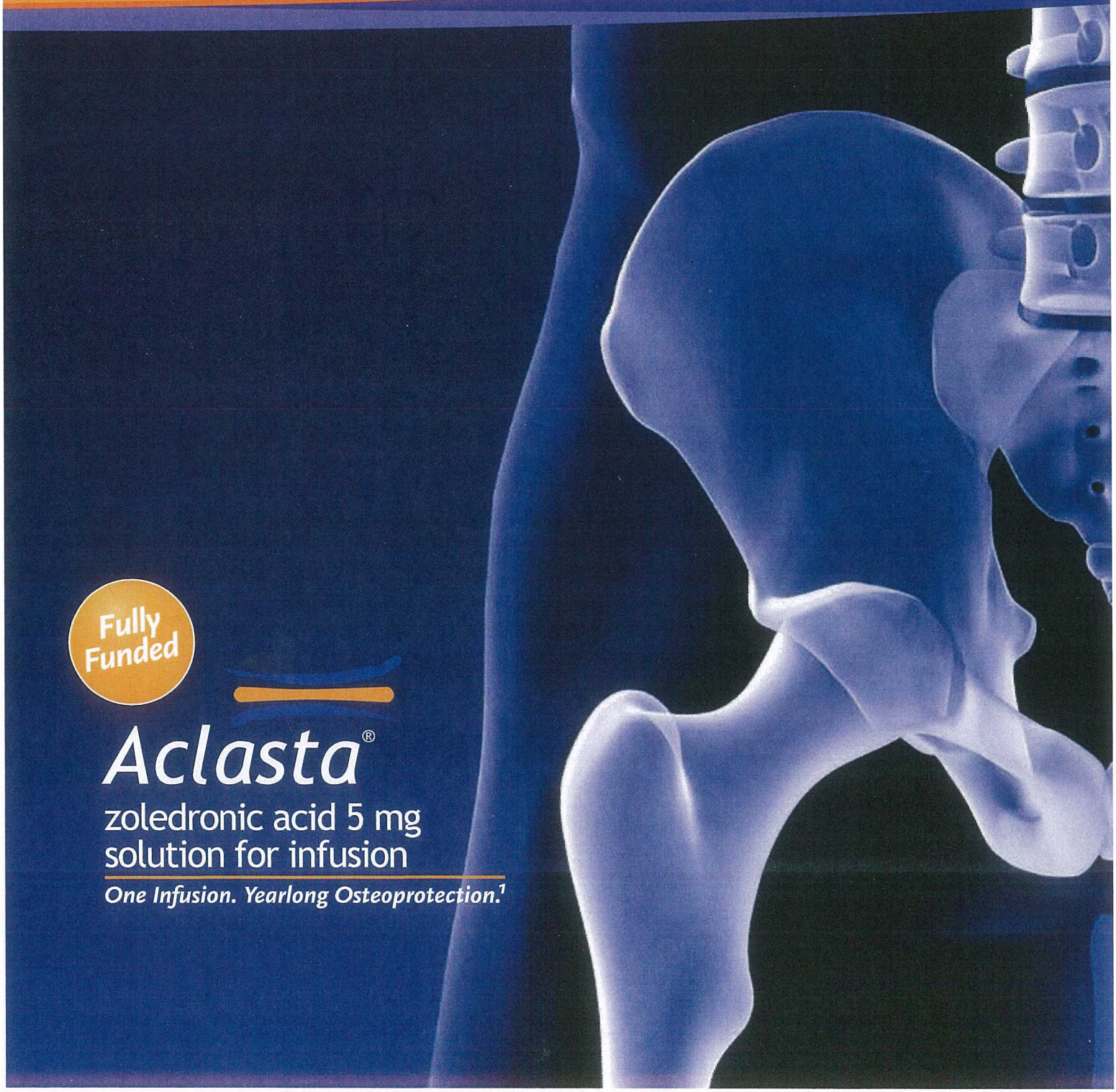
Prescribers Guide to Infusing Aclasta



Fully Funded

Aclasta®

zoledronic acid 5 mg solution for infusion

One Infusion. Yearlong Osteoprotection.[1]

Funded Indications[1]

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density.
- Treatment of osteoporosis in men.
- Treatment of Paget's disease of bone.
- Treatment and prevention of glucocorticoid-induced osteoporosis.
- Prevention of clinical fractures in patients after hip fracture.

Mechanism of Action (MOA)[1]

Zoledronic acid belongs to the class of nitrogen-containing bisphosphonates and acts primarily on bone. It is an inhibitor of osteoclast-mediated bone resorption.

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

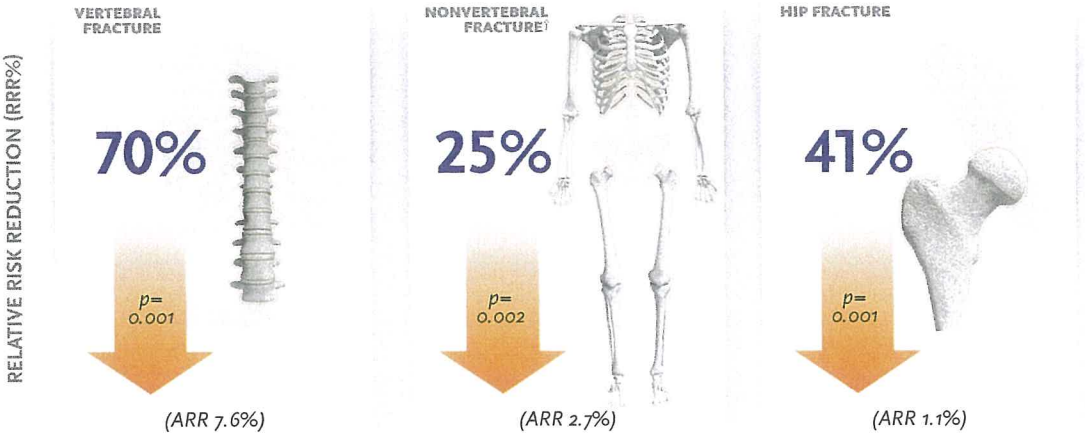
Osteoporosis:

Osteoporosis is a condition where bones become porous and hence fragile and brittle, increasing the risk of fracture after 'minimal trauma' (e.g. a fall or knock).

Aclasta treatment rapidly reduced the rate of bone turnover from elevated postmenopausal levels with the nadir for resorption markers observed at 7 days, and for formation markers at 12 weeks. Thereafter bone markers stabilised within the premenopausal range. There was no progressive reduction of bone turnover markers with repeated annual dosing.[1]

Proven to reduce fracture risk at 3 key osteoporotic sites*

The HORIZON Pivotal Fracture Trial was a 3-year, multinational, randomised, double-blind, placebo controlled study that enrolled 7736 postmenopausal women with osteoporosis, aged 65 to 89 years from 240 clinical centres in 27 countries. Patients received a 15-minute infusion of Aclasta or placebo once a year for 3 years. All women received 1000 to 1500 mg elemental calcium and 400 to 1200 IU vitamin D per day.[2]

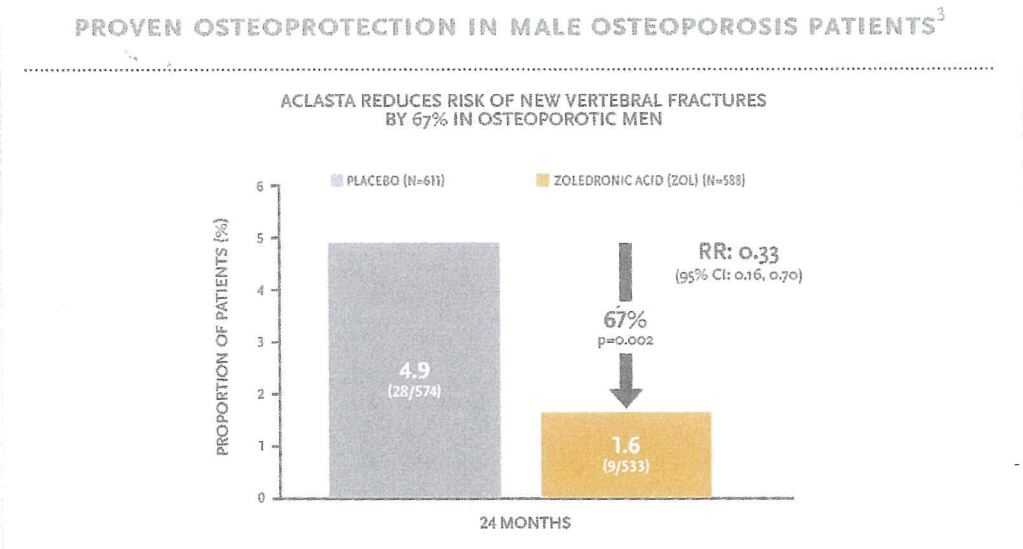


*Relative to placebo. †Nonvertebral fracture is a composite endpoint excluding finger, toe, and facial fractures.
ARR: Absolute Risk Reduction.

Aclasta has demonstrated benefit in fracture outcomes (as primary endpoint) in men with osteoporosis[3]

STUDY DESIGN:

Study M2309 was a multicenter, multinational, randomised, double-blind, placebo controlled, 2 year study in 1199 men with primary osteoporosis or secondary osteoporosis due to hypogonadism. Primary objective was to show reduction in morphometric vertebral fracture for Aclasta compared to placebo in male osteoporosis patients. All patients received 1000 to 1500 mg calcium and 800-1200 IU vitamin D per day. The incidence of serious adverse events (Aclasta 25.3%; placebo 25.2%) and deaths (Aclasta 2.6%; placebo 2.9%) was similar between both treatment groups.



Patient adherence to oral bisphosphonates is poor[4,5]

NON-ADHERENCE CAN TAKE MANY FORMS:[6,7]

- Discontinuation of therapy
- Missed doses
- Not following dosing instructions

FOOD RESTRICTIONS: NEED TO FAST BEFORE AND AFTER DOSING[6,7]

NEED TO REMAIN UPRIGHT AFTER DOSING[6,7]

GASTROINTESTINAL SIDE EFFECTS[6,7]

INCREASED PILL BURDEN[6,7]

Query Build

You may want to consider patients who might benefit from Aclasta by identifying patients in your practice by putting together a query build on your practice management system

- Patients > 50 yrs
- Smokers
- Diagnosis of Osteoporosis
- Patients on oral bisphosphonates
- Diagnosis of Paget's Disease
- Other osteoporosis treatments
- Long term steroid usage (e.g. – prednisone)

Risk factors for osteoporosis[8]

- Age – 50 years or older
- A previous fragility fracture
- A family history of osteoporosis
- Alcohol consumption (more than four standard drinks/day)
- Cigarette smoking

Dosage and Administration

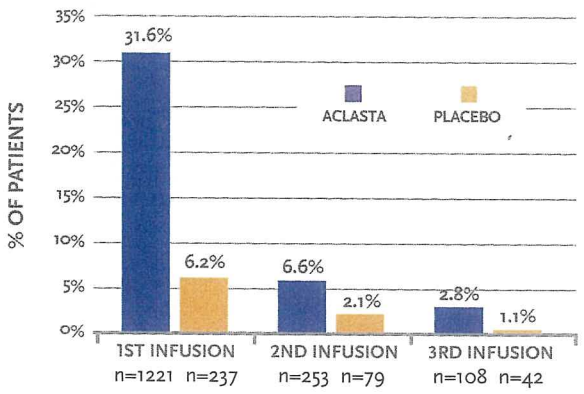
GENERAL

The incidence of post-dose symptoms occurring within the first three days after administration of Aclasta can be reduced with the administration of paracetamol or ibuprofen shortly following Aclasta administration.[1]

FIVE MOST COMMON POST-DOSE SYMPTOMS (≤3 DAYS AFTER INFUSION)

	ACLASTA (N=3862)	PLACEBO (N=3852)
	no. of patients (%)	
Pyrexia	16.1%	2.1%
Myalgia	9.5%	1.7%
Influenza-like symptoms	7.8%	1.6%
Headache	7.1%	2.3%
Arthralgia	6.3%	2.0%

ANY OF THE FIVE MOST COMMON POST-DOSE SYMPTOMS[2]



Patients must be appropriately hydrated prior to administration of Aclasta. This is especially important in the elderly and for patients receiving diuretic therapy.[1]

Treatment of Postmenopausal Osteoporosis, Osteoporosis in Men & Glucocorticoid-induced Osteoporosis - Calcium & Vitamin D Recommendations[1]

The recommended dose is a single intravenous infusion of 5 mg infusion of Aclasta administered once a year. Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate.[1]

Prevention of Clinical Fractures after a Hip Fracture

For the prevention of clinical fractures after a low-trauma hip fracture, the recommended dose is a single intravenous infusion of 5 mg Aclasta administered once a year. In patients with a recent low-trauma hip fracture, it is recommended to give the first Aclasta infusion two or more weeks after hip fracture repair.[1]

In patients with a recent low-trauma hip fracture, a loading dose of 50,000 to 125,000 IU of vitamin D given orally or via the intramuscular route is recommended prior to the first Aclasta infusion. Supplemental calcium and vitamin D intake is recommended for patients treated to prevent clinical fractures after a low-trauma hip fracture.[1]

Treatment of Paget's disease of Bone

For the treatment of Paget's disease, Aclasta should be prescribed only by physicians with experience in treatment of Paget's disease of the bone. The recommended dose is a single intravenous infusion of 5mg Aclasta.[1]

In patients with Paget's disease, adequate vitamin D intake is recommended in association with Aclasta administration. In addition, it is strongly advised that adequate supplemental calcium corresponding to at least 500 mg elemental calcium twice daily is ensured in patients with Paget's disease for at least 10 days following Aclasta administration.[1]

Fully Funded

Aclasta®
zoledronic acid 5 mg
solution for infusion

Protocol for Infusion of Aclasta (zoledronic acid 5mg)

Written in collaboration with Professor Ian Reid and colleagues from Auckland Bone Density.

GUIDELINES:

PRE-INFUSION CHECKS	RECOMMENDATIONS
Calcium and Vitamin D Status* Severe Vitamin D deficiency can result in severe hypocalcaemia following intravenous bisphosphonates. Confirm patient serum calcium is within normal range (2.0 – 2.6 mmol/L)	Adequate supplemental calcium and vitamin D intake is important in women with osteoporosis if dietary intake is inadequate
Renal Function Confirm patients creatinine clearance is >35 mL/min	Aclasta should not be used in patients with renal impairment (creatinine clearance of <35 mL/min)
Confirm the patient is adequately hydrated. Warn patients of 30% risk of flu-like symptoms within first 3 days of infusion	Patient should eat normally on day of infusion and drink an extra 2 glasses of fluid. Paracetamol can reduce flu-like symptoms significantly
Contraindications*	Aclasta should not be given to patients with hypocalcaemia or those with an allergy to bisphosphonates

* See Data Sheet for further information

INFUSION PROCEDURE

- The infusion should be given in the form provided by the manufacturer (in 100 mL normal saline) over at least 15 minutes, by a drip into a peripheral vein
- Some doctors may infuse more slowly in older patients, and in those with GFR <50ml/min
- Patients can be sitting up or lying down
- Flushing of the line is recommended

POST-INFUSION RECOMMENDATIONS

- Advise patients to maintain adequate fluid intake
- Advise patients to take paracetamol if they experience flu-like symptoms

DOSE AND DOSE INTERVAL

- Aclasta is given in a dose of 5 mg
- For osteoporosis treatment, the approved dose interval is 1 year. After 3 years of treatment the patient's individual risk should be reassessed to see who might benefit from the continuation of annual treatment with Aclasta.[9]

Checklist before infusing Aclasta*

	CHECKLIST	RESPONSE
1	Has patient had their normal (or greater) fluid intake such as tea, coffee and water?	Yes No
2	Is patients **creatine clearance >35ml/min**?	Yes No
3	Consider the patient's Vitamin D status.	Yes No
4	Is their **serum Calcium** normal?	Yes No
5	Have the **patient's questions** been answered?	Yes No
6	Have you checked the patient's **list of current medications** to ensure there are no contraindications to prescribing Aclasta?	Yes No
7	Has the patient signed the consent form?	Yes No
8	Has the patient been instructed to **stop any oral bisphosphonate** tablets (if they were currently taking them)?	Yes No
9	Does the patient have paracetamol at home or do they need a prescription?	Yes No

*Adapted from Auckland Bone Density

Fully Funded

Aclasta®
zoledronic acid 5 mg
solution for infusion

How to Administer Aclasta (zoledronic acid 5 mg):

- Assemble supplies including a vented infusion line or venting needle
- Obtain IV access (ensure aseptic techniques are used during preparation of the infusion)
- Prepare Aclasta by removing vial cap, insert giving set, prime tubing
- Do not mix Aclasta or give intravenously with any other medication
- Infuse for no less than 15 minutes at a constant infusion rate
- Some healthcare professionals may choose to infuse more slowly in older patients
- Flushing of the line is recommended
- Remove IV catheter and dispose of properly

Aclasta is provided in ready-to-use plastic bottles as a single 5 mg dose in 100 mL aqueous solution. A single dose should not exceed 5 mg.

RECOMMENDED INFUSION SUPPLIES

- IV administration set **with vent**/needle
- IV administration catheter
- Tourniquet
- Alcohol pads
- 20ml normal saline

Frequently Asked Questions[1]

Who cannot take Aclasta?

Aclasta contains zoledronic acid, the same active ingredient found in Zometa® (zoledronic acid 4mg) injection, and a patient already being treated with Zometa should not be treated with Aclasta. Patients hypersensitive to zoledronic acid or bisphosphonates; are hypocalcaemic; pregnant; or lactating, should not receive Aclasta.

What can my patients expect post infusion?

In clinical trials, transient postdose symptoms (fever, myalgia, flu-like symptoms, headache, and arthralgia) were the most common adverse events. The majority occurred within 3 days of infusion and most resolved within 3 days of onset but rarely took up to 7-14 days. The incidence of these symptoms was markedly decreased with subsequent doses of Aclasta. Treatment with ibuprofen or paracetamol can significantly reduce the incidence of postdose symptoms.

How do you store Aclasta?

Keep unopened vial below 30°C

Opened vials should be used immediately

Unused, opened vials can be stored up to 24hrs at 2-8°C

Discard any unused contents of the vial after infusion

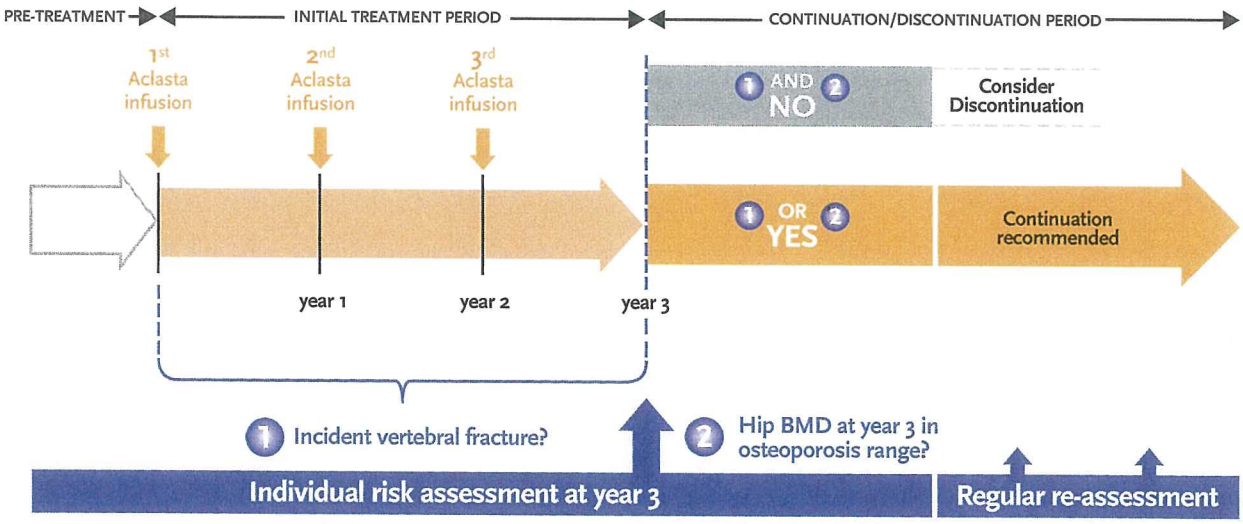
Aclasta must reach room temperature prior to infusion if refrigerated.

How long to treat?

- The long-term efficacy and safety profile of Aclasta for the treatment of osteoporosis has been well established and is based on both safety and efficacy data now out to 9 years duration.[9-11]

Who could benefit from continuation of treatment beyond 3 years?

INDIVIDUAL RISK ASSESSMENT IDENTIFIES PATIENTS, WHO WOULD BENEFIT FROM TREATMENT WITH ACLASTA BEYOND 3 YEARS[9,10]



After 3 years of treatment with Aclasta (initial treatment period) the patient's individual risk should be assessed based on two criteria:[9]

1) Was there a vertebral fracture in the 3 year treatment period with Aclasta?

2) Is the hip BMD at year 3 still within the Osteoporosis range (≤-2.5 T score)?

If either of these two criteria are fulfilled, the patient is at high risk for vertebral fractures and will benefit from the continuation of annual treatment with Aclasta beyond 3 years.

For all patients a re-assessment of individual risk factors should be done on a periodic basis together with calculation of absolute fracture risk.

Fully Funded

Aclasta®
zoledronic acid 5 mg
solution for infusion

Special Authority Criteria[12]

INITIAL APPLICATION - Underlying cause - Osteoporosis

Applications from any relevant practitioner. Approvals valid without further renewal unless notified.

Prerequisites (tick boxes where appropriate).

☐ History of one significant osteoporotic fracture demonstrated radiologically and documented bone mineral density (BMD) ≥ 2.5 standard deviations below the mean normal value in young adults (i.e. T-Score ≤ -2.5) (see Note)

or

☐ History of one significant osteoporotic fracture demonstrated radiologically, and either the patient is elderly, or densitometry scanning cannot be performed because of major logistical, technical or pathophysiological reasons. It is unlikely that this provision would apply to many patients under 75 years of age.

or

☐ History of two significant osteoporotic fractures demonstrated radiologically

or

☐ Documented T-Score ≤ -3.0 (see Note)

or

☐ A 10-year risk of hip fracture ≥ 3%, calculated using a published risk assessment algorithm (e.g. FRAX or Garvan) which incorporates BMD measurements (see Note).

or

☐ Patient has had a Special Authority approval for alendronate (Underlying cause - Osteoporosis) or raloxifene.

and ☐ The patient will not be prescribed more than one infusion in a 12-month period.

INITIAL APPLICATION - Underlying cause - glucocorticosteroid therapy

Applications from any relevant practitioner. Approvals valid for 1 year.

Prerequisites (tick boxes where appropriate)

☐ The patient is receiving systemic glucocorticosteroid therapy (≥5 mg per day prednisone equivalents) and has already received or is expected to receive therapy for at least three months

and

☐ The patient has documented BMD ≥ 1.5 standard deviations below the mean normal value in young adults (i.e. T-Score ≤ -1.5) (see Note)

or

☐ The patient has a history of one significant osteoporotic fracture demonstrated radiologically

or

☐ The patient has had a Special Authority approval for alendronate (Underlying cause - glucocorticosteroid therapy) or raloxifene

and ☐ The patient will not be prescribed more than one infusion in the 12-month approval period.

RENEWAL - Underlying cause was and remains, glucocorticosteroid therapy

Current approval Number (if known):.....

Applications from any relevant practitioner. Approvals valid for 1 year. The patient must have had no more than 1 prior approval in the last 12 months

Prerequisites (tick boxes where appropriate)

☐ The patient is continuing systemic glucocorticosteroid therapy (≥5 mg per day prednisone equivalents)

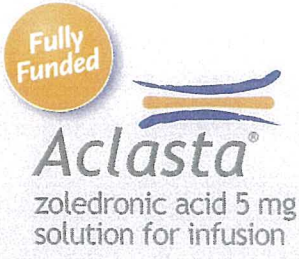
and

☐ The patient will not be prescribed more than one infusion in the 12-month approval period.

Minimum Prescribing Information

Aclasta®(zoledronic acid) 5mg/100mL solution is a Prescription Medicine, fully funded under Special Authority criteria for any patient who has ◆ had a prior Special Authority for alendronate • a T score ≤ -3.0 • a T score ≤ -2.5 with an osteoporotic fracture • a history of two osteoporotic fractures • a history of one osteoporotic fracture with x-ray confirmation in frail elderly unable to access DXA scan • a 10 year risk of hip fracture ≥ 3% calculated using a risk assessment algorithm (FRAX or GARVAN) • receiving glucocorticosteroid therapy (≥ 5mg/day prednisone equivalent) for at least 3 months and either a T score of ≤ -1.5 or one osteoporotic fracture demonstrated radiologically. Note: Special Authorities are not interchangeable and the funding does not include the cost of infusion. Aclasta is indicated for the treatment of various causes of osteoporosis to prevent hip, vertebral and non-vertebral fractures. It is also indicated for Paget's disease. **Contraindications:** Severe renal impairment (creatinine clearance < 35 mL/min), hypocalcaemia, pregnancy and lactation and hypersensitivity to any bisphosphanates. **Precautions:** Aclasta should not be used in children and adolescents. Patients should have creatinine clearance calculated before receiving Aclasta. Proper hydration is necessary, especially in the elderly, and patients receiving diuretic therapy. Caution is indicated with medicines that can significantly impact renal function e.g. diuretics and aminoglycosides. Pre-existing hypocalcaemia must be treated by adequate intake of calcium and vitamin D before initiating Aclasta. Other disturbances of mineral metabolism must also be effectively treated e.g. diminished parathyroid reserve. Supplemental calcium and vitamin D intake is important and it is advised that Paget's patients receive adequate supplemental calcium corresponding to 500 mg of elemental calcium twice a day and vitamin D during the initial 10 days following Aclasta administration. During treatment with Aclasta it is prudent to maintain good oral hygiene, have regular dental check-ups and immediately report any oral symptoms. **Dosage:** A single IV infusion of 5mg Aclasta in 100ml over no less than 15 minutes once a year. **Interactions:** Concomitant administration with medicines that significantly impact renal function. **Adverse Effects:** Possible side effects are fever, headache, dizziness, nausea, vomiting, diarrhoea, myalgia, arthralgia, bone pain, pain in extremities, flu-like symptoms, chills, fatigue, asthenia, pain, malaise, anorexia, tremor, conjunctivitis, eye pain, iritis, abdominal pain, constipation, night sweats, pain in the jaw, neck pain, peripheral oedema & infusion site reactions. Bisphosphonates have been associated with osteonecrosis of the jaw (primarily in patients receiving treatment for cancer), and also rarely associated with atypical femoral fractures in patients on long-term treatment for osteoporosis. For full prescribing information refer to full Data Sheet at www.medsafe.govt.nz. Aclasta is a registered trade mark of Novartis AG, Switzerland. Novartis New Zealand Limited, Auckland. Ph 0800 652 422.

References: **1.** Aclasta Data Sheet, Novartis New Zealand Limited. **2.** Black DM, et al. N Engl J Med. 2007; 356:1809-1822. **3.** Boonen S, et al. N Engl J Med 2012;367:1714-23. **4.** Landfeldt E, et al. Osteoporos Int 2012; 23:433–443. **5.** Osterberg L and Blaschke T. N Engl J Med 2005;353:487-97. **6.** International Osteoporosis Foundation. The adherence gap: why osteoporosis patients don't continue with treatment. 2005. **7.** Fosamax Data Sheet, Merck Sharp & Dohme (New Zealand) Limited. http://www.medsafe.govt.nz/profs/datasheet/f/Fosamaxtab.pdf. **8.** "The Burden of Osteoporosis in New Zealand" Osteoporosis New Zealand Paper produced by University of Auckland, 2007. **9.** Black DM, et al. J Bone Miner Res. 2012;27(2):243-54. **10.** September 9, 2011 Joint Meeting of the Reproductive Health Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee - Novartis Pharmaceuticals Cooperation Meeting Materials. FDA webpage accessed November 25th, 2011 http://www.fda.gov/downloads/AdvisoryCommitteesCommitteesMeetingMaterials/DrugsReproductiveHealthDrugsAdvisoryCommittee/UCM271911.pdf. **11.** Black DM, et al. Oral Presentation ASBMR, October 2013, Presentation #SA0389. **12.** http://www.pharmac.govt.nz/2014/06/01/SA1187.pdf



Fully Funded

Aclasta®

zoledronic acid 5 mg solution for infusion

One Infusion. Yearlong Osteoprotection.[1]

NOVARTIS
PHARMACEUTICALS

ACL 1015-280
TAPS NA7210