLASTA* and alendronate treatment groups (17.6% vs. 20.9%, respectively). The percentage of patients who withdrew from the study due to serious adverse events was 4.6% and 3.4% for the ACLASTA* and alendronate groups, respectively. The percentage of patients experiencing at least one adverse event was comparable between the ACLASTA* and alendronate treatment groups (93.5% compared to 93.2%), with the exception of a higher incidence of post-dose symptoms in the ACLASTA* group that occurred within 3 days after infusion. The incidence of these post-dose symptoms were reported as follow for ACLASTA* and alendronate, respectively: myalgia (17.1% vs. 2.7%), fever (15.7% vs. 1.4%), fatigue (12.4% vs. 1.4%), arthralgia (11.1% vs.

0.7%), pain (10.5% vs. 2.7%), chills (9.8% vs. 0.7%), headache (9.8% vs. 2.0%), influenza-like illness (8.5% vs. 2.0%), malaise (5.2% vs. 0.7%), and back pain (3.3% vs. 0.7%).

- *Glucocorticoid-induced osteoporosis*

In general, ACLASTA* was well tolerated in the glucocorticoid-induced osteoporosis trial (see **CLINICAL TRIALS**).

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

The overall percentage of adverse events was higher for the zoledronic acid group compared to the risedronate group (77.4% vs. 66.9%, respectively) driven by a higher incidence of post-dose symptoms in the ACLASTA* group that occurred within 3 days after infusion. The most common post-dose symptoms were reported as follows for ACLASTA* and risedronate, respectively: pyrexia (12.7% vs. 3.6%), arthralgia (9.9% vs. 7.4%), nausea (9.6% vs. 8.4%), myalgia (9.1% vs. 3.4%), and influenza-like illness (6% vs. 1%).

The incidence of serious adverse events was similar between the ACLASTA* and risedronate treatment groups (14.7% vs. 14.4%, respectively). The percentage of patients who withdrew from the study due to adverse events was 7.9% for the ACLASTA* group and 5.3% for the risedronate group.

- *Prevention of postmenopausal osteoporosis*

The safety of ACLASTA* in postmenopausal women with osteopenia (low bone mass) was assessed in a 2-year randomized, double-blind, placebo-controlled trial of postmenopausal women aged 45 years or older. 181 women were exposed to ACLASTA* as a single 5 mg dose administered at randomisation and 202 patients were exposed to placebo for two years (see **CLINICAL TRIALS**). All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day.

The incidence of serious adverse events was 9.4% and 11.4% for the zoledronic acid and the placebo groups, respectively. The percentage of patients who withdrew from the study due to adverse events was 1.7% and 0.5% for the zoledronic acid and the placebo groups, respectively.

The incidence of the most frequent treatment-emergent adverse events for the zoledronic acid group was reported as follows: myalgia (22.7%), pyrexia (21%), headache (20.4%), chills (18.2%), pain in extremity (16%), pain (14.9%), nausea (11.6%), fatigue (9.9%), influenza (8.3%), non-cardiac chest pain (7.7%), dizziness (6.1%), hypercholesterolemia (5.5%), sciatica (5%), bone pain (3.3%), asthenia (2.8), and hypoesthesia (2.2%).

- *Paget's disease of bone*

In general, ACLASTA* (zoledronic acid 5 mg/100 mL) was well-tolerated in Paget's disease trials. Consistent with intravenous administration of bisphosphonates, ACLASTA* has been most commonly associated with the following signs and symptoms, the majority of which occur within 3 days following the administration: influenza-like illness (transient post-dose symptoms), pyrexia, myalgia, arthralgia, and bone pain. In Paget's disease trials, one or more of these events which were suspected to be related to drug were reported in 25% of patients in the ACLASTA*-

treated group compared to 8% in the risedronate-treated group within the first 3 days following the ACLASTA* administration. After the first 3 days, rates for these symptoms were reduced to 3% for ACLASTA*-treated patients and 3% for risedronate-treated patients. The majority of these symptoms resolved within 3 days of their onset.

Clinical Trial Adverse Drug Reactions

> *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates*.

- *Postmenopausal osteoporosis*

Adverse reactions reported in at least 2.0% of the postmenopausal osteoporosis patients, and more frequently in the ACLASTA*-treated patients than placebo-treated patients are shown in Table 1.

Table 1. Adverse Reactions Occurring in ≥ 2.0% of Postmenopausal Osteoporosis Patients Receiving ACLASTA* (5 mg IV Infusion Once Yearly) and More Frequently than in Placebo - Treated Patients Over 3 Years

System Organ Class	5 mg IV ACLASTA* once per year % (N=3862)	Placebo once per year % (N=3852)
Blood and the Lymphatic System Disorders		
Anemia	4.4	3.6
Metabolism and Nutrition Disorders		
Anorexia	2.0	1.1
Nervous System Disorders		
Headache	12.4	8.1
Dizziness	7.6	6.7
Vascular Disorders		
Hypertension	12.7	12.4
Ear and Labyrinth Disorders		
Vertigo	4.3	4.0
Cardiac Disorders		
Atrial Fibrillation	2.4	1.9
Gastrointestinal Disorders		
Nausea	8.5	5.2
Diarrhea	6.0	5.6
Vomiting	4.6	3.2
Abdominal Pain Upper	4.6	3.1

System Organ Class	5 mg IV ACLASTA* once per year % (N=3862)	Placebo once per year % (N=3852)
Dyspepsia	4.3	4.0
Musculoskeletal, Connective Tissue and Bone Disorders		
Arthralgia	23.8	20.4
Myalgia	11.7	3.7
Pain in Extremity	11.3	9.9
Shoulder Pain	6.9	5.6
Bone Pain	5.8	2.3
Neck Pain	4.4	3.8
Muscle Spasms	3.7	3.4
General Disorders and Administrative Site Conditions		
Pyrexia	17.9	4.6
Influenza-like Illness	8.8	2.7
Fatigue	5.4	3.5
Chills	5.4	1.0
Asthenia	5.3	2.9
Peripheral Edema	4.6	4.2
Pain	3.3	1.3
Malaise	2.0	1.0

The incidence of post-dose symptoms decreased after each annual infusion. Table 2 presents the overall incidence of adverse events by time of onset from infusion by first, second and third infusion.

Table 2: Overall incidence of adverse events in the postmenopausal osteoporosis trial by infusion and time of onset (Safety population)

Infusion	1st infusion		2nd infusion		3rd infusion	
	ACLASTA* n (%)	Placebo n (%)	ACLASTA* n (%)	Placebo n (%)	ACLASTA* n (%)	Placebo n (%)
Total no. of patients with infusion	3862	3852	3409	3517	3106	3190
Time of onset ≤ 3 days	1726 (44.69)	571 (14.82)	570 (16.72)	462 (10.29)	316 (10.17)	270 (8.46)

Table 3: Adverse reactions occurring in at least 2% of men and women with a low trauma hip fracture receiving ACLASTA* (5 mg IV Infusion once yearly) and greater than placebo

System Organ Class	5 mg IV ACLASTA* once per year % (N=1054)	Placebo once per year % (N=1057)
Nervous System Disorders		
Headache	3.8	2.5
Vascular disorders		
Hypertension	6.8	5.4
Musculoskeletal, Connective Tissue and Bone Disorders		
Pain in extremity	5.9	4.8
Myalgia	4.9	2.6
Bone pain	3.2	1.0
Musculoskeletal pain	3.1	1.2
General Disorders and Administrative Site Conditions		
Pyrexia	8.7	3.1
Edema peripheral	5.5	5.3
Hyperthermia	2.2	0.3
Fatigue	2.1	1.2
Injury, poisoning, and procedural complications		
Post procedure complication	3.8	3.3
Osteoarthritis	5.7	4.5
Cataracts	3.0	2.3
Urinary tract infection	10.6	9.6

- *Osteoporosis in men*

The overall safety and tolerability profile of ACLASTA* in male osteoporosis was similar to that reported in the ACLASTA* postmenopausal osteoporosis trial (HORIZON-PFT). Adverse events reported in at least 2% of men with osteoporosis that were either not reported in the postmenopausal osteoporosis trial (HORIZON-PFT) or reported more frequently in the osteoporosis trial in men are presented in Table 4.

Table 4: Adverse reactions occurring in $\geq$ 2%$^{+}$ of patients with male osteoporosis receiving ACLASTA* (5-mg IV Infusion once yearly) or 70 mg once weekly of alendronate over 24 months

System Organ Class	5 mg IV Aclasta* once per year % (N=153)	Alendronate 70 mg/once weekly % (N=148)
Nervous System Disorders		
Headache	15.0	6.1
Lethargy	3.3	1.4
Eye Disorders		
Eye pain	2.0	0.0
Cardiac disorders		
Atrial fibrillation	3.3	2.0
Palpitations	2.6	0.0
Gastrointestinal disorder		
Abdominal pain$^{\Delta}$	7.9	4.1
Respiratory, thoracic and mediastinal disorders		

Dyspnea	6.5	4.7
Skin and subcutaneous tissue disorders		
Hyperhidrosis	2.6	2.0
Rash	2.0	2.7
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	19.6	6.8
Musculoskeletal pain**	12.4	10.8
Musculoskeletal stiffness	4.6	0.0
Back pain	12.4	17.6
Renal and urinary disorders		
Blood creatinine increased	2.0	0.7
General Disorders and Administrative Site Conditions		
Fatigue	17.6	6.1
Pain	11.8	4.1
Chills	9.8	2.7
Influenza like illness	9.2	2.0
Malaise	7.2	0.7
Acute phase reaction	3.9	0.0
Investigations		
C-reactive protein increased	4.6	1.4

+ includes adverse reactions that occurred in ≥2% of patients which were either not reported in the postmenopausal osteoporosis trial or reported more frequently in the trial of men with osteoporosis

$^{\Delta}$ Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR

** Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

- *Glucocorticoid-induced osteoporosis*

The overall safety and tolerability profile of ACLASTA* in the glucocorticoid-induced osteoporosis trial was similar to that reported in the ACLASTA* postmenopausal osteoporosis clinical trial (HORIZON-PFT). Adverse events reported in at least 2% of patients that were either not reported in the postmenopausal osteoporosis trial (HORIZON-PFT) or reported more frequently in the glucocorticoid-induced osteoporosis trial included the following: abdominal pain^{+} (ACLASTA* 7.5%; risedronate 5.0%), and musculoskeletal pain^{++} (ACLASTA* 3.1%; risedronate 1.7%). In addition, the following adverse events occurred more frequently than in the postmenopausal osteoporosis trial: nausea (ACLASTA* 9.6%; risedronate 8.4%), rheumatoid arthritis (ACLASTA* 6.3%; risedronate 5%), dyspepsia (ACLASTA* 5.5%; risedronate 4.3%), urinary tract infection (ACLASTA* 5%; risedronate 4.1%) and back pain (ACLASTA* 4.3%; risedronate 6.2%).

$^{+}$ Combined abdominal pain, abdominal pain upper, and abdominal pain lower as one ADR

$^{++}$ Combined musculoskeletal pain and musculoskeletal chest pain as one ADR

In the one-year glucocorticoid-induced osteoporosis trial, arrhythmia and tachycardia were reported in 1% (4 out of 416) of zoledronic acid-treated patients compared to 0.0% arrhythmia and 0.5% (2 out of 417) tachycardia in the risedronate-treated patients.

- *Prevention of postmenopausal osteoporosis*

Table 5: Adverse reactions occurring in at least 2% of women with osteopenia receiving ACLASTA* 5 mg IV infusion (administered as a single dose at randomisation) and greater than placebo in the prevention of postmenopausal osteoporosis trial over 2 years

System Organ Class	ACLASTA* 5 mg IV % (N=181)	Placebo % (N=202)
Endocrine Disorders		
Hypothyroidism	2.8	1.5
Gastrointestinal disorders		
Nausea	11.6	7.9
Constipation	7.2	6.9
Dyspepsia	6.6	5.0
Vomiting	5.0	4.5
Vascular disorders		
Hypertension	8.3	6.9
Musculoskeletal, Connective Tissue and Bone Disorders		
Myalgia	22.7	6.9
Back pain	16.6	11.9
Pain in extremity	16.0	9.9
Neck pain	6.6	5.0
Musculoskeletal pain	5.5	5.4
Pain in jaw	3.9	2.5
Bone pain	3.3	1.0
Arthritis	2.2	1.5
General Disorders and Administrative Site Conditions		
Pyrexia	21.0	4.5
Chills	18.2	3.0
Pain	14.9	3.5
Fatigue	9.9	4.0
Non-cardiac chest pain	7.7	3.0
Edema peripheral	3.9	3.5
Influenza-like illness	3.3	2.0
Asthenia	2.8	1.0
Malaise	2.2	0.5
Immune system disorders		
Seasonal allergy	2.8	1.5
Infections and infestations		
Influenza	8.3	5.9
Tooth infection	2.8	1.0
Injury, poisoning, and procedural complications		
Joint sprain	2.8	1.5
Post-traumatic pain	2.8	2.5
Metabolism and nutrition disorders		
Hypercholesterolemia	5.5	2.0
Nervous system disorders		
Headache	20.4	11.4
Dizziness	6.1	3.5
Sciatica	5.0	2.0
Hypoesthesia	2.2	2.0
Reproductive system and breast disorders		

Vulvovaginal dryness	2.2	2.0
Respiratory, thoracic and mediastinal disorders		
Cough	6.1	5.0
Pharyngolaryngeal pain	3.9	2.5
Nasal congestion	2.2	2.0

- *Paget's disease of bone*

Adverse reactions suspected (investigator assessment) to be drug related and occurring in at least 2% of the Paget's patients receiving ACLASTA* (single, 5 mg, intravenous infusion) or risedronate (30 mg, oral, daily dose for 2 months) over a 6-month study period are listed by system organ class in Table 6.

Table 6: Adverse reactions suspected[a] to be drug related occurring in at least 2% of Paget's patients receiving ACLASTA* (single 5 mg i.v. infusion) or risedronate (oral 30 mg daily for 2 months) over a 6-month follow-up period

System organ class	single 5 mg i.v. ACLASTA* administration % (N = 177)	30 mg/day x 2 months risedronate % (N = 172)
Metabolism and nutrition disorders		
Hypocalcemia	3	1
Nervous system disorders		
Headache	7	4
Lethargy	4	1
Gastrointestinal disorders		
Diarrhea	2	0
Nausea	6	2
Dyspepsia	2	2
Infections and infestations		
Influenza	3	0
Musculoskeletal, connective tissue and bone disorders		
Myalgia	6	4
Bone pain	5	1
Arthralgia	4	2
General disorders and administrative site conditions		
Influenza-like illness	9	5
Pyrexia	7	1
Rigors	7	1

Fatigue	5	2
Pain	3	2
Asthenia	2	1
Respiratory, thoracic and mediastinal disorders		
Dyspnea	2	0

[a] Investigator assessment.

Table 7: Most frequent adverse reactions occurring in at least 5% of Paget's patients in any group receiving ACLASTA* (single 5 mg i.v. infusion) or risedronate (oral 30 mg daily for 2 months) by time of occurrence

	AE occurrence ≤ 3 days after treatment initiation		AE occurrence > 3 days after treatment initiation	
System organ class	**Single 5 mg i.v. ACLASTA* administration**	**30 mg/day x 2 months risedronate**	**single 5 mg i.v. ACLASTA* administration**	**30 mg/day x 2 months risedronate**
	%	**%**	**%**	**%**
	(N = 177)	**(N = 172)**	**(N = 177)**	**(N = 172)**
Nervous system disorders				
Headache	7	4	4	6
Dizziness	3	1	5	3
Gastrointestinal disorders				
Diarrhea	2	1	4	5
Nausea	6	2	3	5
Infections and infestations				
Nasopharyngitis	1	0	5	8
Musculoskeletal, connective tissue and bone disorders				
Myalgia	7	4	1	1
Bone pain	5	1	4	4
Arthralgia	5	0	5	11
Back pain	2	1	2	7
Pain in extremity	0	1	7	7
General disorders and administrative site conditions				
Influenza-like illness	10	4	1	2
Pyrexia	7	1	1	1
Rigors	7	1	1	1
Fatigue	7	2	2	2

Local reactions: In the postmenopausal osteoporosis trial, local reactions at the infusion site such as itching, redness and/or pain have been reported in 0.7% of patients following the administration of ACLASTA* and 0.5% of patients following the administration of placebo. In the male osteoporosis trial, the event rate was 2.6% in the zoledronic acid treatment group and 1.4% in the alendronate treatment group. In the prevention of postmenopausal osteoporosis trial, the event rate was 1.1% in ACLASTA* treated patients compared to 2.0% in placebo treated patients.

Iritis/uveitis/episcleritis/conjunctivitis: Cases of iritis/uveitis/episcleritis/conjunctivitis have been reported in patients treated with bisphosphonates, including zoledronic acid. In the postmenopausal osteoporosis trial, 9 (0.2%) patients treated with ACLASTA* and 1 (< 0.1%) patient treated with placebo developed iritis/uveitis/episcleritis. Of the ocular conditions known to be related to bisphosphonate use, one case of iritis in a zoledronic acid-treated patient was reported in the HORIZON-RFT trial. In the male osteoporosis trial, two cases of conjunctivitis and one case of eye pain were reported in zoledronic acid-treated patients. In addition, one case of iritis was reported in the alendronate group. One case of conjunctivitis in a zoledronic acid-treated patient was reported in the glucocorticoid-induced osteoporosis trial. In the prevention of postmenopausal osteoporosis trial, conjunctivitis was reported in two patients (1.1%) in the zoledronic acid group. Uveitis/iritis was reported in 3 patients (1.7%) in the zoledronic acid group and in no patients (0%) in the placebo group.

Renal dysfunction: In the postmenopausal osteoporosis HORIZON-PFT trial, 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 (see Table 8). In the clinical trial for postmenopausal osteoporosis, patients with baseline creatinine clearance < 30 mL/min, urine dipstick ≥ 2+ protein or increase in serum creatinine of > 0.5 mg/dL (44.2 μmol/L) during the screening visits were excluded. Overall, there was a transient increase in serum creatinine observed within 10 days of dosing in 42 (1.8%) ACLASTA*-treated patients versus 19 (0.8%) placebo-treated patients which resolved without specific therapy. Severe renal dysfunction was rarely reported, and in most of these patients recovery was not achieved by the end of the trial. Adjudicated changes in renal function and renal adverse events over the 3 year trial are described in Tables 8 and 9.

Table 8 : **Adverse renal events associated with change in renal function confirmed by adjudication, regardless of study drug relationship, by preferred term (safety population of the HORIZON-PFT trial)**

Preferred term	ACLASTA* (N=3862) n (%)	Placebo (N=3852) n (%)
Total	90 (2.33)	74 (1.92)
Creatinine decreased renal clearance	29 (0.75)	33 (0.86)
Blood creatinine increased	22 (0.57)	6 (0.16)
Renal failure	16 (0.41)	14 (0.36)
Renal impairment	11 (0.28)	20 (0.52)
Proteinuria	9 (0.23)	6 (0.16)
Renal failure acute	9 (0.23)	2 (0.05)
Renal failure chronic	1 (0.03)	2 (0.05)
Azotemia	4 (0.10)	0 (0.00)

Table 9: **Change in renal function confirmed by adjudication, safety population of the HORIZON-PFT trial**

	Zoledronic acid (N=3862)		Placebo (N=3852)	
	n	(%)	n	(%)
Overall	178	(4.6)	157	(4.1)
Renal adverse event	175	(4.5)	154	(4.0)
Increase in serum creatinine >0.5 mg/dL	55	(1.4)	41	(1.1)
Calculated creatinine clearance <30 mL/min	62	(1.6)	57	(1.5)
Baseline calculated creatinine clearance ≤60 mL/min and declined by ≥30%	114	(3.0)	115	(3.0)

N = the number of patients in the analysis population.
n = the number of patients with the event.
(%) = n/N * 100

In the HORIZON-RFT 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.

In the male osteoporosis trial, the incidence of confirmed renal adverse events was higher in the zoledronic acid group (4.6%) relative to the alendronate group (1.4%). There was a transient increase in serum creatinine from baseline (> 0.5 mg/dL) observed 9-11 days post-infusion in 7 (4.6%) zoledronic acid-treated patients versus 1 (0.7%) alendronate-treated patient which subsequently decreased to baseline or near baseline levels. Adjudicated changes in renal function and renal adverse events over the 2 year trial are described in tables 10 and 11.

Table 10: Change in renal function confirmed by adjudication, safety population of male osteoporosis trial

	Zoledronic Acid N=153 n (%)	Alendronate N=148 n (%)
Overall	7 (4.6)	2 (1.4)
Renal adverse event	7 (4.6)	2 (1.4)
Increase in serum creatinine > 0.5 mg/dL	7 (4.6)	1 (0.7)
Creatinine clearance < 30 mL/min	2 (1.3)	1 (0.7)
Baseline calculated creatinine clearance ≤60 and declined ≥ 30%	5 (3.3)	1 (0.7)
Significant proteinuria	1 (0.7)	0 (0.0)

- N = the number of patients in the analysis population.
- n=the number of patients with the event.
(%) = n/N * 100

Table 11: **Adverse renal events associated with change in renal function, regardless of study drug relationship, by preferred term (safety population of male osteoporosis trial)**

Preferred term	ACLASTA* (N=153) n (%)	Alendronate (N=148) n (%)
Total	7 (4.6)	6 (4.1)
Blood creatinine increased	3 (2.0)	1 (0.7)
Renal impairment	2 (1.3)	1 (0.7)
Azotemia	1 (0.7)	0
Proteinuria	1 (0.7)	0
Renal failure	1 (0.7)	1 (0.7)
Creatinine renal clearance decreased	0	2 (1.4)
Renal failure acute	0	1 (0.7)

In the glucocorticoid-induced osteoporosis trial, the incidence of confirmed renal adverse events was 2.2% for zoledronic acid-treated patients versus 1.4% for risedronate-treated patients. There was a greater incidence of confirmed increases in serum creatinine from baseline (> 0.5% mg/dL) observed in 9 (2.2%) zoledronic acid-treated patients compared to 3 (0.7%) risedronate-treated patients. Adjudicated laboratory changes in renal function and renal adverse events over the one year trial are described in table 12. In addition, the incidence of renal failure was 0.7% in the zoledronic acid patients and 0.0% in the risedronate patients and the incidence of acute renal failure was 0.2% in the zoledronic acid patients and 0.5% in the risedronate patients.

Table 12: Renal laboratory criteria confirmed as a significant renal adverse event by adjudication (GIO safety population)

	Zoledronic Acid N = 416 n (%)	**Risedronate N = 417 n (%)**
Overall	**9 (2.2)**	**6 (1.4)**
Renal adverse event*	9 (2.2)	6 (1.4)
Increase in serum creatinine > 0.5 mg/dL (1)	9 (2.2)	3 (0.7)
Creatinine clearance < 30 mL/min	1 (0.2)	0 (0.0)
Baseline CrCl ≤60 and declined ≥30%	0 (0.0)	1 (0.2)
Significant proteinuria	3 (0.7)	2 (0.5)

- N = the number of patients in the analysis population.
- n=the number of patients with the event.
(%) = 100*n/N.
* The adjudication committee determined that a clinically significant renal adverse event had occurred independent of an event being reported by the investigator.

In the prevention of postmenopausal osteoporosis trial, one zoledronic acid-treated patient (0.6%) reported a creatinine clearance value of <30 mL/min. One zoledronic acid-treated patient (0.6%) reported a creatinine clearance value of <30 mL/min and a ≥30% decline in CrCl during the study from a baseline value of ≤60 mL/min. One zoledronic acid-treated patient (0.6%) had renal failure confirmed by adjudication. No patients in the placebo group had renal failure, acute renal failure, or decreased CrCl.

Bronchoconstriction in ASA (acetylsalicylic acid) Sensitive Asthma Patients: While not observed in clinical trials with ACLASTA* there have been previous reports of bronchoconstriction in ASA-sensitive patients receiving bisphosphonates.

Osteonecrosis of the Jaw (ONJ): In the postmenopausal osteoporosis trial (HORIZON-PFT) in 7,736 patients, symptoms consistent with ONJ occurred in one patient treated with ACLASTA* and one patient treated with placebo. Both cases resolved after appropriate treatment. ONJ has not been observed in the HORIZON-RFT, the male osteoporosis, the glucocorticoid-induced osteoporosis, the prevention of postmenopausal osteoporosis, or the Paget's disease trials with ACLASTA*.

Avascular necrosis and delayed fracture union/non-union: In the postmenopausal osteoporosis trial, 3 cases (2 zoledronic acid, 1 placebo patients) were confirmed to be cases of delayed union of fracture, one of which occurred in a patient with fracture that pre-existed at baseline. 7 cases of avascular necrosis (zoledronic acid = 4, placebo = 3) were reported (6 cases occurred in the hip region and 1 case was in the knee region). In the HORIZON-RFT trial, 3 (0.3%) patients had confirmed events of delayed union/non-union in the zoledronic acid group (2 incident hip and 1 humerus) and 3 (0.3%) patients had confirmed events in the placebo group (1 incident hip, 1 contralateral hip, and 1 shoulder). Six (0.6%) patients in the zoledronic acid group and 3 (0.3%) patients in the placebo group had confirmed events of avascular necrosis, all of which involved the hip. In the glucocorticoid-induced osteoporosis trial, 5 cases of avascular necrosis (zoledronic acid = 2 and risedronate = 3) were reported.

Abnormal Hematologic and Clinical Chemistry Findings

Serum creatinine and creatinine clearance-

- *Postmenopausal osteoporosis*

A transient increase in serum creatinine (> 0.5 mg/dL (44.2μmol/L)) was observed within 10 days following administration in 42 (1.8%) ACLASTA*-treated patients versus 19 (0.8%) placebo-treated patients (see **ADVERSE REACTIONS**-*Renal dysfunction*).

Severe renal dysfunction was rarely reported, and in most of these patients recovery was not achieved by the end of the trial. Adjudicated changes in renal function and renal adverse events over the 3 year trial are described in Tables 8 and 9 (see **ADVERSE REACTIONS**).

- *Osteoporosis in men*

There was a transient increase in serum creatinine from baseline (> 0.5 mg/dL) observed 9-11 days post-infusion in 7 (4.6%) zoledronic acid-treated patients versus 1 (0.7%) alendronate-treated patient which subsequently decreased to baseline or near baseline levels. Adjudicated changes in renal function and renal adverse events over the two year trial are described in Tables 10 and 11 (see **ADVERSE REACTIONS**).

- *Glucocorticoid-induced osteoporosis*

Confirmed increases in serum creatinine from baseline (> 0.5% mg/dL) were observed in 9 (2.2%) zoledronic acid-treated patients compared to 3 (0.7%) risedronate-treated patients. Adjudicated laboratory changes in renal function and renal adverse events over the one year trial are described in Table 12.

- *Paget's disease of bone*

No clinically significant changes in serum creatinine have occurred in the Paget's disease trials.

Hypocalcemia-

- *Postmenopausal osteoporosis*

In the postmenopausal osteoporosis trial (HORIZON-PFT), mild, transient, asymptomatic decrease in calcium levels, have been observed with ACLASTA* primarily after the first dose. 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 this trial, patients received supplemental daily doses of elemental calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU).

In the prevention of postmenopausal osteoporosis trial, one patient (0.5%) treated with ACLASTA* (administered at randomization and at Month 12, see **CLINICAL TRIALS**) had a confirmed event of hypocalcemia with a notable decline of calcium level of 1.70 mmol/L from a screening value of 2.17 mmol/L one month following the first infusion of ACLASTA*.

- *Paget's disease of bone*

In the Paget's disease trials, early, transient decreases in serum calcium and phosphate levels, that were usually asymptomatic, have been observed. Approximately 21% of subjects had serum calcium levels <2.1 mmol/L (<8.4 mg/dL) 9-11 days following ACLASTA* infusion. In the Paget's disease trials, symptomatic hypocalcemia was observed in approximately 1% of patients, all of which resolved.

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

Post-Market Adverse Drug Reactions

Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or clearly establish a causal relationship to ACLASTA* exposure.

The following adverse reactions have been identified during the post approval use of this drug: hypocalcaemia, arthralgia, myalgia, flu-like symptoms, fever and headache. Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema, and very rare cases of anaphylactic reactions/shock have also been reported.

DRUG INTERACTIONS

Overview

ACLASTA* is not metabolized in humans. Zoledronic acid is eliminated by renal excretion (see **PART II, PHARMACOLOGY, Pharmacokinetics**).

Drug-Drug Interactions

No *in vivo* drug interaction studies have been performed for ACLASTA*. In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. *In vitro* mean zoledronic acid protein binding in human plasma ranged from 28% at 200 ng/mL to 53% at 50 ng/mL. *In vivo* studies showed that zoledronic acid is not metabolized, and is excreted into the urine as the intact drug.

Table 13: Established or Potential Drug-Drug Interactions
(Legend: CT = Clinical Trial; T = Theoretical)

Zoledronic acid	Ref	Effect	Clinical comment
Aminoglycosides	T	↓ serum calcium level	Caution is advised when bisphosphonates, including zoledronic acid, are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. This effect has not been reported in zoledronic acid clinical trials.
Loop Diuretics	T	↑ risk of hypocalcemia	Caution should also be exercised when ACLASTA* is used in combination with loop diuretics due to an increased risk of hypocalcemia.
Nephrotoxic Drugs	T		Caution is indicated when ACLASTA* is used with other potentially nephrotoxic drugs such as nonsteroidal anti-inflammatory drugs.

Drug-Food Interactions

The interaction of zoledronic acid has not been studied with regards to food.

Drug-Herb Interactions

The interaction of zoledronic acid with herbal medications or supplements has not been studied.

Drug-Laboratory Interactions

No data suggest that zoledronic acid interferes with laboratory tests.

Drug-Lifestyle Interactions

Specific drug-lifestyle interaction studies have not been conducted with zoledronic acid.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

- *Treatment of postmenopausal osteoporosis*

The recommended dose is a once yearly single intravenous infusion of ACLASTA*.

- *Treatment to increase bone mineral density in men with osteoporosis*

The recommended dose is a once yearly single intravenous infusion of ACLASTA*.

- *Treatment and prevention of glucocorticoid-induced osteoporosis, to increase bone mineral density*

The recommended dose is a once yearly single intravenous infusion of ACLASTA*.

- *Prevention of postmenopausal osteoporosis*

The recommended dose is a single intravenous infusion of ACLASTA*.

Re-treatment for prevention of postmenopausal osteoporosis

Specific re-treatment data after 24 months are not available. After one treatment with ACLASTA* 5 mg intravenous infusion in the prevention of postmenopausal osteoporosis trial, the effect on lumbar spine BMD was observed for up to 24 months (see **PART II – CLINICAL TRIALS-Table 25**). There are no clinical efficacy data available beyond the 24 months' duration of the trial.

- *Treatment of Paget's disease of bone*

The recommended dose is a single intravenous infusion of ACLASTA*.

ACLASTA* (5 mg in 100 mL ready to infuse solution) is administered intravenously via a vented infusion line.

Patients should be advised to be appropriately hydrated before the administration of ACLASTA*.

The infusion time **must not be less than 15 minutes** (see **WARNINGS AND PRECAUTIONS**) and the infusion rate should be constant. ACLASTA* should only be given by intravenous infusion. The total volume of the ACLASTA* solution should be infused. ACLASTA* must never be given as a bolus injection.

Renal

Zoledronic acid is not recommended for use in patients with severe renal impairment (creatinine clearance < 30mL/min). No dosage adjustment is necessary in patients with a creatinine clearance ≥ 30 mL/min. Patients must be appropriately hydrated prior to administration of ACLASTA*, and this is especially important for patients receiving diuretic therapy (see **WARNINGS AND PRECAUTIONS**).

Calcium and vitamin D intake

It is strongly advised that patients receive adequate calcium and vitamin D supplementation especially in the days before and following ACLASTA* administration (see **WARNINGS AND PRECAUTIONS**). All patients should be counseled regarding the importance of calcium and vitamin D supplementation in maintaining serum calcium levels, and on the symptoms of hypocalcemia. The recommended daily vitamin D supplement should be determined by the treating physician based on the patient's individual needs. In the postmenopausal osteoporosis trial (HORIZON-PFT), patients received 1000 to 1500 mg of elemental calcium plus 400 to 1200 IU of vitamin D supplements per day.

Post-Infusion Management

About 25% of patients experienced transient post-dose symptoms within the first 3 days of their ACLASTA* infusion (see **ADVERSE REACTIONS**). Symptomatic management can be considered on an individual basis. No anaphylactic reactions have been observed in the clinical trials but good medical practice dictates caution (see **CONTRAINDICATIONS**).

Re-treatment of Paget's disease

Specific re-treatment data are not available. After one treatment with ACLASTA* in Paget's disease, an extended remission period of up to 19 months was observed in 98% (143/146) of patients (see **PART II – CLINICAL TRIALS– Figure 5**).

OVERDOSAGE

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

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

ACLASTA* belongs to the class of nitrogen containing bisphosphonates and acts primarily on bone in order to protect the bone against excessive and abnormal osteoclastic and osteoblastic activity. It is an inhibitor of osteoclast-mediated bone resorption.

The selective action of bisphosphonates on bone is based on their high affinity for mineralized bone. Intravenously administered zoledronic acid rapidly partitions to bone and, as with 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 (FPP) which is critical for the regulation of a variety of cell processes important for osteoclast function, but this does not exclude other inhibitory mechanisms. In vitro assays have demonstrated that zoledronic acid has the highest potency to inhibit FPP synthase amongst available nitrogen containing bisphosphonates. This higher inhibition of FPP synthase correlated with a greater anti-resorptive potency as observed *in vivo* in rats. 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

In long-term animal studies, zoledronic acid inhibits bone resorption without adversely affecting bone formation, mineralization or mechanical properties of bone. Histomorphometric data from long-term rat and monkey studies showed the typical response of bone to an anti-resorptive agent with a dose-dependent reduction in osteoclastic activity and in 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.

Bone histology and bone markers

- *Postmenopausal osteoporosis*

Dynamic bone histomorphometry was evaluated in 93 postmenopausal patients with osteoporosis after being treated with 3 annual doses of ACLASTA*. These results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defects. Microcomputed tomography analysis demonstrated preservation of trabecular bone architecture in patients treated with ACLASTA* compared to placebo. In summary, the bone biopsies and biomarkers indicate ongoing bone remodeling with qualitatively normal bone.

In the osteoporosis treatment trial, the effect of ACLASTA* treatment on markers of bone resorption (serum beta-C-telopeptides (b-CTx)) and bone formation (bone specific alkaline phosphatase (BSAP), serum N-terminal propeptide of type I collagen (P1NP)) was evaluated in patients (subsets ranging from 517 to 1,246 patients) at periodic intervals. Treatment with a 5 mg annual dose of ACLASTA* reduces bone turnover markers to the pre-menopausal range with an approximate 55% reduction in b-CTx, a 29% reduction in BSAP and a 52% reduction in P1NP over 36 months. There was no progressive reduction of bone turnover markers with repeated annual dosing.

ACLASTA* treatment rapidly reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 months. Thereafter bone markers stabilized within the pre-menopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing

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

- *Paget's disease*

Bone histology was evaluated in 7 patients with Paget's disease 6 months after being treated with ACLASTA*. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodeling and no evidence of mineralization defect. These results were consistent with biochemical marker evidence of normalization of bone turnover.

Pharmacokinetics

Pharmacokinetic data in patients with postmenopausal osteoporosis, osteoporosis and Paget's disease of bone are not available.

Distribution: Single or multiple (q 28 days) 5-minute or 15-minute infusions of 2, 4, 8 or 16 mg zoledronic acid were given to 64 cancer patients. The post-infusion decline of zoledronic acid concentrations in plasma was consistent with a triphasic process showing a rapid decrease from peak concentrations at end-of-infusion to <1% of C_{max} 24 hours post infusion with population half-lives of $t_{1/2\alpha}$ 0.24 hours and $t_{1/2\beta}$ 1.87 hours for the early disposition phases of the drug. The terminal elimination phase of zoledronic acid was prolonged, with very low concentrations in plasma between days 2 and 28 post infusion, and an estimated terminal elimination half-life $t_{1/2\gamma}$ of 146 hours. The area under the plasma concentration versus time curve (AUC_{0-24h}) of zoledronic acid was dose proportional from 2 to 16 mg. The accumulation of zoledronic acid measured over three cycles was low, with mean AUC_{0-24h} ratios for cycles 2 and 3 versus 1 of 1.13 ± 0.30 and 1.16 ± 0.36, respectively.

In vitro and *ex vivo* studies showed low affinity of zoledronic acid for the cellular components of human blood. Binding to human plasma proteins was approximately 43-55% at 50 ng/mL, a concentration of zoledronic acid within the range observed after 15 minute infusion of the 5 mg

dose. It was only slightly less (about 43%) at 500 ng/mL a concentration of zoledronic acid greater than the expected C_{max}. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Metabolism: Zoledronic acid is not metabolized in humans. It was found to have little or no capacity as a direct acting and/or irreversible metabolism-dependent inhibitor of P450 enzymes. Therefore, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolized via the cytochrome P450 enzyme systems. In animal studies, <3% of the administered intravenous dose was found in the feces, with the balance either recovered in the urine or taken up by bone, indicating that the drug is eliminated intact via the kidney.

Excretion: In 64 patients, on average 39 ± 16% (± SD) of the administered zoledronic acid dose was recovered in the urine within 24 hours with only trace amounts of drug found in urine after 48 hours. The cumulative percentage of drug excreted in the urine over 0-24 hours was independent of dose. The balance of drug not recovered in urine over 0-24 hours, representing drug presumably bound to bone, is slowly released back into the systemic circulation, giving rise to the observed prolonged low plasma concentrations. The 0-24 hour renal clearance of zoledronic acid was 3.7 ± 2.0 L/h (± SD).

Zoledronic acid clearance was independent of dose but dependent upon the patient's creatinine clearance. In a study with patients, increasing the infusion time of a 4 mg dose of zoledronic acid from 5 minutes (n=5) to 15 minutes (n=7) resulted in a 34% decrease in the zoledronic acid plasma concentration at the end of the infusion ([mean ± SD] 403 ± 118 ng/mL vs. 264 ± 86 ng/mL) and a 10% increase in the total AUC (378 ± 116 ng x h/mL vs. 420 ± 218 ng x h/mL). The difference between the AUC means was not statistically significant.

Special Populations and Conditions

Pediatrics: Pharmacokinetic data of zoledronic acid in pediatric patients are not available.

Geriatrics: The pharmacokinetics of zoledronic acid were not affected by age in patients who ranged in age from 38 years to 84 years.

Gender: The pharmacokinetics of zoledronic acid were not affected by gender.

Race: The pharmacokinetics of zoledronic acid were not affected by race.

Hepatic Insufficiency: No clinical studies were conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of zoledronic acid. Zoledronic acid does not inhibit human P450 enzymes *in vitro*, shows no biotransformation, suggesting no relevant role of liver function in the pharmacokinetics of zoledronic acid and no required dosage adjustment. Following an intravenous dose of 20 nCi 14C-zoledronic acid in a patient with cancer and bone metastases, only a single radioactive species with chromatographic properties identical to those of parent drug was recovered in urine, which suggests that zoledronic acid is not metabolized.

Renal Insufficiency: The pharmacokinetic studies conducted in 64 patients represented typical clinical populations with normal to moderately impaired renal function. Compared to patients with normal renal function (creatinine clearance > 80 mL/min, N=37), patients with mild renal impairment (creatinine clearance =50 to 80 mL/min, N=15) showed an average increase in

plasma AUC of 15%, whereas patients with moderate renal impairment (creatinine clearance =30 to 50 mL/min, N=11) showed an average increase in plasma AUC of 43%. No dosage adjustment is required in patients with a creatinine clearance of ≥ 30 mL/min. Based on population PK/PD modeling, the risk of renal deterioration appears to increase with AUC, the risk is doubled at a creatinine clearance of 10 mL/min. Zoledronic acid is not recommended for patients with severe renal impairment (creatinine clearance < 30 mL/min) due to lack of adequate clinical experience in this population (see **WARNINGS AND PRECAUTIONS**).

STORAGE AND STABILITY

Store ACLASTA* at room temperature between 15°C-30°C. The ACLASTA* bottle is for single use only. ACLASTA* should be used immediately and the entire volume in the bottle should be administered. Any unused solution should be discarded.

SPECIAL HANDLING INSTRUCTIONS

Note: **Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.**

- Solution does not need to be diluted before administration.
- Strict adherence to the intravenous route is recommended for the parenteral administration of ACLASTA*.
- The entire volume in the bottle should be administered.

Compatibility

- ACLASTA* must not be allowed to come in contact with any calcium- or other divalent cations-containing solutions, and it should be administered as a single dose through a separate vented infusion line.
- ACLASTA* is considered to be compatible with the typical vented infusion line materials polyvinylchloride (PVC), polyurethane (PUR) and polyethylene (PE).

DOSAGE FORMS, COMPOSITION AND PACKAGING

ACLASTA* (zoledronic acid 5 mg/100 mL) is available as a ready-to-use solution for intravenous infusion (sterile solution at a pH between 6.0 to 7.0). Each plastic bottle contains 5.330 mg zoledronic acid monohydrate (equivalent to 5 mg zoledronic acid on an anhydrous basis), 4950 mg of mannitol, 30 mg of sodium citrate, and 100 mL water for injection. The colourless plastic bottle is sealed with a rubber stopper which is held in place with an aluminum cap with flip component. The stopper is made of bromobutyl rubber coated with fluorocarbon polymer and contains no latex. The ACLASTA* plastic bottle comes with a convenient plastic hanger to facilitate the infusion set-up.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

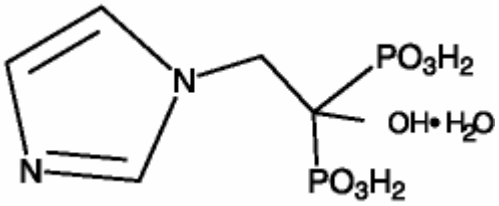
Common name: zoledronic acid

Chemical name: (1-Hydroxy-2-imidazol-1-ylethylidene) disphosphonic acid, monohydrate

Molecular formula: $C_5H_{10}N_2O_7P_2 \bullet H_2O$

Molecular mass: 290.1 g/Mol

Structural formula:



Physicochemical properties: Zoledronic acid monohydrate is a white crystalline powder. Zoledronic acid monohydrate is highly soluble in 0.1N sodium hydroxide solution, sparingly soluble in water and 0.1N hydrochloric acid, and practically insoluble in organic solvents. The pH of a 0.7% solution of zoledronic acid in water is approximately 2.0.

CLINICAL TRIALS

Postmenopausal osteoporosis

Study demographics and trial design

The efficacy and safety of ACLASTA* were demonstrated in a Pivotal Fracture Trial (PFT) for the treatment of osteoporosis in postmenopausal women (HORIZON-PFT: Health Outcomes & Reduced Incidence with Zoledronic Acid Once Yearly – Pivotal Fracture Trial), a randomized, double-blind, placebo-controlled, multinational study of 7,736 women aged 65-89 years. Entry criteria were either: a femoral neck Bone Mineral Density (BMD) T- score less than or equal to -1.5 and at least two mild or one moderate existing vertebral fracture(s); or a femoral neck BMD T-score less than or equal to -2.5 with or without evidence of an existing vertebral fracture(s). ACLASTA* was administered once a year for three consecutive years, as a single 5 mg dose in 100 mL solution infused over at least 15 minutes.

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. Participants were placed into 1 of 2 treatment strata (Stratum I and Stratum II). 7,736 women were evaluated for the incidence of hip and all clinical fractures. All clinical fractures were verified based on the radiographic and/or clinical evidence. Of these, 5,661 women were evaluated annually for incidence of vertebral fractures. In Stratum I, 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 in Stratum II. Concomitant osteoporosis therapy included: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone (not approved in Canada); 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.

Non-vertebral fractures represent fractures at sites other than the vertebral spine. Clinical fractures represent fractures that are clinically apparent and usually present with pain. These include both clinical vertebral and clinical non-vertebral fractures such as at the hip and wrist. All clinical fractures were verified based on the radiographic and/or clinical evidence. All efficacy assessments of non-vertebral fractures and clinical fractures are based on both Stratum I and Stratum II. Although morphometric vertebral fracture endpoints are based on Stratum I alone, clinical vertebral fracture because it is a clinical fracture endpoint, is assessed across both Stratum I and Stratum II.

Table 14: Summary of patient demographics for clinical trial in postmenopausal osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N= population treated)		Mean age (Range)		Gender Male/Female (N= randomized patients)
			Aclasta*	Placebo	Aclasta*	Placebo	
2301 HORIZON-PFT	Multicenter, randomized, double-blind, placebo-controlled efficacy and safety trial	Three doses of 5 mg ACLASTA* /100 mL over 15 min (or placebo infusion) per 12 months Duration: 36 months	N = 3862	N = 3852	73.1 (64-89)	73.0 (64-89)	7736 (0% male/ 100% female)

Study results

Effect on Vertebral Fracture in the HORIZON-PFT study

ACLASTA* significantly reduces the relative risk of new vertebral fractures by 70% (absolute reduction in fracture incidence 7.6% over 3 years), over three years, as compared to placebo, and this reduction was demonstrated as early as the one year timepoint (see Table 15).

Table 15: Summary of vertebral fracture efficacy at 12 months, 24 months, and 36 months (Stratum I)

Endpoints	N		Patients with new vertebral fractures		Absolute reduction in fracture incidence % (95% CI)	Relative risk reduction in fracture incidence % (95% CI)	P-value
	Aclasta*	Placebo	Aclasta* n (%)	Placebo n (%)			
At least one new vertebral fracture (over 12 months)	2822	2853	42 (1.5)	106 (3.7)	2.2 (1.4 - 3.1)	60 (43 - 72)	< 0.0001
At least one new vertebral fracture (over 24 months)	2822	2853	63 (2.2)	220 (7.7)	5.5 (4.4 - 6.6)	71 (62 - 78)	< 0.0001
At least one new vertebral fracture (over 36 months)	2822	2853	92 (3.3)	310 (10.9)	7.6 (6.3 - 9.0)	70 (62 - 76)	< 0.0001

ACLASTA* significantly decreased the relative risk of new vertebral fractures at 12 months (relative risk reduction 60%) (absolute risk reduction 2.2%), at 24 months (relative risk reduction 71%) (absolute risk reduction 5.5%), and at 36 months (relative risk reduction 70%) (absolute risk reduction 7.6%) (all $p < 0.0001$).

ACLASTA* significantly decreased the relative risk of one or more new/worsening vertebral fractures at 1 year as compared to placebo (relative risk reduction 58%) (absolute reduction in fracture incidence 2.3%), 2 years (68%) (absolute reduction in fracture incidence 5.7%) and 3 years (68%) (absolute reduction in fracture incidence 7.9%) (all p<0.0001). ACLASTA* significantly decreased the relative risk at 1 year as compared to placebo, of at least one new moderate or severe vertebral fracture at 1 year (60%; absolute reduction in fracture incidence 1.9%), 2 years (71%; absolute reduction in fracture incidence 4.6%) and 3 years (70%; absolute reduction in fracture incidence 6.6%) (all p<0.0001). ACLASTA* significantly decreased the relative risk of at least 2 new vertebral fractures over 3 years as compared to placebo (89%; absolute reduction in fracture incidence 2.1%) (p<0.0001).

These 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% relative risk reduction in the risk of vertebral fractures (absolute reduction in fracture incidence 7.2%) compared to placebo patients (p<0.0001).

Effect on Hip fracture over 3 years in the HORIZON-PFT study

ACLASTA* significantly reduced the risk of new hip fractures by 41% (RR 0.60) at 3 years compared to placebo (p= 0.0024). The hip fracture event rate was 1.45% for ACLASTA*-treated patients compared to 2.50% for placebo-treated patients. ACLASTA* demonstrated a 1.1% absolute reduction and 41% reduction in the risk of hip fractures over a median duration of follow-up of 3 years. The incidence of first hip fracture over time is displayed in Table 16.

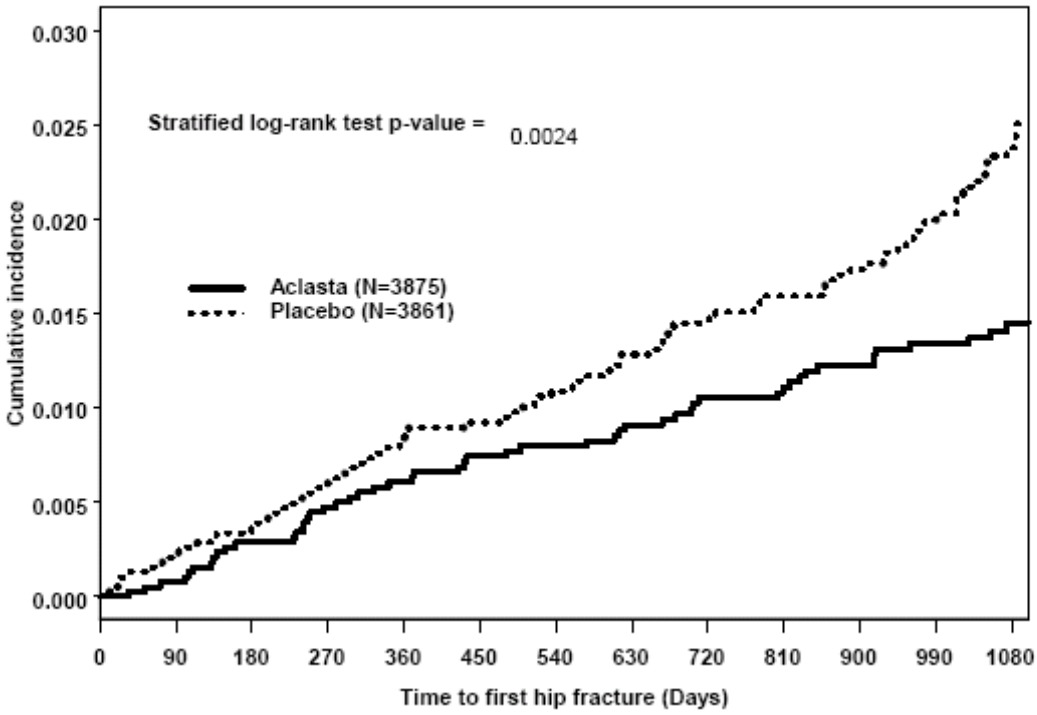
Table 16: Between-treatment comparison of the incidence of the first hip fracture over time (Stratum I and II)

Treatment	N	n (%)[1]	Hazard ratio (95% CI)[2]	P-value[3]
Aclasta*	3875	52 (1.44)	0.59 (0.42 -0.83)	0.0024
Placebo	3861	88 (2.49)		

[1] n is the number of patients with hip fracture over time, and % is Kaplan-Meier estimate of event rate at Month 36.
[2] The hazard ratio of ACLASTA* versus placebo and the 95% confidence interval (CI) are based on a stratified Cox proportional hazards regression model with treatment as a factor and stratified by stratum. A hazard ratio < 1 implies that patients treated with ACLASTA* have a lower risk of experiencing a hip fracture than patients treated with placebo.
[3] The p-value is calculated from a stratified log-rank test analyzed by study population stratum.

The time to first hip fracture is shown in Figure 1.

Figure 1: **Cumulative risk reduction of hip fracture over 3 years (Strata I + II)**



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

Effect observed in the Stratum in the HORIZON-PFT study

Participants of the osteoporosis study were placed into one of the 2 treatment strata (Stratum I: patients not taking concomitant osteoporosis therapy and Stratum II: patients who were allowed taking concomitant osteoporosis therapy). The study was not powered a priori to evaluate differences across subgroups. However, despite this, zoledonic acid demonstrated a 51% reduction in the risk of hip fractures in patients who were bisphosphonate-naïve, this corresponds to an absolute risk reduction of 1.4% (HR=0.49, 95% CI: 0.33 to 0.72; p< 0.001). In contrast, a relatively small number of patients who were previously treated with bisphosphonates had numerically more hip fractures in the zoledronic acid treatment group (12/565 patients) compared to the placebo group (8/557 patients), this corresponds to an absolute risk increase of 0.8%. (HR=1.49, 95% CI: 0.61 to 3.64; p =0.3817).

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

Effect on All Clinical Fractures in the HORIZON-PFT study

ACLASTA* demonstrated superiority to placebo in reducing the incidence of all clinical fractures, clinical (symptomatic) vertebral and non-vertebral fractures (excluding finger, toe, facial, and clinical thoracic and lumbar vertebral fractures). All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 17.

Table 17: Between –Treatment Comparisons of the Incidence of Clinical Fracture Variables Over 3 Years

Outcome	Aclasta* (N=3875) Event rate n (%)	Placebo (N=3861) Event rate n (%)	Absolute reduction in fracture incidence (%) (95% CI)	Relative risk reduction in fracture incidence (%) (95% CI)
Any clinical fracture (1)	308 (8.4)	456 (12.8)	4.4 (3.0, 5.8)	33 (23, 42) p-value <0.001
Clinical vertebral fracture (2)	19 (0.5)	84 (2.6)	2.1 (1.5, 2.7)	77 (63, 86) p-value <0.001
Non-vertebral fracture (3)	292 (8.0)	388 (10.7)	2.7 (1.4, 4.0)	25 (13, 36) p-value <0.0001

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

Effect on Bone Mineral Density (BMD) in the HORIZON-PFT study

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) ($p< 0.0001$ for all). Treatment with ACLASTA* resulted in an 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 ($p< 0.0001$ for all).

Change in Patients Height in the HORIZON-PFT study

Standing height was measured annually using a stadiometer at baseline and months 12, 24 and 36. The ACLASTA*-treated patients had significantly less reduction in height at 3 years compared to placebo (4.2 mm vs. 6.7 mm, respectively ($p< 0.0001$)).

The efficacy and safety of ACLASTA* in the prevention of clinical fractures in osteoporotic patients who suffered a recent low-trauma hip fracture were evaluated in the prevention of clinical fractures after hip fracture trial HORIZON-RFT. This was a randomized, double-blind, placebo-controlled, multinational fracture endpoint-driven study of 2,127 men (23.88%) and women (76.12%) aged 50-95 years (mean age of 74.5) and 91% of the patients were Caucasian. The incidence of clinical fractures, including vertebral, non-vertebral, and hip fractures, was evaluated in patients with a recent (within 90 days) low-trauma hip fracture who were followed

for an average of 2 years on study drug. The following concomitant osteoporosis therapies were allowed: calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone, dehydroepiandrosterone (DHEA(s)), ipriflavone, and testosterone, as hormone replacement in the case of hypogonadal men; but excluded other bisphosphonates and parathyroid hormone.

ACLASTA* was administered once a year as a single 5 mg dose in 100 mL solution, infused over at least 15 minutes, until at least 211 patients had confirmed clinical fractures in the study population. All participants received 1000 to 1500 mg of elemental calcium plus 800 to 1200 IU of vitamin D supplementation per day. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Table 18: Summary of patient demographics in the HORIZON-RFT study

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects**		**Mean age (Range)**		**Gender**
			Aclasta*	Placebo	Aclasta*	Placebo	Male/Female (N= randomized patients)
2310 HORIZON-RFT	Multi-national, randomized, double-blind, placebo-controlled efficacy and safety trial	Single dose of 5 mg ACLASTA* /100 mL over 15 min (or placebo infusion) per 12 months Duration: Event-driven	N = 1065	N = 1062	74.4 (65-84)	74.6 (65-849)	2127 (23.88% male/ 76.12% female)

Effect on All Clinical Fractures in the HORIZON-RFT study

Treatment with ACLASTA* significantly reduced the incidence of any clinical fracture by 35%. There was also a 46% reduction in the risk of a clinical vertebral fracture; a 27% reduction in the risk for non-vertebral fractures with ACLASTA*. There was a non-significant 30% risk reduction for a subsequent hip fracture for the ACLASTA* group compared to placebo. There was a non-significant reduction in the incidence of clinical fractures in men compared to placebo, although the study was not powered to determine significance in this subgroup; the incidence of clinical fracture was 7.5% in men treated with ACLASTA* versus 8.7% for placebo.

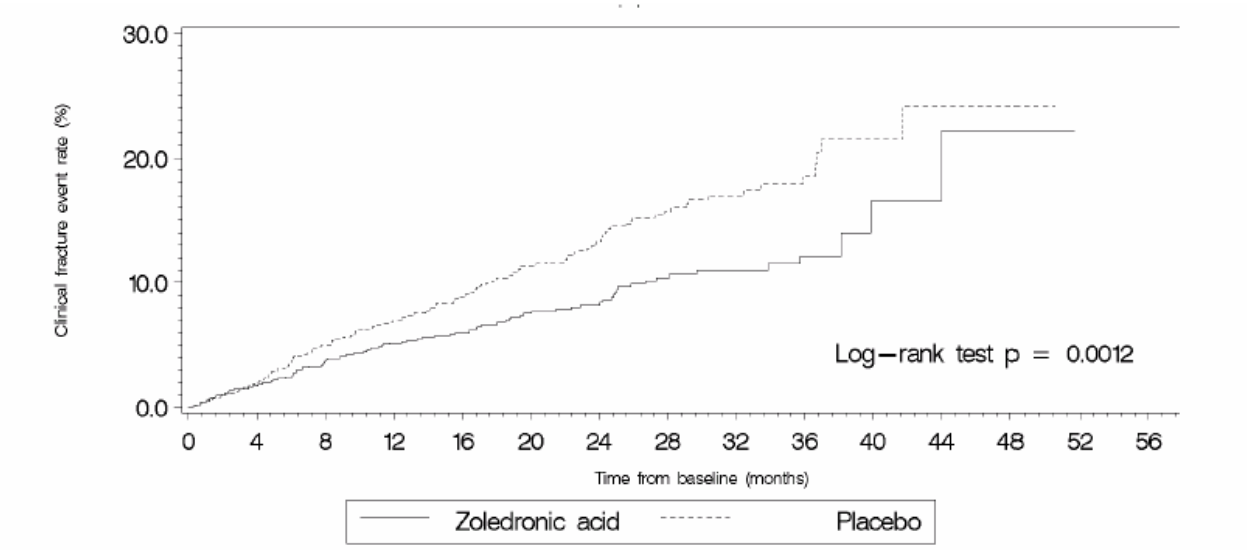
Table 19 Between treatment comparisons of the incidence of key clinical fracture variables

Outcome	ACLASTA* (N=1064) event rate (%)	Placebo (N=1063) event rate (%)	Absolute reduction in fracture event rate (%) (95% CI)	Relative risk reduction in fracture incidence (%) (95% CI)	P-value
Any clinical fracture (1)	8.6	13.9	5.3 (2.3, 8.3)	35 (16, 50)	0.001
Clinical vertebral fracture (2)	1.7	3.8	2.1 (0.5, 3.7)	46 (8, 68)	0.02
Non-vertebral fracture (1)	7.6	10.7	3.1 (0.3,5.9)	27 (2,45)	0.03
Hip fracture	2.0	3.5	1.5 (-0.1, 3.1)	30 (-19, 59)	0.18

(1) Excluding finger, toe and facial fractures
(2) Including clinical thoracic and clinical lumbar vertebral fractures

The incidence of first clinical fracture with ACLASTA*, represents a 35% reduction in the risk of clinical fractures over time for the ACLASTA* group versus the placebo group (Hazard ratio of 0.65 (95% CI: 0.50 to 0.84) (p = 0.0012)).

Figure 2: Kaplan-Meier curve of time to first clinical fracture – placebo-controlled study, Study 2310 (ITT population)



Effect on Bone Mineral Density (BMD) in the HORIZON-RFT study

Treatment with ACLASTA* resulted in significant increases of BMD measures for the total hip and femoral neck (5.4% increase at the total hip and 4.3% increase at the femoral neck over 24 months as compared to placebo).

Osteoporosis in men

Study demographics and trial design

The efficacy and safety of ACLASTA* in men with osteoporosis were assessed in a randomized, multicentre, double-blind, active-controlled study of 302 men aged 25-86 years (mean age of 64 years) and 95.4% Caucasian. 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 solution 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.

Table 20: Summary of patient demographics for clinical trial in male osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N= population treated)		Mean age (Range)		Gender Male/Female (N= randomized patients)
			Aclasta*	alendronate	Aclasta*	alendronate	
M2308	Multicenter, randomized, double-blind, double-dummy, active-controlled efficacy trial	One dose of 5 mg ACLASTA* /100 mL over 15 min (or placebo infusion) per 12 months Alendronate (or placebo) 70 mg once a week Duration: 24 months	N = 154	N = 148	64.5 (25-85)	63.5 (29-86)	302 (100% male/ 0% female)

Study results

Effect on Bone Mineral Density (BMD)

An annual infusion of ACLASTA* was non-inferior to weekly alendronate for the percentage change in lumbar spine BMD at month 24 relative to baseline (ACLASTA* 6.1% compared to alendronate 6.2%).

Glucocorticoid-induced osteoporosis

Study demographics and trial design

The efficacy and safety of ACLASTA* in the glucocorticoid-induced osteoporosis trial were assessed in a randomized, multicentre, double-blind, stratified (treatment and prevention), active-controlled study of 833 Caucasian (95.1%), 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 randomization, and those in the treatment subpopulation were treated with glucocorticoids ≥ 3 months prior to randomization. The duration of the trial was one year. Patients were randomized 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 followed by superiority 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.

Table 21: Summary of patient demographics for clinical trial in Glucocorticoid-induced osteoporosis

Study #	Trial design	Dosage, route of administration and duration	Study subjects (N= population treated)		Mean age (Range)		Gender Male/Female (N= randomized patients)
			Aclasta*	risedronate	Aclasta*	risedronate	
O2306	Randomized, double-blind, double-dummy, stratified, active controlled parallel group efficacy and safety trial	1 dose of 5 mg ACLASTA* /100 mL over 15 min Risedronate 5 mg p.o./once daily Duration: 12 months	Treatment arm: N = 272 Prevention arm: N = 144	Treatment arm: N = 273 Prevention arm: N = 144	54.3 (18-83)	54.6 (19-84)	833 Aclasta*: (31.5% male/ 68.5% female) Risedronate: (32.1% male/ 67.9% female)

Study Results

Effect on Bone Mineral Density (BMD)

The increases in lumbar spine BMD at 12 months were significantly greater in the ACLASTA*-treated group compared to the risedronate group in both the treatment and prevention subpopulations. The results at this skeletal site were also statistically significant for the subgroup of men and postmenopausal women but were not significant for the subgroup of pre-menopausal women when analyzed separately for the treatment and the prevention subpopulations, although the study was not powered to determine significance in these subgroups.

Table 22: Effects of ACLASTA* and risedronate on bone mineral density of the lumbar spine

Population	Location		Aclasta* n LS Mean (SE)	Risedronate n LS Mean (SE)	LS Mean difference (95% CI) [1]	p-value
Treatment	Lumbar spine	All	249 4.06 (0.28)	245 2.71 (0.28)	1.36 (0.67, 2.05)	0.0001
		men	75 4.69 (0.52)	77 3.27 (0.52)	1.42 (0.20, 2.64)	0.0232
		Pre-menopausal women	63 3.12 (0.56)	60 1.74 (0.54)	1.38 (-0.08, 2.85)	0.0636
		Postmenopausal women	111 3.68 (0.52)	108 2.31 (0.52)	1.37 (0.31, 2.43)	0.0118
Prevention	Lumbar spine	All	129 2.60 (0.45)	136 0.64 (0.46)	1.96 (1.04, 2.88)	<0.0001
		men	38 2.46 (0.84)	40 -0.24 (0.90)	2.70 (0.99, 4.42)	0.0024
		Pre-menopausal women	28 1.76 (0.75)	29 0.72 (0.72)	1.04 (-0.85, 2.92)	0.2746
		Postmenopausal women	63 3.25 (0.49)	67 1.32 (0.49)	1.92 (0.55, 3.29)	0.0063

n: number of patients

LS : Least Squares

SE: Standard Error

[1] 95% CI computed from three-way ANOVA model with treatment, geographical region, and gender (for all patients only) as factors

In both the treatment and prevention subpopulations, the increases in BMD at 12 months were significantly greater in the ACLASTA*-treated group compared to the risedronate group at the femoral neck, total hip, and trochanter (all $p < 0.03$). For the distal radius, the increases in BMD at 12 months were statistically significant for ACLASTA* compared to risedronate for the treatment subpopulation ($p= 0.0223$), but were not statistically significant for the prevention subpopulation ($p= 0.278$). A summary of the key results appear in Table 23.

Table 23: **Effects of ACLASTA* and risedronate on bone mineral density of the total hip, femoral neck, trochanter and distal radius (modified ITT population), at 12 months**

Population	Location	Aclasta* n LS Mean (SE)	Risedronate n LS Mean (SE)	LS Mean difference (95% CI) [1]	p-value
Treatment	Total hip	247 1.65 (0.21)	239 0.45 (0.20)	1.21 (0.71, 1.79)	<0.0001
	Femoral neck	247 1.45 (0.31)	239 0.39 (0.30)	1.06 (0.32, 1.79)	0.0050
	Trochanter	247 1.97 (0.31)	239 0.63 (0.31)	1.34 (0.59, 2.08)	0.0005
	Distal radius	239 0.85 (0.27)	237 0.09 (0.26)	0.76 (0.11, 1.40)	0.0223
Prevention	Total hip	126 1.54 (0.36)	135 0.03 (0.36)	1.51 (0.78, 2.23)	<0.0001
	Femoral neck	126 1.30 (0.45)	135 -0.03 (0.46)	1.33 (0.41, 2.25)	0.0049
	Trochanter	126 2.75 (0.55)	135 0.48 (0.56)	2.27 (1.15, 3.39)	<0.0001
	Distal radius	128 0.06 (0.36)	131 0.47 (0.38)	-0.42 (-1.17, 0.34)	0.2784

n: number of patients

LS : Least Squares

SE: Standard Error

[1] 95% CI computed from three-way ANOVA model with treatment, geographical region, and gender as factors

Prevention of postmenopausal osteoporosis

Study demographics and trial design

The efficacy and safety of ACLASTA* in the prevention of osteoporosis in postmenopausal women were assessed in a 2-year randomized, multicenter, double-blind, placebo-controlled study of 581 postmenopausal women aged 45 years and older. Women were stratified by years since menopause into two strata; Stratum I women < 5 years from menopause (n=224) and Stratum II women > 5 years from menopause (n=357).

At the baseline visit, women in both Strata I and II were randomized to one of three treatment groups:

- ACLASTA* 5 mg i.v. given as a single dose at randomization and placebo given at Month 12 (n=70 in Stratum I and n=111 in Stratum II)
- ACLASTA* 5 mg i.v. given annually at randomization and at Month 12 (n=77 in Stratum I and n=121 in Stratum II)
- placebo given at randomization and at Month 12 (n=77 in Stratum I and n=125 in Stratum II)

ACLASTA* was administered as a 5 mg dose in 100 mL solution infused over at least 15 minutes. All women received 500 to 1200 mg elemental calcium plus 400 to 800 IU vitamin D supplementation per day. The primary efficacy variable was the percent change of BMD at 24 Months relative to baseline. Women were Caucasian (94% in Stratum I and 92% in Stratum II) and had osteopenia (lumbar spine BMD T-score -1.0 to -2.5 and femoral neck BMD T-score greater than -2.5).

Table 24: Summary of patient demographics in the Prevention of postmenopausal osteoporosis study

Study #	Trial design	Dosage, route of adminis-tration and duration	Study subjects		Mean age (Range)		Gender Male/ Female (N= randomized patients)
			Aclasta*	Placebo	Aclasta*	Placebo	
N2312	Randomized, double-blind, stratified placebo-controlled parallel group efficacy/safety study	Single dose of 5 mg ACLASTA* /100 mL over 15 min (or placebo infusion) per 12 months Duration: 24 months	**Stratum I:** ZOL 2x5 mg N = 77 ZOL 1x5 mg N = 70 **Stratum II:** ZOL 2x5 mg N = 121 ZOL 1x5 mg N = 111	N = 202 **Stratum I:** N = 77 **Stratum II:** **N =** 125	**Stratum I:** ZOL 2x5 mg 53.6 (46.0 – 63.0) ZOL 1x5 mg 53.7 (46.0 – 65.0) **Stratum II:** ZOL 2x5 mg 63.9 (46.0 – 78.0) ZOL 1x5 mg 63.4 (47.0 – 83.0)	**Stratum I:** 54.4 (45.0 – 68.0) **Stratum II:** 64.2 (46.0-81.0)	581 (0 % male/ 100% female)

Study Results

Effect on Bone Mineral Density (BMD)

ACLASTA* significantly increased lumbar spine BMD relative to placebo at Month 24 across both strata. Treatment with ACLASTA* given as a single dose at randomization (and placebo given at Month 12) resulted in 4.0% increase in BMD in Stratum I patients and 4.8% increase in Stratum II patients over 24 months. Placebo given at randomization and at Month 12 resulted in 2.2% decrease in BMD in Stratum I patients and 0.7% decrease in BMD in Stratum II patients over 24 months. Therefore, treatment with a single dose of ACLASTA* resulted in 6.3% increase in lumbar spine BMD in Stratum I patients and 5.4% increase in Stratum II patients over 24 months relative to placebo (both $p<0.0001$). Similar increases in lumbar spine BMD were observed in both Strata when zoledronic acid was administered annually. There was no significant difference seen in either Stratum for the percent increase from baseline in lumbar spine BMD over 24 months relative to placebo when zoledronic acid was administered either as a single dose or annually.

Table 25: Between-treatment comparison for percentage change in lumbar spine BMD at Month 24 (LOCF) relative to baseline, by stratum (ITT population)

Treatment	n	LSM	Pair-wise treatment comparison	LSM difference	95% CI of difference (1)	p-value (2)
Stratum I						
ZOL 1x5 mg	70	4.03	ZOL 1x5 mg - placebo	6.27	5.15, 7.39	<0.0001
Placebo	77	-2.24				
Stratum II						
ZOL 1x5 mg	111	4.76	ZOL 1x5 mg - placebo	5.41	4.46, 6.36	<0.0001
Placebo	125	-0.65				

LSM = least squares mean, CI = confidence interval
Stratum I: women < 5 years from menopause, Stratum II: women ≥ 5 years from menopause
(1) 95% confidence interval is calculated based on a t-distribution.
(2) p-value is obtained from ANOVA with treatment and pooled country as explanatory variables.

Treatment with a single dose of ACLASTA* significantly increased BMD at 24 months relative to placebo at other bone sites including total hip**,** femoral neck, trochanter, and distal radius.

Table 26: Effects of ACLASTA* on bone mineral density of the total hip, femoral neck, trochanter, and distal radius (ITT population), at 24 months, by stratum, for zoledronic acid 5 mg vs. placebo

Stratum	Location	ACLASTA* n LS Mean (SE)	Placebo n LS Mean (SE)	LS Mean difference (95% CI) [1]	p-value
Stratum I					
	Total hip	58 2.55 (0.317)	71 -2.10 (0.293)	4.65 (3.86, 5.43)	<0.0001
	Femoral neck	58 2.01 (0.549)	71 -1.55 (0.508)	3.56 (2.20, 4.92)	<0.0001
	Trochanter	58 4.51 (0.449)	71 -1.93 (0.415)	6.44 (5.32, 7.55)	<0.0001
	Distal radius	57 -0.27 (0.424)	71 -3.23 (0.384)	2.96 (1.92, 4.00)	<0.0001
Stratum II					
	Total hip	97 2.11 (0.282)	115 -1.04 (0.265)	3.16 (2.40, 3.91)	<0.0001
	Femoral neck	97 1.46 (0.366)	115 -1.18 (0.343)	2.65 (1.67, 3.62)	<0.0001
	Trochanter	97 3.97 (0.372)	115 -0.65 (0.348)	4.62 (3.63, 5.61)	<0.0001
	Distal radius	96 -0.13 (0.336)	112 -1.85 (0.317)	1.72 (0.82, 2.61)	0.0002

n: number of patients
LS : Least Squares
SE: Standard Error
[1] 95% CI computed from three-way ANOVA model with treatment, geographical region, and gender as factors

Paget's disease of bone

Study demographics and trial design

ACLASTA* (zoledronic acid 5 mg) was studied in male (approximately 70%) and female (approximately 30%) 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). Diagnosis of Paget's disease of bone was confirmed by radiographic evidence.

The efficacy of one infusion of ACLASTA* versus oral daily doses of 30 mg risedronate for 2 months was demonstrated in two, 6-month, double-blind, active-controlled comparative clinical trials. Therapeutic response was defined as either normalization of serum alkaline phosphatase (SAP) or a reduction of at least 75% from baseline in total SAP excess at the end of six months. SAP excess was defined as the difference between the measured level and midpoint of normal range. The normal laboratory reference range for SAP is 31-110 U/L for females and males between 20-58 years, and 35-115 U/L for females and males >58 years.

Table 27: Summary of patient demographics for clinical trials in Paget's disease of bone

Study #	**Trial design**	**Dosage, route of administration and duration**	**Study subjects (N=population treated)**	**Mean age (Range)**		**Gender** Male/Female n (%)
				Aclasta*	**RIS**	
2304	international, randomized, double-blind, safety and efficacy trials	One dose of 5 mg Aclasta* /100 mL over 15 min (or placebo infusion) or 30 mg oral risedronate o.d. for 2 months (or placebo capsules). Duration: 6 months	Aclasta*: N = 89 RIS: N = 82	70.4 (42.0 – 94.0)	72.1 (44.0 – 87.0)	Aclasta*: 62 (68.9)/ 28 (31.1) RIS: 61 (74.4)/ 21 (25.6)
				≥65 years: 65 (72.2)	≥65 years: 65 (79.3)	
2305			Aclasta*: N = 88 RIS: N = 90	71.3 (45.0 – 92.0)	68.2 (34.0 – 88.0)	Aclasta*: 62 (67.4)/ 30 (32.6) RIS: 57 (61.3)/ 36 (38.7)
				≥65 years: 71 (77.2)	≥65 years: 64 (68.8)	

Study results

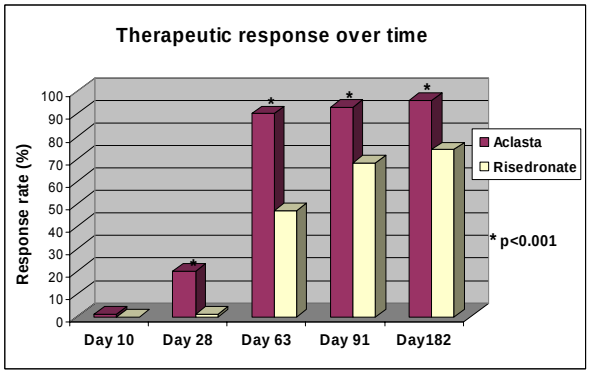
In both trials, ACLASTA* demonstrated a significantly greater and more rapid therapeutic response compared with the active comparator risedronate and returned more patients to normal levels of bone turnover, as evidenced by biochemical markers of bone formation (SAP, serum N-terminal propeptide of type I collagen (P1NP)) and bone resorption (serum CTx 1 (cross-linked C-telopeptides of type I collagen) and urine α-CTx). In the Paget's trials, ACLASTA* reduced the bone markers to the normal laboratory reference ranges (see Table 28).

Table 28: Combined study results in the Paget's disease of bone

Primary Endpoints	ACLASTA* 5mg	Risedronate 30mg	p-value
Primary efficacy variable			
Proportion of therapeutic responders at 6 months	96% (169/176)	74% (127/171)	< 0.001
SAP Normalization	89% (156 /176)	58% (99/171)	< 0.0001
Secondary efficacy variables			
Bone Turnover Markers			
Comparison for log serum CTx ratio at Day 10	0.09	0.50	< 0.001
Comparison for log urine α-CTx ratio at Day 10	0.05	0.54	< 0.001
Comparison for log SAP ratio at Day 28	0.49	0.71	< 0.001
Responders			
Proportion of subjects who achieved normalization at Day 28	7% (13/176)	1% (1/170)	< 0.001
Time to first therapeutic response (mean/median days)	62.8/64	100.6/89	< 0.001

At 6 months (182 days), combined data from both trials showed that 96.0% (169/176) of ACLASTA*-treated patients achieved a therapeutic response as compared with 74.3% (127/171) of patients treated with risedronate (p <0.001) (see Figure 3). In addition, at 6 months, 88.6% (156/176) of ACLASTA*-treated patients achieved remission (normalization of SAP levels) compared to 57.9% (99/171) of patients treated with risedronate (p<0.0001) (see Figure 4).

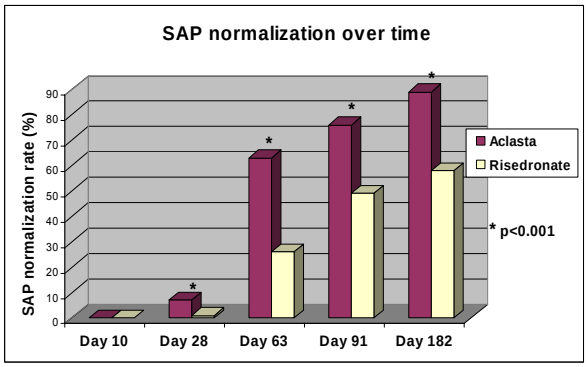
Figure 3 Therapeutic response



Therapeutic response over time:

Visit n/N (proportion): Day 10: Aclasta* 2/165 (0.01); RIS 0/165 (0.00); Day 28: Aclasta* 35/176 (0.20); RIS 2/170 (0.01); Day 63 Aclasta* 158/176 (0.90) RIS 81/171 (0.47); Day 91 Aclasta* 163/176 (0.93) RIS 116/171 (0.68); Day 182 Aclasta* 169/176 (0.96) RIS 127/171 (0.74).

Figure 4 SAP normalization over time



SAP normalization overtime:

Visit n/N (proportion): Day 10: Aclasta* 0/165 (0.00) RIS 0/165 (0.00); Day 28 : Aclasta* 13/176 (0.07) RIS 1/170 (0.01); Day 63 Aclasta* 111/176 (0.63) RIS 45/171 (0.26); Day 91 Aclasta* 134/176 (0.76) RIS 83/171 (0.49); Day 182 Aclasta* 156/176 (0.89) 99/171 (0.58).

Onset of action

ACLASTA* treatment results in a more rapid treatment response than treatment with risedronate. The median time to therapeutic response was significantly faster (64 days) for zoledronic acid compared to risedronate-treated patients (89 days) (see Table 29).

Table 29: Time to first therapeutic response (Intent-to-treat patients)

Treatment	Mean (median) days	N	Number of Responders	P-value [1]
ACLASTA*	62.8 (64)	182	169	<0.0001
Risedronate	106.6 (89)	175	131	---

A therapeutic response is defined as normalization of SAP or a reduction of ≥75% from baseline in SAP excess. N is the number of patients

[1] P-value is calculated from the Wald test of the Cox proportional hazards regression model.

Therapeutic response by disease factor

The therapeutic response to zoledronic acid was similar across all demographic and disease severity groups (gender, age, previous bisphosphonate use, and disease severity). At 6 months, in each of the baseline disease severity subgroups (baseline SAP <3xULN, ≥3xULN) the percentage of ACLASTA*-treated patients who achieved therapeutic response was 96.7% and 95.3% compared to risedronate-treated patients at 74.7% and 73.6%, respectively both at p <0.0001 (see Table 30).

In patients who had previously received treatment with oral bisphosphonates, a significantly greater therapeutic response was observed with ACLASTA* (96.4%) relative to risedronate (55.0%) (p< 0.0001). In patients naïve to previous treatment, a greater therapeutic response was also observed with ACLASTA* (97.6%) relative to risedronate (85.5%) (p =0.0075) (see Table 30).

Table 30: Proportion of patients who achieved therapeutic response at 6 months by disease factors

Subgroup	ACLASTA* n/N (Proportion)	Risedronate n/N (Proportion)	p-value [1] 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
Symptomatic pain at screening			
No	60/60 (1.00)	54/66 (0.82)	0.0006
Yes	109/116 (0.94)	73/105 (0.70)	<0.0001

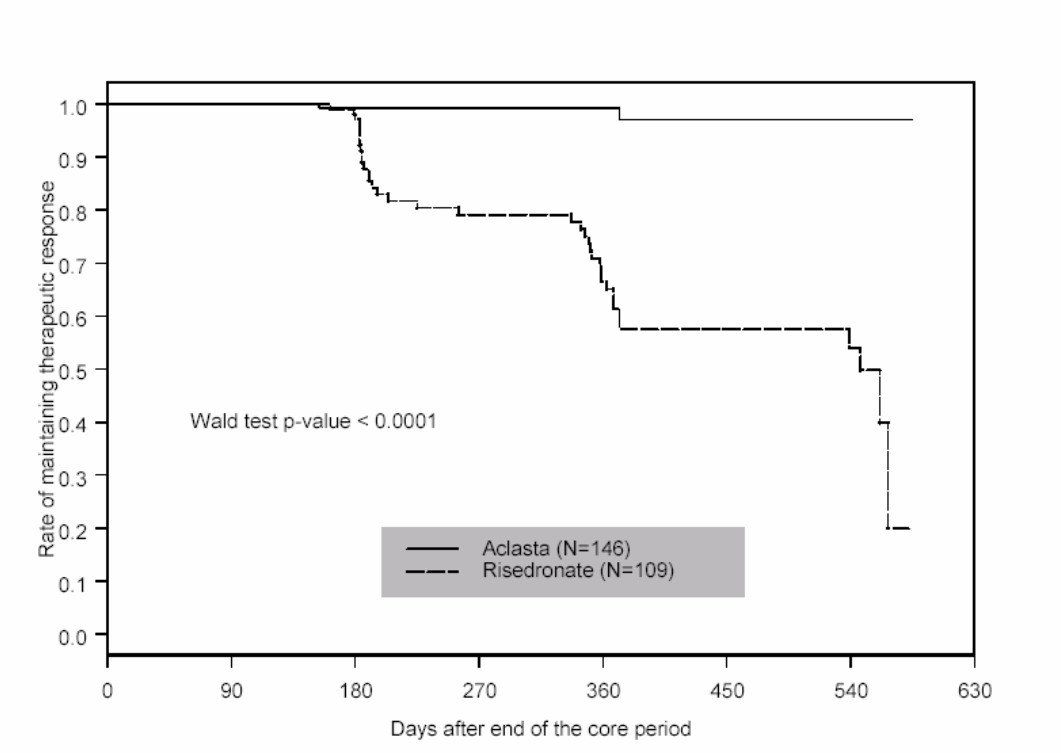
SAP = serum alkaline phosphatase.
ULN = upper limit of normal.
A therapeutic response is defined as normalization of SAP or a reduction of ≥ 75% from baseline in SAP excess.
N=number of patients with baseline and at least one post-baseline SAP measurements.
n = number of patients with therapeutic response at visit.
[1]p-value is based on a Mantel-Haenszel test controlling for study for each category.

The relative change in SAP at Day 28 (the third of seven secondary efficacy variables in the closed testing procedure) for the combined pivotal trials demonstrated a statistically significant reduction relative to baseline for zoledronic acid compared to risedronate ($p < 0.001$). The statistically significant reduction in SAP for ACLASTA* compared to risedronate was also demonstrated at Days 10, 63, 91, and 182 in the extended observation period.

Extended observation period

Paget's disease of bone: Patients who were classified as responders at the end of the 6 month core study were eligible to enter an extended observation period. Since a larger population of ACLASTA*-treated patients achieved therapeutic response, a larger number of patients in the ACLASTA* group (N=146) entered the extended observation period compared to the risedronate group (N=109).

Figure 5 Rate of maintaining of therapeutic response during extension to 6-months core studies (1)



DETAILED PHARMACOLOGY

Bone safety studies

Dose-response and duration of action of a single intravenous injection of zoledronic acid (0.8–500 µg/kg) were investigated in ovariectomized (OVX) adult rats for 8 months after dosing, which corresponds to approximately 8 remodeling 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 µg/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 µg/kg. This dose in rats is approximately 3.4 fold higher than the 5 mg dose administered to a 50 kg patient.

In addition, two studies were performed in OVX rats (12-months treatment with 0.3, 1.5 and 7.5 µg/kg) and OVX rhesus monkeys (16-months treatment with 0.5, 2.5 and 12.5 µg/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, 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 mineralizing 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. Overall, the results provide preclinical evidence for the efficacy and bone safety of zoledronic acid.

TOXICOLOGY

Acute Toxicity

Table 31: Acute Toxicology

Species	Route	Doses (mg/kg)	Findings
Rat	i.v.	0.6, 6, 30, 60, 80	$\geq$ 6 mg/kg: mortality and clinical signs 6 mg/kg: renal findings LD_{50} = approximately 13 mg/kg
Rat	i.v.	1.6, 8, 16, 32	$\geq$ 8 mg/kg: mortality, clinical signs, necropsy findings in kidney, liver, GI tract $\geq$ 1.6 mg/kg: ↓ BW, FC, injection site irritation max. non lethal dose: 1.6 mg/kg min. lethal dose: 8 mg/kg
Dog	i.v.	2,10	2 mg/kg: no clinical signs 10 mg/kg: mortality
Mouse	s.c.	10,50	10 mg/kg: no clinical signs 50 mg/kg: mortality, clinical signs LD_{50} = 10-50 mg/kg in males and > 10 mg/kg in females
Rat	p.o.	200, 2000	$\geq$ 200 mg/kg: ↓ FC,BW, clinical signs, necropsy findings in stomach: enlarged, red lesions 2000 mg/kg: 100% mortality

The acute parenteral toxicity of zoledronic acid was moderate to marked in the mouse, rat and dog. The estimated LD_{50} in the mouse (s.c.) and rat (i.v.) was 10-50 mg/kg (males)/>10 mg/kg (females) and 13 mg/kg (males), respectively. Compound-related renal tubular lesions were observed in the rat after one dose at 6 mg/kg. A single intravenous injection in the dog produced clinical signs, intestinal hemorrhage and mortality after 6 days in one male at 10 mg/kg. The other male received 2 mg/kg and survived the 14-day post-dose observation period without clinical signs.

Subacute and Chronic Toxicity

Table 32: Subacute and Chronic Toxicity

Study Type	Species	Route	Doses (mg/kg)	Findings
Intravenous				
10-Day range-Finding	Rat	i.v.	0.06, 0.6, 6	0.06 mg/kg: well tolerated 0.6 mg/kg: clin. signs; micro in kidneys, liver 6 mg/kg: sacrifice due to severe clin. signs; micro in bone, kidneys, stomach, liver, thymus, spleen, lymph nodes NOAEL: 0.06 mg/kg
2-Week	Rat	i.v.	0.06, 0.6, 3.2 (every third day for 18 days)	≥ 0.06 mg/kg: local irritation, pharmacol bone changes ≥ 0.6 mg/kg: gastric lesions 3.2 mg/kg: mortality, clin signs; ↓ BW/FC, clin lab alterations, ↑ adrenal, kidney, liver wgts, nephropathy, hepatocellular hypertrophy NOAEL: not established
10-Day range-finding	Dog	i.v.	0.1, 1	≥ 0.1 mg/kg: micro in bone rib, injection sites 1 mg/kg: clin. signs; micro findings in stomach, intestine, liver, lung, thymus NOAEL: 0.1 mg/kg
4-Week + 1 mo. Recovery	Dog	i.v.	0.02, 0.06, 0.2	≥ 0.06 mg/kg: clinical signs 0.2 mg/kg: clin. signs; micro in GI tract NOAEL: 0.02 mg/kg
3-Month + 1 mo. Recovery	Dog	i.v.	0.01,0.03, 0.1→0.2	≥0.01 mg/kg: genital tract atrophy (F); ↑ primary spongiosa in bone; splenic histiocytosis; lung inflammation, thymic atrophy ≥ 0.03 mg/kg: moribund sacrifice at 0.1→0.2 mg/kg due to inj.site irritation, ↓ BW/FC, ↑ ALAT/ASAT, ↓ bone AP, PO4, creatinine and ↓ RBC indices; inj. site ulceration, kidney lesions, genital tract (M) & pancreatic atrophy, inflammation of urinary bladder, esophagus, stomach and liver. NOAEL: not established

26/52-wk+ 6 mo. Recovery	Dog	i.v.	0.005,0.03, 0.1	All doses: inj site irritation; ↓ phosphate; pharmacol. bone changes ≥0.03 mg/kg : micro in kidneys, GI tract; ↓ BUN, ↑ total protein. 0.1 mg/kg: ↓ creatinine, ↑ ASAT, ↓Ca. NOAEL: 0.005 mg/kg
Bone analyses (26/52-wk + 6 mo. Recovery)	Dog	i.v.	0.005,0.03, 0.1	All biomechanical parameters assessing bone quality showed either no deleterious effect or an increase in quality at pharmacologically efficacious doses.
Subcutaneous				
10-Day range-finding	Rat	s.c.	0.2,0.6,2	2 mg/kg: clin. signs; microscopic changes in kidneys, liver; spleen, thymus, lymph nodes, lung and adrenals. ≥ 0.6 mg/kg: clin. signs ≥ 0.2 mg/kg: Local irritation at the injection sites
1-Month + 1 mo recovery	Rat	s.c.	0.02,0.06,0.2	0.2 mg/kg: swelling at injection site; clin. signs; micro findings in liver, lymph nodes ≥ 0.06 mg/kg: clin. signs; micro findings of spleen, injection sites, skeletal muscle; NOAEL: 0.02 mg/kg
3-Month + 1 mo recovery	Rat	s.c.	0.01,0.03,0.1	Tolerated without mortality at doses up to and including 0.1 mg/kg. Pharmacologic bone changes. NOAEL 0.01 mg/kg in females. No NOAEL in males due to reduced BW/FC at all doses.
6/12-Month + 6 mo recovery	Rat	s.c.	0.001,0.003, 0.01	0.001 mg/kg: ↓ bone AP, ↑ reticulocyte count, splenic hemosiderosis and congestion, ↑ splenic hematopoiesis, ↑ cellularity of femoral/tibial marrow, pharmacological bones changes. Following bone morphometry, no deleterious effects after administration for 12 months. 0.003 mg/kg: ↓ RBC parameters, ↑ fibrinogen, renal tubular changes, progressive nephropathy. 0.01 mg/kg: testicular tubular atrophy Bone morphometry on bone (tibia) did not reveal deleterious effects NOAEL: 0.001 mg/kg
Oral				
13-week	Mouse	p.o.	0, 0.3, 3, 10, 30→20	0.3 – 30→20 mg/kg: mortality; respiratory signs; ↓ FC; pharmacologic bone changes 3 - 30→20 mg/kg: ↓BW; laryngeal, tracheal & bronchial inflammation

10-Day range-finding	Rat	p.o.	1,10,100	1 and 10 mg/kg: well-tolerated 100 mg/kg: mortality & moribund sacrifice after 1 wk; clin. signs; gastritis, GI tract necrosis, acute renal tubular lesions, liver changes; lymphoid depletion spleen, thymus.
1-Month + 1 mo recov.	Rat	p.o.	62060	6 mg/kg: well-tolerated ≥20 mg/kg: clin signs; liver, spleen, lymph nodes 60 mg/kg: mortality; GI tract, kidneys, salivary glands, thymus, adrenal, lung, trachea NOAEL: 6 mg/kg
6-Month + 1 mo recov.	Rat	p.o.	0.1,1, 10	≥0.1 mg/kg: bone ≥1 mg/kg: clin signs 10 mg/kg: mortality NOAEL: 0.1 mg/kg
10-Day	Dog	p.o.	1→30, 10 (for 9d); 30 (for 10d) [a]	1→30 mg/kg: clin. signs; micro findings in kidneys, esophagus, liver; pharmacol bone changes. 10 mg/kg: no significant findings
1-Month	Dog	p.o.	3,10, 30	≥ 3 mg/kg: clin signs ≥ 10 mg/kg: mortality; liver, lung, thymus 30 mg/kg: gingiva, pancreas, adrenals
6-Month + 1 mo. Recov	Dog	p.o.	0.01, 0.1, 1	Well-tolerated at doses of up to 1 mg/kg. Histological bone changes were considered pharmacologic NOAEL: 1 mg/kg

[a] From day 9 of dosing: 30 mg/kg for an additional 10 days

Reproductive Toxicity Studies

Table 33: Reproductive Toxicity Studies

Study Type	Species	Route	Doses (mg/kg)	Findings
Segment I	Rat	s.c.	0.01, 0.03, 0.1	≥ 0.01: maternal toxicity and severe effects on parturition such that the study was terminated on lactation day 7.
Segment II range-finding	Rat	s.c.	0.2, 0.6, 2	≥ 0.2 mg/kg: irritation at injection site ≥ 0.6 mg/kg: ↓ maternal BW. 9/10 dams with total resorption (embryo/fetal death) of progeny; remaining dam w/ only 2 fetuses (one with cleft palate).
Segment II	Rat	s.c.	0.1, 0.2, 0.4	≥ 0.2 mg/kg: ↓ maternal BW; ↓ fetal wgt; anomalies of viscera and/or skeleton w/ wavy ribs & delay in skeletal maturation. 0.4 mg/kg: 9/24 dams with total resorption of fetuses; some fetuses with edema, cleft palate, short lower jaw, abnormal ossification
Segment II range-finding (non-pregnant)	Rabbit	s.c.	0.2,0.6,2	0.6 or 0.2 mg/kg suitable doses for main study.
Segment II range-finding (pregnant)	Rabbit	s.c.	0.1,0.2,0.4	0.2, 0.4 mg/kg: early termination due to severe clinical signs/toxicity. 0.1 mg/kg: ↓ fetal wgt; no signs of abnormal fetal development.
Segment II	Rabbit	s.c.	0,01, 0.03, 0.1	Maternal toxicity at 0.01 mg/kg due to ↓ blood calcium. No embryo/fetotoxicity or teratogenicity.

Carcinogenesis

Standard lifetime carcinogenicity bioassays were conducted in mice and rats. Mice were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. There was an increased incidence of Harderian gland adenomas in males and females in all treatment groups (at doses ≥0.002 times the anticipated human intravenous dose, based on a comparison of relative body surface areas). These increases were not considered to be related to zoledronic acid administration as their occurrence lacked a dose response and the incidences were within the historical control range for animals of this age and strain in the testing facility. Moreover these neoplasms are not biologically relevant as the Harderian gland is a unique, highly specialized organ which is not present or known to have any correlate in the human. Rats were given oral doses of zoledronic acid of 0.1, 0.5, or 2.0 mg/kg/day. No increased incidence of tumors was observed.

Table 34: Carcinogenesis

Species	Route	Doses (mg/kg)	Findings
Mouse	p.o.	0.1,0.3,1.0	≥ 0.1 mg/kg: nonproliferative hyperostosis ≥ 0.3 mg/kg: ↓ BW
Rat	p.o.	0.1,0.5,2.0	≥ 0.1 mg/kg: nonproliferative hyperostosis ≥ 0.5 mg/kg: ↓ BW,FC 2.0 mg/kg: ↑ extramedullary hematopoiesis

Mutagenesis

Zoledronic acid was not genotoxic in the Ames bacterial mutagenicity assay, in the Chinese hamster ovary cell assay, or in the Chinese hamster gene mutation assay, with or without metabolic activation. Zoledronic acid was not genotoxic in the *in vivo* rat micronucleus assay.

Table 35: Mutagenesis

Study Type	Findings
in vitro: Ames [a], Ames [b] , Ames[c] Range: [a]5000 µg/plate (-S9/+S9), [b]390 - 25000 µg/plate, [c]1250 µg/plate (-S9/+S9)	Negative
in vitro: Cytogenetics test on Chinese hamster cells Range: 9.7 – 1250 µg/mL	Negative
in vitro: Gene mutation test using V79 Chinese hamster cells Range: 2 – 15 µg/mL	Negative
in vivo: Micronucleus in rats Range: 2.6 – 10.4 mg/kg	Negative

[a] Bacterial test systems (S. typhimurium), with/without metabolic activation. [b]Batch control

[c]Bacterial test system (S. typhimurium/ E. coli), with/without metabolic activation.

There was no evidence of mutagenicity for zoledronic acid in a battery of tests covering various endpoints of genotoxicity.

Impairment of Fertility:

Female rats were given daily subcutaneous doses of zoledronic acid of 0.01, 0.03, or 0.1 mg/kg beginning 15 days before mating and continuing through gestation. Effects observed in the high-dose group (equivalent to human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included inhibition of ovulation and a decrease in the number of pregnant rats. Effects observed in both the mid-dose group and high-dose group (0.3 to 1 times human systemic exposure following a 5 mg intravenous dose, based on AUC comparison) included an increase in pre-implantation losses and a decrease in the number of implantations and live fetuses.

REFERENCES

1. Arden-Cordone M, Siris E, Lyles K, et al., Antiresorptive effect of a single infusion of microgram quantities of zoledronate in Paget's disease of bone. *Calcif Tissue Int* 1997; 60: 415-418.

2. Buckler H, Fraser W, Hosking D, et al., Single infusion of zoledronate in Paget's disease of bone: a placebo-controlled, dose-ranging study. *Bone* 1999; 24 (S5): 81S-85S.

3. Garnero P, Gineyts E, Schaffer A, et al., Measurement of urinary excretion of nonisomerized and beta-isomerized forms of type I collagen breakdown products to monitor the effects of the biphosphonate zoledronate in Paget's disease. *Arthritis Rheum* 1998; 41: 354-360.

4. Green JR, Müller K, Jaeggi KA. Preclinical Pharmacology of CGP 42-446, a new, potent, heterocyclic bisphosphonate compound. *J Bone Miner Res* 1994; 9: 745-751.

5. Green J, Seltenmeyer Y, Jaeggi K, Widler L, Renal tolerability profile of novel, potent bisphosphonates in two short-term rat models, *Pharmacol Toxicol* 1997; 80: 225-230.

6. Risser F, Pfister C, Degen P, An enzyme inhibition assay for the quantitative determination of the new bisphosphonate zoledronate in plasma. *J Pharm Biomed Anal* 1997; 15: 1877-1880.

7. Body JJ, Diel I, Bell R. Profiling the safety and tolerability of bisphosphonates. *Semin Oncol.* 2004 Oct;31(5 Suppl 10):73-8.

8. Reid IR, et al. Intravenous zoledronic acid in post menopausal women with low bone mineral density. *N Engl J Med* 2002; 346:653-661.

9. Hornby SB, Evans GP, Hornby SL, Pataki A, Glatt M, Green JR. Long-Term Zoledronic Acid Treatment Increases Bone Structure and Mechanical Strength of Long Bones of Ovariectomized Adult Rats. *Calcif Tissue Int* 2003; 72:519–527.

10. Reid IR, Miller P, Lyles K, Fraser W, Brown JP, Saidi Y, Mesenbrink P, Su G, Pak J, Zelenakas K, Luchi M, Richardson P, Hosking D. Comparison of a single infusion of zoledronic acid with risedronate for Paget's disease. *N Engl J Med.* 2005 Sep 1;353(9):898-908.
11. Rogers MJ. New insights into the molecular mechanism of action of bisphosphonates. *Curr Pharmaceut Design* 2003; 9 (32):2643-2658

12. Dunford JE, Thompson K, Coxon FP, Luckman SP, Hahn FM, Poulter CD, Ebetino FH, Rojers MJ. Structure-Activity Relationships for inhibition of Farnesyl diphosphate synthase in vitro and inhibition of bone resorption in vivo by nitrogen-containing bisphosphonates. *J Pharmacol Exper Ther* 2001; 296(2):235-242.

13. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA,et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis (HORIZON Pivotal Fracture Trial). *N Engl J Med.* 2007; 356(18):1809-22.
14. Lyles KW, Colòn-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture. *N Engl J Med.* 2007;Sept 17, [Epub ahead of print].
15. Reid DM, Devogelaer J-P, Saag K, Roux C, Lau C-S, Reginster J-Y, et al. Zoledronic acid and risedronate in the prevention and treatment of glucocorticoid-induced osteoporosis (HORIZON): a multicentre, double-blind, double-dummy, randomised controlled trial. *Lancet* 2009; 373: 1253–63

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