



Aclasta soln

Search Singapore

[Advanced Search](#)
[Search Tips](#)

MIMS SearchMedica Google

Quick Links

Select Quick Link

Latest Updates

New Molecule

- [Avamys nasal spray®](#)
- [Eraxis vial®](#)
- [Revlimid cap®](#)
- [Tredaptive tab®](#)
- [TS-ONE TS-One cap 20®](#)

[More new molecules](#)

New Formulations

- [Ganfort eye drops®](#)
- [Priorix-Tetra syringe®](#)

New Highlights

- [CME Accreditation \(Medical Prog...\)](#)
- [MIMS Pediatrics](#)

Featured Drugs

- | | |
|------------------------------|--------------------------------|
| Actifed | Actonel |
| Aprovel | Caltrate 600 |
| Champix | Detrusitol |
| Exforge | Gliadel |
| Levemir | Lyrica |
| Meteospasmyl | Nicorette |
| Os-Cal | Pinetarsol Bar |
| Plavix | Precedex |
| Prevenar | Priorix-Tetra |
| QV Bath Oil | Spasmolyt |
| Viagra | Viartiril-S |
| Zimor | |

Industry Links

- | | |
|------------------------------------|--|
| Abbott | Allergan |
| AstraZeneca | Baxter Oncology |
| Bayer Schering ... | Biotest |
| Bristol-Myers S... | Daiichi Sankyo |
| DEY | Douglas |
| Ego | Eisai |
| Eli Lilly | Genzyme |
| GlaxoSmithKline | Hermal |
| Indevus | iNova |
| Janssen-Cilag | Medinova |
| Meiji Seika | Merck Santé |
| Merck Serono | Merck Sharp & D... |
| Merck Theramex | MGI Pharma |
| Novartis | Novartis Ophtha... |
| Pfizer | Pierre Fabre Me... |

Browse Therapeutic Class

1. [Gastrointestinal & hepa...](#)
2. [Cardiovascular & hemato...](#)
3. [Respiratory system](#)
4. [Central Nervous System](#)
5. [Musculo-Skeletal System](#)
6. [Hormones](#)
7. [Contraceptive agents](#)
8. [Anti-Infectives \(System...](#)
9. [Oncology](#)
10. [Genito-urinary system](#)
11. [Endocrine & metabolic s...](#)
12. [Vitamins & minerals](#)
13. [Nutrition](#)
14. [Eye](#)
15. [Ear & Mouth / Throat](#)
16. [Dermatologicals](#)
17. [Anaesthetics- local & g...](#)
18. [Allergy & immune system](#)
19. [Antidotes Detoxifying](#)

Approved Full Prescribing Information

Aclasta® [soln]

[Novartis](#) | [Zuellig](#) |

MIMS Class : [Agents Affecting Bone Metabolism](#)



[See related Aclasta soln information](#)

Contents	Zoledronic acid
Indications	<p>Treatment of osteoporosis in postmenopausal women and osteoporosis in men at increased risk of fracture including those with a recent low-trauma hip fracture.</p> <p>Treatment of Paget's disease of the bone.</p>
Dosage	<p>Postmenopausal Osteoporosis and Osteoporosis in Men: Recommended Dose: Single IV infusion of 5 mg Aclasta administered once a year.</p> <p>Recent Low-trauma Hip Fracture: Aclasta infusion should be given ≥2 weeks after hip fracture repair (see Pharmacodynamics under Actions).</p> <p>Paget's Disease: Aclasta should be prescribed only by physicians with experience in treatment of Paget's disease of the bone. Recommended Dose: Single IV infusion of 5 mg Aclasta. Re-treatment of Paget's Disease: Specific re-treatment data are not available. After a single treatment with Aclasta in Paget's disease, an extended remission period is observed in responding patients (see Pharmacodynamics under Actions).</p> <p>Administration: Aclasta (5 mg in 100 mL ready-to-infuse solution) is administered via a vented infusion line and given at a constant infusion rate. The infusion time must not be <15 min (see Cautions For Usage).</p> <p>Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important for the elderly and for patients receiving diuretic therapy.</p> <p>Adequate calcium and vitamin D intake are recommended in association with Aclasta administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Aclasta administration (see Precautions).</p> <p>In patients with a recent low-trauma hip fracture, a loading dose of 50,000-125,000 iu of vitamin D given orally or via the IM route is recommended prior to the first Aclasta infusion.</p> <p>The incidence of post-dose symptoms occurring within the first 3 days after administration of Aclasta can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration.</p> <p>Elderly (≥65 years): No dose adjustment is necessary since bioavailability, distribution and elimination were similar in elderly patients and younger subjects.</p> <p>Children and Adolescents: Aclasta is not recommended for use in children and adolescents <18 years due to lack of data on safety and efficacy.</p> <p>Patients with Renal Impairment: Use of Aclasta in patients with creatinine clearance <35 mL/min is not recommended due to limited clinical experience in this population.</p>

Can't find someth
GIVE US YOUR FEED

Prime Links -

World Congress on Cardiology

The Specialist Care Clinic
Register NOW-Pedia Care CME (2 PTS, Oct GP, OB/GYN, Ped

Prevenar - A World of Experience Makes the Difference

GO-ON
Sodium Hyaluronate (25mg/2.5ml, syringe)
For Visco Supplement and Visco Induction

Pactrim
Pan-Asian Committee Treatment & Research Multiple Sclerosis

Venice
Venice, October 4-7, 2009

CLEXANE
Enoxaparin sodium
Preventing VTE in As Patients

MEDICAL PROGRES
Reviewed CME journals Asian clinicians

MedicalTRIBUN
Asia's only regional newspaper

I	J	K	L	M	N	O	P	Q
R	S	T	U	V	W	X	Y	Z
Browse Diagnoses								
#	A	B	C	D	E	F	G	H
I	J	K	L	M	N	O	P	Q
R	S	T	U	V	W	X	Y	Z
Browse Manufacturer								
#	A	B	C	D	E	F	G	H
I	J	K	L	M	N	O	P	Q
R	S	T	U	V	W	X	Y	Z
Medical Events								
2009 Annual Meeting of The Amer...								
2009 Annual Meeting of The Amer...								
18th Congress of The European A...								
2009 Annual Meeting of The Orth...								
PACS 2009 International Symposi...								
More events								
MIMS Reference System								
MIMS Publications								
MIMS POINT OF CARE								
Useful Links								
Health Promotion Board								
Health Sciences Authority								
Ministry of Health								
Singapore Medical Council								
NHG Partners								
More useful links								

Overdosage	<p>There is no experience of acute intoxication with Aclasta. Patients who have received doses higher than those recommended should be carefully monitored. In the event of overdose leading to clinically significant hypocalcaemia, reversal may be achieved with supplemental oral calcium and/or an IV infusion of calcium gluconate.</p>
Contraindications	<p>Hypersensitivity to zoledronic acid or to any of the excipients of Aclasta or to any bisphosphonates.</p> <p>Aclasta is contraindicated for patients with hypocalcaemia (see Precautions).</p> <p>Use in pregnancy & lactation: There are no adequate data on the use of zoledronic acid in pregnant women. Studies in animals with zoledronic acid have shown reproductive toxicological effects including malformations (see Preclinical Safety Data in Toxicology under Actions). The potential risk for humans is unknown. It is not known whether zoledronic acid is excreted into human breast milk. Aclasta is contraindicated during pregnancy and breastfeeding women.</p>
Special Precautions	<p>The dose of zoledronic acid 5 mg must be administered over at least 15 min.</p> <p>Renal Impairment: Aclasta is not recommended in patients with severe renal impairment (creatinine clearance <35 mL/min) due to limited clinical experience in this population. Patients should have their serum creatinine level measured before receiving Aclasta.</p> <p>Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important in the elderly and for patients receiving diuretic therapy. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (eg, aminoglycosides or diuretics that may cause dehydration) (see Interactions).</p> <p>Preexisting hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating therapy with Aclasta (see Contraindications). Other disturbances of mineral metabolism must also be effectively treated (eg, diminished parathyroid reserve, intestinal calcium malabsorption). Physicians should consider clinical monitoring for these patients.</p> <p>Elevated bone turnover is a characteristic of Paget's disease of the bone. Due to the rapid onset of effect of zoledronic acid on bone turnover, transient hypocalcaemia, sometimes symptomatic, may develop and is usually maximal within the first 10 days after infusion of Aclasta (see Adverse Reactions).</p> <p>Adequate calcium and vitamin D intake are recommended in association with Aclasta administration. In addition, in patients with Paget's disease, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured for at least 10 days following Aclasta administration (see Dosage & Administration). Patients should be informed about symptoms of hypocalcaemia and receive adequate clinical monitoring during the period of risk. Measurement of serum calcium before infusion of Aclasta is recommended for patients with Paget's disease.</p> <p>Severe and occasionally incapacitating bone, joint and/or muscle pain have been infrequently reported in patients taking bisphosphonates, including Aclasta.</p> <p>Aclasta contains the same active substance found in Zometa (zoledronic acid), used for oncology indications and a patient being treated with Zometa should not be treated with Aclasta.</p> <p>Osteonecrosis of the Jaw (ONJ): Osteonecrosis of the jaw has been reported predominantly in patients with cancer receiving regimens including bisphosphonates, including zoledronic acid. Many of these patients were also receiving chemotherapy and corticosteroids. The majority of reported cases have been associated with dental procedures eg, tooth extraction. Many had signs of local infection including osteomyelitis. A dental examination with appropriate</p>

	<p>bisphosphonate therapy, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest whether discontinuation of bisphosphonate treatment reduces the risk of osteonecrosis of the jaw. The clinical judgment of the treating physician should guide the management plan of each patient based on individual benefit/risk assessment.</p> <p>Effects on the Ability to Drive or Operate Machinery: No studies on the effects on the ability to drive and use machines have been performed.</p>
<p>Adverse Drug Reactions</p>	<p>The overall percentage of patients who experienced post-dose symptoms were 44.7, 16.7 and 10.2% after the 1st, 2nd and 3rd infusion, respectively. Incidence of individual symptoms following the 1st infusion was: Fever (17.1%), myalgia (7.8%), flu-like symptoms (6.7%), arthralgia (4.8%) and headache (5.1%). The incidence of these symptoms decreased markedly with subsequent doses of Aclasta. The majority of these symptoms occur within the first 3 days following Aclasta administration. The majority of these symptoms were mild to moderate and resolved within 3 days of the event onset. The percentage of patients who experienced post-dose symptoms was lower in a smaller study (19.5, 10.4, 10.7% after the 1st, 2nd and 3rd infusion, respectively) where prophylaxis against post-dose symptoms was used as described in the succeeding text.</p> <p>The incidence of post-dose symptoms occurring within the first 3 days after administration of Aclasta can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration (see Dosage & Administration).</p> <p>In the HORIZON-Pivotal Fracture Trial (PFT) (see Pharmacodynamics under Actions), the overall incidence of atrial fibrillation was 2.5% (96 out of 3862) and 1.9% (75 out of 3852) in patients receiving Aclasta and placebo, respectively. The rate of atrial fibrillation serious adverse events was increased in patients receiving Aclasta (1.3%, 51 out of 3862) compared with patients receiving placebo (0.6%, 22 out of 3852). The mechanism behind increased incidence of atrial fibrillation is unknown. In the osteoporosis trials (PFT, HORIZON - Recurrent Fracture Trial [RFT]), the pooled atrial fibrillation incidences were comparable between Aclasta (2.6%) and placebo (2.1%). For atrial fibrillation serious adverse events, the pooled incidences were 1.3% for Aclasta and 0.8% for placebo.</p> <p>Very common ($\geq 1/10$), common ($\geq 1/100$, $< 1/10$), uncommon ($\geq 1/1000$, $< 1/100$), rare ($\geq 1/10,000$, $< 1/1000$) adverse drug reactions are as follows. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.</p> <p>Investigations: Uncommon: Increased blood pressure.</p> <p>Cardiac Disorders: Common: Atrial fibrillation.</p> <p>Nervous System Disorders: Common: Headache, dizziness. Uncommon: Lethargy, paraesthesia, somnolence, tremor, syncope.</p> <p>Eye Disorders: Uncommon: Conjunctivitis, eye pain. Rare: Uveitis, episcleritis, iritis.</p> <p>Ear and Labyrinth Disorders: Uncommon: Vertigo.</p> <p>Respiratory, Thoracic and Mediastinal Disorders: Uncommon: Dyspnoea.</p> <p>Gastrointestinal Disorders: Common: Nausea, vomiting. Uncommon: Diarrhoea, dyspepsia, abdominal pain, dry mouth.</p> <p>Renal and Urinary Disorders: Uncommon: Increased blood creatinine, pollakiuria.</p> <p>Skin and Subcutaneous Tissue Disorders: Uncommon: Rash, night sweats, hyperhidrosis, pruritus, erythema.</p> <p>Musculoskeletal and Connective Tissue Disorders: Common: Myalgia, arthralgia, bone and back pain, pain in extremity. Uncommon: Neck pain, musculoskeletal stiffness, joint swelling, shoulder pain, muscle spasms, musculoskeletal pain, noncardiac chest pain, muscular weakness, joint stiffness.</p>

Vascular Disorders: Uncommon: Hypertension, flushing.

General Disorders and Administration Site Conditions: Very common: Fever. Common: Flu-like symptoms, chills, fatigue, asthenia, pain, malaise, rigors*. Uncommon: Peripheral oedema, thirst.

Immune System Disorders: Not known (based on post-marketing reports. Since these reports are from a population of uncertain size and are subject to confounding factors, it is not possible to reliably estimate their frequency or establish a causal relationship to exposure to Aclasta): Hypersensitivity reactions including rare cases of bronchoconstriction, urticaria and angioedema and very rare cases of anaphylactic reaction/shock.

Psychiatric Disorders: Uncommon: Insomnia.

Additional adverse events which were reported in the individual studies but were not included due to the pooled presentation are: Uncommon: Dysgeusia, oesophagitis, toothache.

* Common in Paget's disease only. For hypocalcaemia, see text as follows.

Class Effects: Renal Dysfunction: Zoledronic acid has been associated with renal dysfunction manifested as deterioration in renal function (ie, increased serum creatinine) and in rare cases acute renal failure. Renal dysfunction has been observed following the administration of zoledronic acid, especially in patients with preexisting renal compromise or additional risk factors (eg, oncology patients with chemotherapy, concomitant nephrotoxic medications, severe dehydration), the majority of whom received a 4-mg dose every 3-4 weeks, but it has been observed in patients after a single administration.

In clinical trials in osteoporosis, the change in creatinine clearance (measured annually prior to dosing) and the incidence of renal failure and impairment was comparable for both the Aclasta and placebo treatment groups over 3 years. There was a transient increase in serum creatinine observed within 10 days in 1.8% of Aclasta-treated patients versus 0.8% of placebo-treated patients.

Hypocalcaemia: In clinical trials in osteoporosis, approximately 0.2% of patients had notable declines of serum calcium levels (<1.87 mmol/L) following Aclasta administration. No symptomatic cases of hypocalcaemia were observed.

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

Based on laboratory assessment, transient asymptomatic calcium levels below the normal reference range (<2.1 mmol/L) occurred in 2.3% of Aclasta-treated patients in a large clinical trial compared to 21% of Aclasta-treated patients in the Paget's disease trials. The frequency of hypocalcaemia was much lower following subsequent infusions.

All patients received adequate supplementation with vitamin D and calcium in both the postmenopausal osteoporosis trial, the prevention of clinical fractures after hip fracture trial and the Paget's disease trials (see Dosage & Administration). In the trial for the prevention of clinical fractures following a recent hip fracture, vitamin D levels were not routinely measured but the majority of patients received a loading dose of vitamin D prior to Aclasta administration (see Dosage & Administration).

Local Reactions: In a large clinical trial, local reactions at the infusion site eg, redness, swelling and/or pain were reported (0.7%) following the administration of zoledronic acid.

Osteonecrosis of the Jaw: Uncommonly, cases of osteonecrosis (primarily of the jaw) have been reported predominantly in cancer patients treated with bisphosphonates, including zoledronic acid. Many of these patients had signs of local infection including osteomyelitis and the majority of the reports refer to cancer patients following tooth extractions or other dental surgeries. Osteonecrosis of the jaw has multiple, well documented risk factors including a

	<p>as recovery may be prolonged (see Precautions). In a large clinical trial in 7736 patients, osteonecrosis of the jaw has been reported in 1 patient treated with Aclasta and 1 patient treated with placebo. Both cases resolved.</p> <p>Click to view ADR Monitoring Form</p>										
Drug Interactions	<p>Specific drug-drug interaction studies have not been conducted with zoledronic acid. Zoledronic acid is not systemically metabolised and does not affect human cytochrome P-450 enzymes <i>in vitro</i> (see Pharmacokinetics under Actions). Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and interactions resulting from displacement of highly protein-bound drugs are therefore unlikely.</p> <p>Zoledronic acid is eliminated by renal excretion. Caution is indicated when Aclasta is administered in conjunction with medicinal products that can significantly impact renal function (eg, aminoglycosides or diuretics that may cause dehydration).</p> <p>Incompatibilities: Aclasta must not be allowed to come into contact with any calcium-containing solutions. Aclasta must not be mixed or given IV with any other medicinal products.</p> <p>Click here for more Interaction Checks</p>										
Pregnancy Category (US FDA)	<table border="1"> <tr> <td>A</td> <td>B</td> <td>C</td> <td style="background-color: #f4a460;">D</td> <td>X</td> </tr> <tr> <td colspan="5" style="text-align: center;">▲</td> </tr> </table> <p>Category D: There is positive evidence of human foetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).</p>	A	B	C	D	X	▲				
A	B	C	D	X							
▲											
Cautions For Usage	<p>Special Precautions for Disposal and Other Handling: For single use only. Any unused solution should be discarded. Only clear solutions, free from particles and discolouration should be used.</p> <p>If refrigerated, allow the refrigerated solution to reach room temperature before administration. Aseptic techniques must be followed during the preparations of the infusion.</p>										
Storage	<p>From a microbiological point of view, Aclasta should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hrs at 2-8°C.</p> <p>Shelf-life: Unopened Bottle: 3 years.</p> <p>After Opening: 24 hrs at 2-8°C.</p>										
Description	<p>Each bottle with 100 mL solution contains anhydrous zoledronic acid 5 mg, corresponding to zoledronic acid monohydrate 5.33 mg.</p> <p>Each mL contains anhydrous zoledronic acid 0.05 mg, corresponding to zoledronic acid monohydrate 0.0533 mg.</p> <p>Aclasta also contains the following excipients: Mannitol, sodium citrate and water for injections.</p>										
Mechanism of Action	<p>Pharmacotherapeutic Group: Bisphosphonate. ATC Code: M05BA08.</p> <p>Pharmacology: Mechanism of Action: Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on the bone. It is an inhibitor of osteoclast-mediated bone resorption.</p> <p>Pharmacodynamics: Aclasta treatment rapidly reduced the rate of bone turnover from elevated post-menopausal levels with the nadir for resorption markers observed at 7 days and for formation markers at 12 weeks. Thereafter bone markers stabilised within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.</p> <p>Clinical Efficacy in the Treatment of Postmenopausal Osteoporosis (PFT): The efficacy and safety of Aclasta 5 mg once a year for 3 consecutive years were demonstrated in post-menopausal women (7736 women aged 65-89 years) with either: A femoral neck bone</p>										

Women who were evaluated for the incidence of vertebral fractures did not receive concomitant osteoporosis therapy, which was allowed for women contributing to the hip and all clinical fracture evaluations. Concomitant osteoporosis therapy included: Calcitonin, raloxifene, tamoxifen, hormone replacement therapy, tibolone; but excluded other bisphosphonates. All women received 1000-1500 mg of elemental calcium plus 400-1200 iu of vitamin D supplements daily.

Effect on Morphometric Vertebral Fractures: Aclasta significantly decreased the incidence of 1 or more new vertebral fractures over 3 years and as early as the 1 year time point (see Table 1).



[Click on icon to see table/diagram](#)

Aclasta-treated patients age greater than or equal to 75 years exhibited a 60% reduction in the risk of vertebral fractures compared to placebo patients ($p < 0.0001$).

Effect on Hip Fractures: Aclasta demonstrated a consistent effect over 3 years, resulting in a 41% reduction in the risk of hip fractures (95% CI, 17-58%). The hip fracture event rate was 1.44% for Aclasta-treated patients compared to 2.49% for placebo-treated patients. The risk reduction was 51% in bisphosphonate-naïve patients and 42% in patients allowed to take concomitant osteoporosis therapy.

Effect on All Clinical Fractures: All clinical fractures were verified based on the radiographic and/or clinical evidence. A summary of results is presented in Table 2.



[Click on icon to see table/diagram](#)

Effect on Bone Mineral Density (BMD): Aclasta significantly increased BMD at the lumbar spine, hip and distal radius relative to treatment with placebo at all time points (6, 12, 24 and 36 months). Treatment with Aclasta resulted in a 6.7% increase in BMD at the lumbar spine, 6% at the total hip, 5.1% at the femoral neck and 3.2% at the distal radius over 3 years as compared to placebo.

Bone Histology: Bone biopsies were obtained from iliac crest 1 year after the 3rd annual dose in 152 postmenopausal patients with osteoporosis treated with Aclasta (N=82) or placebo (N=70). Histomorphometric analysis showed a 63% reduction in bone turnover. In patients treated with Aclasta, no osteomalacia, marrow fibrosis or woven bone formation were detected. Tetracycline label was detectable in all but 1 of 82 biopsies obtained from patients on Aclasta. Microcomputed tomography analysis demonstrated increased trabecular bone volume and preservation of trabecular bone architecture in patients treated with Aclasta compared to placebo.

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

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

Days of Disability: Aclasta significantly reduced the mean days of limited activity and the days of bed rest due to back pain by 17.9 days

Clinical Efficacy in the Treatment of Osteoporosis in Patients at Increased Risk of Fracture After A Recent Hip Fracture (RFT): The incidence of clinical fractures, including vertebral, nonvertebral and hip fractures, was evaluated in 2127 men and women aged 50-95 years (mean age 74.5 years) with a recent (within 90 days) low-trauma hip fracture who were followed for an average of 2 years on study medication. Approximately 42% of patients had a femoral neck BMD T-score <-2.5 and approximately 45% of the patients had a femoral neck BMD T-score >-2.5 . Aclasta was administered once a year, until at least 211 patients in the study population had confirmed clinical fractures. Vitamin D levels were not routinely measured but a loading dose of vitamin D (50,000-125,000 iu orally or via the IM route) was given to the majority of patients 2 weeks prior to infusion. All participants received 1,000-1,500 mg of elemental calcium plus 800-1,200 iu of vitamin D supplementation per day. Ninety-five percent (95%) of the patients received their infusion greater than or equal to 2 weeks after the hip fracture repair and the median timing of infusion was approximately 6 weeks after the hip fracture repair. The primary efficacy variable was the incidence of clinical fractures over the duration of the study.

Effect on All Clinical Features: The incidence rates of key clinical fracture variables are presented in Table 3 (see Table 3).



[Click on icon to see table/diagram](#)

The study was not designed to measure significant differences in hip fracture, but a trend was seen towards reduction in new hip fractures.

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

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

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

Clinical Efficacy in Men: In the HORIZON-RFT study, 508 men were randomised into the study and 185 patients had BMD assessed at 24 months. At 24 months, a similar significant increase of 3.6 % in total hip BMD was observed for patients treated with Aclasta as compared to the effects observed in postmenopausal women in the HORIZON-PFT study. The study was not powered to show a reduction in clinical fractures in men; the incidence of clinical fractures was 7.5% in men treated with Aclasta versus 8.7% for placebo.

In another study in men (study CZOL446M2308) 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.

Clinical Efficacy in the Treatment of Paget's Disease of the Bone: Aclasta was studied in male and female patients aged >30 years with primarily mild to moderate Paget's disease of the bone (median serum alkaline phosphatase level 2.6-3 times the upper limit of the age-specific normal reference range at the time of study entry) confirmed by radiographic evidence.

The efficacy of 1 infusion of 5 mg zoledronic acid versus daily doses of 30 mg risedronate for 2 months was demonstrated in two 6-month comparative trials. After 6 months, Aclasta showed 96% (169/176) and 89% (156/176) response and serum alkaline phosphatase (SAP) normalisation rates compared to 74% (127/171) and 58% (99/171) for risedronate (all $p<0.001$).

In the pooled results, a similar decrease in pain severity and pain interference scores relative to baseline were observed over 6 months for Aclasta and risedronate.

patients maintained their therapeutic response compared to 71 risedronate-treated patients. This corresponds to a 96% reduction of risk of relapse in Aclasta versus risedronate-treated patients.

Bone histology was evaluated in 7 patients with Paget's disease 6 months after treatment with 5 mg zoledronic acid. Bone biopsy results showed bone of normal quality with no evidence of impaired bone remodelling and no evidence of mineralisation defects. These results were consistent with biochemical marker evidence of normalisation of bone turnover.

Pharmacokinetics: Single and multiple 5 and 15-min infusions of 2, 4, 8 and 16 mg zoledronic acid in 64 patients yielded the following pharmacokinetic data, which were found to be dose independent.

After initiation of the zoledronic acid infusion, plasma concentrations of the active substance increased rapidly, achieving their peak at the end of the infusion period, followed by a rapid decline to <10% of peak after 4 hrs and <1% of peak after 24 hrs, with a subsequent prolonged period of very low concentrations not exceeding 0.1% of peak levels.

IV administered zoledronic acid is eliminated by a triphasic process: Rapid biphasic disappearance from the systemic circulation, with half-lives of $t_{1/2\alpha}$ 0.24 and $t_{1/2\beta}$ 1.87 hrs, followed by a long elimination phase with a terminal elimination half-life of $t_{1/2\gamma}$ 146 hrs. There was no accumulation of the active substance in plasma after multiple doses given every 28 days. The early disposition phases (α and β , with $t_{1/2}$ values previously mentioned) presumably represent rapid uptake into bone and excretion via the kidneys.

Zoledronic acid is not metabolised and is excreted unchanged via the kidney. Over the first 24 hrs, $39 \pm 16\%$ of the administered dose is recovered in the urine, while the remainder is principally bound to bone tissue. From the bone tissue, it is released very slowly back into the systemic circulation and eliminated via the kidney. The total body clearance is 5.04 ± 2.5 L/hr, independent of dose and unaffected by gender, age, race or body weight. The inter- and intrasubject variation for plasma clearance of zoledronic acid was shown to be 36 and 34%, respectively. Increasing the infusion time from 5-15 min caused a 30% decrease in zoledronic acid concentration at the end of the infusion, but had no effect on the area under the plasma concentration versus time curve.

No specific drug-drug interaction studies have been conducted with zoledronic acid. Since zoledronic acid is not metabolised in humans and the substance was found to have little or no capacity as a direct-acting and/or irreversible metabolism-dependent inhibitor of P-450 enzymes, zoledronic acid is unlikely to reduce the metabolic clearance of substances which are metabolised via the cytochrome P-450 enzyme systems. Zoledronic acid is not highly bound to plasma proteins (approximately 43-55% bound) and binding is concentration independent. Therefore, interactions resulting from displacement of highly protein-bound drugs are unlikely.

Special Populations (see Dosage & Administration): The renal clearance of zoledronic acid was correlated with creatinine clearance, renal clearance representing $75 \pm 33\%$ of the creatinine clearance, which showed a mean of 84 ± 29 mL/min (range 22-143 mL/min) in the 64 patients studied. Small observed increases in $AUC_{(0-24 \text{ hrs})}$ by about 30-40% in mild to moderate renal impairment, compared to a patient with normal renal function and lack of accumulation of drug with multiple doses irrespective of renal function, suggest that dose adjustments of zoledronic acid in mild (creatinine clearance=50-80 mL/min) and moderate renal impairment down to a creatinine clearance of 35 mL/min are not necessary. As only limited data are available in severe renal impairment (creatinine clearance <30 mL/min), no dosing recommendations are possible for this population.

Toxicology: Preclinical Safety Data: Acute Toxicity: The highest nonlethal single IV dose was 10 mg/kg body weight in mice and 0.6 mg/kg in rats. In the single-dose dog infusion studies, 1 mg/kg (6 fold the recommended human therapeutic exposure based on AUC) administered over 15 min was well tolerated with no renal effects.

human therapeutic exposure) while five 15-min infusions of 0.25 mg/kg administered at 2-3 week intervals (a cumulative dose that corresponded to 7 times the human therapeutic exposure) were well tolerated in dogs. In the IV bolus studies, the doses that were well tolerated decreased with increasing study duration: 0.2 and 0.02 mg/kg daily was well tolerated for 4 weeks in rats and dogs, respectively but only 0.01 mg/kg and 0.005 mg/kg in rats and dogs, respectively, when given for 52 weeks.

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

Reproduction Toxicity: Teratology studies were performed in 2 species, both via SC administration. Teratogenicity was observed in rats at doses greater than or equal to 0.2 mg/kg and was manifested by external, visceral and skeletal malformations. Dystocia was observed at the lowest dose (0.01 mg/kg body weight) tested in rats. No teratological or embryo/foetal effects were observed in rabbits, although maternal toxicity was marked at 0.1 mg/kg due to decreased serum calcium levels.

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

MIMS Class	Agents Affecting Bone Metabolism
ATC Classification	M05BA08 - Zoledronic acid ; Belongs to the class of bisphosphonates. Used in the treatment of bone diseases.
Poison Schedule	POM
Packing/Presentation	Soln 5 mg/100 mL (clear, colourless) x 100 mL.

Manufacturer: [Novartis](#)

Distributor: [Zuellig](#)



Related Aclasta soln information:

[Aclasta drug image](#)

[Drugs interacting with Aclasta](#)

[Find Aclasta in other countries](#)

[Search Aclasta in Google](#)

[Search Aclasta in PubMed](#)

[Abbreviation Index](#)

