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# **Intravenous bisphosphonates in osteoporosis: Key questions**

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## Introduction

NSW TAG was requested to update the position statement: *Bisphosphonates for the Treatment of Osteoporosis. May 2000.*

In particular, the following questions were asked:

1. What is the difference between different preparations of zoledronic acid (Aclasta<sup>®</sup> and Zometa<sup>®</sup>)?
2. What is the role of intravenous bisphosphonates in older people in the prevention and/or treatment of a fracture?
3. What is the role of intravenous bisphosphonates in preventing/treating corticosteroid-induced osteoporosis?
4. What is the current evidence regarding the risk of osteonecrosis of the jaw in people receiving intravenous bisphosphonates?
5. What are the safety issues in using IV bisphosphonates in paediatric patients?

## Method:

Guidelines, meta-analyses and systematic reviews were searched for that included information related to intravenous bisphosphonates used in osteoporosis (from 2005-present). The following places were searched:

- Medical data bases (Medline, Embase, Cochrane Database of Systematic Reviews)
- Australian and International websites known to contain guidelines, reviews or other evidence based information
- Websites focussed on quality use of medicines
- Websites related to osteoporosis

Websites searched are listed in appendix 1.

Preference was given to clinical practice guidelines, meta-analyses and systematic reviews that:

- reported the type of professionals and stakeholders involved in the development process (including their potential conflicts of interest);
- outlined the strategy to identify primary evidence; and
- included an explicit grading of recommendations according to the quality of supporting evidence.

Medical data bases were also searched for relevant published case reports, case series, observational studies, and randomised controlled trials for information related to safety issues.

Other sources of information reviewed include:

- Relevant product information monographs
- Information provided by the Pharmaceutical Benefits Scheme (PBS) and the Pharmaceutical Benefits Advisory Committee (PBAC)
- Information provided by the Therapeutic Goods Administration
- Information provided by relevant product sponsor
- Therapeutic Guidelines (Endocrinology), 2009
- Australian Medicines Handbook, 2010.

## Scope:

Only medications in the relevant formulations approved for use in Australia for the relevant indications are discussed.

## 1. What is the difference between different preparations of zoledronic acid (Aclasta<sup>®</sup> and Zometa<sup>®</sup>)?

### Approval status:

Zoledronic acid is available in Australia as two preparations:

- Aclasta<sup>®</sup> which is indicated for osteoporotic conditions (Table A)
- Zometa<sup>®</sup> which is indicated for neoplastic conditions (Table A)

Aclasta<sup>®</sup> and Zometa<sup>®</sup> are presented as different strengths and require different dosing schedules. The key difference is the dosing schedule with Aclasta<sup>®</sup> given as a single 5 mg dose once a year for three years, while Zometa<sup>®</sup> is given as a 4mg dose every 3-4 weeks over a longer term. Differences in formulation, available strengths, administration, dosing, use in older people and the need for supplementation with calcium and vitamin D are summarised in Table B.

### Other information to guide decision making:

Correspondence was undertaken with Novartis Australia, the product sponsor of Aclasta<sup>®</sup> and Zometa<sup>®</sup>, regarding the dosing difference between the two formulations of zoledronic acid. Novartis Australia indicated that previous trials had indicated that a 4 mg yearly dose of zoledronic acid was likely to be suboptimal in terms of preventing fractures. Therefore, a zoledronic acid 5 mg yearly dose was selected for use in the clinical trials assessing zoledronic acid efficacy and safety in osteoporosis. Further Novartis points out that 4mg yearly dose of zoledronic acid has not demonstrated anti-fracture efficacy in other trials and it is not feasible to trial 4 mg vs 5 mg zoledronic acid due to the large number of patients required for such a trial. The full response from Novartis is included as appendix 2 to this paper.

**Comment:** There is no evidence to support the efficacy of a 4 mg yearly dose of zoledronic acid on preventing osteoporotic fracture. Therefore using Zometa<sup>®</sup> instead of Aclasta<sup>®</sup> for people with osteoporosis is not recommended.

**Table A: Indications and PBS listings<sup>1, 2</sup>**

	PBS Indication	Zoledronic acid (Aclasta <sup>®</sup> )	Zoledronic acid (Zometa <sup>®</sup> )
Osteoporotic conditions	Treatment for established osteoporosis in a patient with fracture due to minimal trauma	Authority	⊗
	Treatment as the sole PBS-subsidised anti-resorptive agent for osteoporosis in a patient aged 70 years of age or older with a Bone Mineral Density (BMD) T-score of -3.0 or less.	Authority	⊗
	To prevent glucocorticoid induced BMD loss in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less.	Authority	⊗
Other conditions	Symptomatic Paget's disease of the bone	Authority	⊗
	Tumour induced hypercalcaemia refractory to antineoplastic therapy	⊗	S100 Private hospital authority
	Lytic bone metastases from breast cancer	⊗	S100 Private hospital authority
	Bone metastases from hormone resistant prostate cancer with demonstration of biochemical progression of disease despite maximal therapy with hormone treatments	⊗	S100 Private hospital authority
	Advanced multiple myeloma	⊗	S100 Private hospital authority

**Table B: Differences between dose forms of zoledronic acid<sup>1-3</sup>**

	<b>Zoledronic acid (Aclasta<sup>®</sup>)</b>	<b>Zoledronic acid (Zometa<sup>®</sup>)</b>
<b>Presentation</b>	Solution for infusion	Sterile liquid concentrate for dilution for IV infusion.
<b>Available Strengths</b>	5 mg/100 mL ready to use infusion	4 mg/5mL for dilution with 100mL calcium free infusion solution
<b>Administration</b>	-Infuse intravenously over no less than 15 minutes -Infuse over no less than 15 minutes via a dedicated vented infusion line.	Dilute with 100 mL of calcium free infusion solution -Infuse over no less than 15 minutes. -Use dedicated intravenous infusion line
<b>Dosing</b>	-No more than a single 5 mg infusion once a year for three years for osteoporosis. -A single 5 mg infusion only for Paget's disease.	Dependant on condition – generally 4 mg by infusion every 3-4 weeks
<b>Prehydration</b>	-Required eg 2 glasses fluid before and after infusion	-Required
<b>Monitoring</b>	-Consider after treatment in patients with pre-existing disturbances of mineral metabolism.	-Serum calcium, phosphate, magnesium, potassium, creatinine
<b>Use in the elderly (&gt;75 years)</b>	-No overall differences seen in safety or efficacy patients over and under 75 years. -When used in older people ensure monitor renal function and pre-hydration.	-No information in product information
<b>Use in paediatric patients</b>	Not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.	Safety and efficacy in paediatric patients has not been established.
<b>Supplemental calcium and vitamin D</b>	-Osteoporosis: recommended if diet inadequate -Following hip fracture: recommended -Paget's disease: recommended	Recommended in patients with advanced malignancies.
<b>Key adverse events</b>	-Acute phase reaction (common) -Musculoskeletal pain (infrequent) -Osteonecrosis of the jaw (very rare - predominantly in cancer patients) -Impaired renal function (rare)	-Acute phase reaction (common) -Musculoskeletal pain (infrequent) -Osteonecrosis of the jaw (very rare - predominantly in cancer patients) -Impaired renal function (rare)
<b>Cost per dose</b>	~\$550	~\$450

## Question 2: What is the role of IV bisphosphonates in older people for the prevention and/or treatment of a fracture?

### Approval status:

People older than 70 years qualify for PBS subsidised access to zoledronic acid if they have had a fracture due to minimal trauma or have a Bone Mineral Density (BMD) T-score of -3.0 or less<sup>1</sup>.

### Other information to guide decision making:

#### ***Australian and International published recommendations***

- Evidence-based guidelines for the management of hip fractures in older persons: an update<sup>4</sup>  
This Australian guideline recommends the following:  
*An annual infusion of zoledronic acid is associated with a reduction in rate of new clinical vertebral and non-vertebral fractures and may improve survival after a low-trauma hip fracture (B). B=body of evidence can be trusted to guide practice in most situations*
- Treatment for osteoporosis in Australian residential aged care facilities: consensus recommendations for fracture prevention.<sup>5</sup>  
These Australian consensus recommendations recommend the following:  
*Bisphosphonates are the first-choice pharmacological agents for fracture prevention in older persons at high risk. Intravenous administration is as efficient as oral and has the significant advantage of better adherence.*
- Atypical Subtrochanteric and Diaphyseal Femoral Fractures: Report of a Task Force of the American Society for Bone and Mineral Research<sup>6</sup>  
This US report on atypical fractures related to bisphosphonate use makes the following consensus based recommendation regarding prevention of atypical subtrochanteric femoral and femoral shaft fractures:  
*Decisions to initiate pharmacologic treatment, including [bisphosphonates], to manage patients with osteoporosis should be made based on an assessment of benefits and risks. Patients who are deemed to be at low risk of osteoporosis-related fractures should not be started on [bisphosphonates]. For patients with osteoporosis in the spine and normal or only moderately reduced femoral neck or total hip BMD, one could consider alternative treatments for osteoporosis ...depending on the severity of the patient's condition. It is apparent that therapy must be individualized and clinical judgment must be used because there will not always be sufficient evidence for specific clinical situations.*
- Systematic Review: Comparative Effectiveness of Treatments to Prevent Fractures in Men and Women with Low Bone Density or Osteoporosis.<sup>7</sup>  
This systematic review concluded the data was insufficient to determine relative efficacy or safety of any bisphosphonate agent in preventing osteoporotic fractures.

#### ***Fracture risk assessment tools***

- Garvan Institute fracture risk tool – Australia  
The Garvan Institute fracture risk tool (<http://www.garvan.org.au/bone-fracture-risk/>) provides values for 5 and 10 year fracture risk scores which are equivalent to current PBS reimbursements. These scores may be calculated with or without inclusion of bone mineral density (BMD) measurements and the tool has been validated for an Australian population.<sup>8</sup>
- Fracture Risk Assessment Tool (FRAX) – World Health Organization  
The FRAX tool was developed by the World Health Organization Collaborating Centre for Metabolic Bone Diseases (<http://www.shcf.ac.uk/FRAX/>). Assessments can be made for an Australian population aged between 40 and 90 years.

## ***Other considerations regarding appropriateness of therapy in older people***

### Mortality and survival

There is emerging evidence from a follow-up study from the HORIZON trial that there is reduced mortality from all causes post hip fracture in patients receiving zoledronic acid infusions compared with placebo.<sup>9</sup> Mortality differences were seen after 12 months but the cause for this reduction in mortality was unclear. A post-hoc analysis of this trial looked at the influence of timing of dosing on subsequent fractures and mortality.<sup>10</sup> Patients receiving zoledronic acid within 2 weeks after surgical repair of hip fracture did not have a significant reduction in fractures or mortality whilst those dosed after two weeks did have a reduction in fractures and mortality. This was more likely to be due to differences in baseline risk such as increased frailty, age and comorbidities (eg hypertension, coronary artery disease, diabetes, atrial fibrillation, and stroke) and institutionalisation than entrapment of bisphosphonate at the fracture site. Given that the effect of zoledronic acid treatment on hip fractures and mortality are not apparent until at least 12 months,<sup>9, 11</sup> consideration should be given to total duration of bisphosphonate therapy relative to lifespan. This is important given 19% of nursing home residents die within 3 months of admission and a further 20% die within 3-12 months.<sup>12</sup>

### Atypical fractures

Concerns about long term bisphosphonate use and femoral insufficiency fractures have arisen recently. In addition to the US report on atypical fractures related to bisphosphonate use mentioned above,<sup>6</sup> the US based Food and Drug Administration (FDA) and Health Canada have both provided additional regulatory advice as listed here:

- FDA: Bisphosphonates (Osteoporosis Drugs): Label Change - Atypical Fractures Update <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm229244.htm>
- Health Canada: Safety Review of Bisphosphonate Drugs and the Possible Risk of Rare but Serious Thigh Bone Fractures [http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2010/2010\\_175-eng.php](http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/2010/2010_175-eng.php)

### **Comment:**

Until further evidence is available, there is no basis for choosing an IV bisphosphonate rather than an oral bisphosphonate on the grounds of efficacy or safety. The choice of IV versus oral therapy in these circumstances should be made on clinical grounds. IV administration avoids potential gastro-intestinal irritation and facilitates compliance in those unable to manage recommendations for taking oral bisphosphonates. On cost-effectiveness considerations bisphosphonates should not be provided to those at low risk of osteoporosis related fractures.

Older people may have reduced mortality associated with zoledronic acid use post surgical repair of hip fracture, but age, frailty and other comorbidities may influence this outcome. As with other preventive health care approaches, consideration should be given to what interventions are appropriate in patients unlikely to survive a year. Patient wishes and values should be assessed.

A fracture risk assessment tool may help identify those at low risk. Prescribing IV bisphosphonates to older people based on a fracture risk assessment score that did not include BMD scores may be reasonable. However, this decision should be made cautiously as certain patients may be unable to gain continued access to the medicine in the community. In particular those who have not had a low trauma fracture may have difficulty accessing IV bisphosphonates as they will not have fulfilled current PBS funding criteria without BMD scores.

**All older people administered IV bisphosphonates during hospitalisation should have this clearly communicated in the discharge summary. Plans for continuity of care and appropriate arrangements for follow-up doses should be made by the admitting team and details clearly communicated in the discharge summary.**

### **Question 3: What is the role of IV bisphosphonates in corticosteroid-induced osteoporosis?**

#### **Approval status:**

On 2 July 2009 the TGA registration for zoledronic acid 5 mg in 100 mL (Aclasta<sup>®</sup>) was extended to include the following indications:<sup>13</sup>

- To increase bone mineral density in patients with osteoporosis associated with long term glucocorticoid use;
- To prevent glucocorticoid induced bone mineral density loss.
- To increase bone mineral density in men with osteoporosis

Current requirements for funding for use in corticosteroid induced osteoporosis include:<sup>13</sup>

*Treatment as the sole PBS-subsidised anti-resorptive agent for corticosteroid-induced osteoporosis in a patient currently on long-term (at least 3 months), high-dose (at least 7.5 mg per day prednisolone or equivalent) corticosteroid therapy with a Bone Mineral Density (BMD) T-score of -1.5 or less. The duration and dose of corticosteroid therapy together with the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement must be documented in the patient's medical records when treatment is initiated. Only 1 treatment each year for 3 years per patient in a lifetime will be PBS-subsidised.*

#### **Other information to guide decision making:**

The product information cites one study demonstrating the efficacy of zoledronic acid in treating and preventing corticosteroid induced osteoporosis.<sup>14</sup> It compared 5 mg zoledronic acid infusion with oral 5 mg risedronate daily but was not powered to show differences in fracture rates between the groups. The study authors wrote: *A single 5 mg infusion of zoledronic acid is non-inferior, possibly more effective, and more acceptable to patients than 5 mg of oral risedronate daily for prevention and treatment of bone loss that is associated with glucocorticoid use.*

No specific recommendations regarding comparative safety and efficacy of oral versus intravenous bisphosphonates in the prevention and/or treatment of steroid induced osteoporosis were found in the search undertaken as described above.

A recent Australian paper suggests IV and oral bisphosphonates are both first line therapy for preventing corticosteroid-induced osteoporosis.<sup>15</sup>

A Cochrane review<sup>16</sup> has been conducted and concluded bisphosphonates are effective at preventing and treating corticosteroid-induced bone loss at the lumbar spine and femoral neck. No studies in the review included patients taking zoledronic acid.

#### **Applicability to paediatric patients:**

Approval for funding on the Pharmaceutical Benefits Scheme was determined by the Pharmaceutical Benefits Advisory Committee on the basis of a single study.<sup>14</sup> This study enrolled patients aged 18-85 years of age from 54 centres in 16 countries. However, no paediatric patients were included. Therefore the applicability of its findings to paediatric patients is unknown.

#### **Comment:**

Until further evidence is available, there is no basis for choosing an IV bisphosphonate rather than oral bisphosphonate for the treatment and/or prevention of corticosteroid induced osteoporosis on grounds of efficacy or safety. The choice of IV versus oral bisphosphonate therapy in these circumstances should be made on clinical grounds and guided by factors such as: tolerance for oral therapy; compliance; risk of side effects; and cost. The applicability of IV bisphosphonates for use in treating and/or preventing corticosteroid induced osteoporosis in paediatric patients is unknown.



#### **Question 4: What is the current evidence regarding intravenous bisphosphonates and osteonecrosis of the jaw?**

The following list summarises available Australian resources to inform decision making in prevention and treatment of bisphosphonate related osteonecrosis of the jaw.

##### **Australian resources**

- NSW Health: GL2010\_010 Prevention of Osteonecrosis of the Jaw (ONJ) in Patients on Bisphosphonate Therapies.<sup>17</sup>

This consensus-based guideline is written for NSW Health Public Oral Health Practitioners and covers the following aspects:

- Bisphosphonates: Therapeutic Indications
  - Epidemiology of ONJ
    - Intravenous (IV) Bisphosphonates
    - Oral Bisphosphonates
  - ONJ: Aetiology and Pathogenesis
  - ONJ: Risk Factors
    - Drug-Related Risk Factors
    - Local Risk Factors
    - Demographic and Systemic Factors
  - Prevention of ONJ
    - Identification of Patients at-risk for ONJ
    - Treatment Planning for Patients at-risk for ONJ
    - Risk Stratification and Protocol Recommendations
    - Suggested Preventive Regimes for Dental Procedures
    - Post Operative Review
  - Treatment of Established ONJ
  - Dental Implant Placement
- Therapeutic Goods Administration:
    - 2007 Bisphosphonate drugs and osteonecrosis of the jaw<sup>18</sup>
    - 2006 Osteonecrosis of the jaw with bisphosphonates<sup>19</sup>
  - National Prescribing Service Limited:
    - 2007 Zoledronic acid (Aclasta) for osteoporosis<sup>20</sup>
    - 2007 Incidence and avoidance of osteonecrosis of the jaw associated with use of bisphosphonates<sup>21</sup>

##### **Comment**

- There is little evidence to guide clinical practice regarding prevention of ONJ. The key consensus-based messages specifically relevant for practitioners responsible for prescribing bisphosphonates and caring for patients prescribed bisphosphonate involves careful treatment planning.

### Question 5: What are the safety issues in using IV bisphosphonates in paediatric patients?

Intravenous bisphosphonates are used in children for a range of bone, mineral and joint disorders. More information has been published regarding use of IV pamidronate than zoledronic acid in paediatric patients.<sup>22</sup> Therefore, this paper looks at published reports of safety issues involving zoledronic acid in children used for any indication.

#### Available information regarding safety of zoledronic acid:

- Approved Product Information monographs for zoledronic acid<sup>1, 2</sup> state the following:
  - Zoledronic acid is contraindicated in the following conditions: Hypersensitivity to the active substance or to any of the excipients or to any bisphosphonates; hypocalcaemia; renal impairment (creatinine clearance < 35 mL/minute); current or recent uveitis, or a history of bisphosphonate associated uveitis; pregnancy and lactation.
  - Zoledronic acid is not recommended for use in children and adolescents below 18 years of age due to lack of data on safety and efficacy.
- Adverse reaction reports associated with zoledronic acid in children aged 18 years and under provided by the Therapeutic Goods Administration are listed in Table C:

**Table C: Adverse Drug Reaction reports provided by TGA**

Age (years)	Gender	Reason for treatment	Dose (mg)	Dose frequency	Reaction and treatment	Outcome
18	Male	Not recorded	4	Daily	Myalgia – peripheral leg aches lasting 3 days. Treated with prednisolone.	Unrelated death
10	Unknown	Acute lymphocytic leukaemia, B precursor type	1.7	One dose only	Hypocalcaemia. Treated with calcitriol and caltrate.	Recovered
7	Male	Not recorded	0.7	Daily	Vomiting and headache	Recovered
10	Male	Not recorded	Unknown	One dose	Crying, oropharyngeal pain, chest pain. Symptoms resolved spontaneously and infusion restarted.	Recovered
10	Male	Not recorded	4mg	One dose	Received adult dose not calculated dose of 1.7 mg.	Recovered with normal renal function
3 / 12	Female	Off-label use for idiopathic infantile arterial calcification	Not recorded	Not recorded	Not recorded	Infant died 5 weeks after presentation, causality not clear.

- A 2007 Cochrane review found the evidence does not support bisphosphonates as standard therapy for secondary osteoporosis. Nevertheless, short-term (3 years or less) bisphosphonate use appeared to be well-tolerated.<sup>23</sup>

- Other published reports regarding adverse events related to use of zoledronic acid in children are summarised below:
  - Acute phase reaction:
    - Symptoms include fever malaise, nausea, diarrhoea, and muscle or bone pain.
    - Usually occurs within 1-3 days of first dose and rarely recurs with subsequent doses.
    - Occurs commonly children<sup>24-26</sup>
    - May occur with zoledronic acid in up to 85% of patients<sup>27</sup>
  - Hypocalcaemia
    - Usually asymptomatic and resolves within days.<sup>24, 26</sup>
    - Symptomatic hypocalcaemia may also occur and is associated with corresponding increase in serum parathyroid hormone. Symptoms include confusion, dysarthria, parasthesia. Recommend 25-hydroxy vitamin D level of  $\geq 50$  nmol/L prior to zoledronic acid therapy.<sup>28</sup>
    - Symptomatic hypocalcaemia has been reported with zoledronic acid infusion 0.1 mg/kg (total dose 4 mg) in a patient with recessive dystrophic epidermolysis bullosa and secondary osteopenia.<sup>29</sup>
    - Reducing the initial dose of zoledronic acid from 0.02-0.025 mg/kg to 0.0125 mg/kg reduces incidence and severity of hypocalcaemia from 74-42% in children with various bone disorders. Resolved within 6 weeks.<sup>28</sup>
  - Mild isolated intermittent elevations in bilirubin of unknown clinical significance
    - Seen in 27% of 30 patients with severe osteogenesis imperfecta treated with either pamidronate or zoledronic acid.<sup>22</sup>

**Comment:**

Zoledronic acid is not recommended for use in children aged under 18 due to lack of data on safety and efficacy. Off label use of zoledronic acid in children may be appropriate if:<sup>30</sup>

- There is high quality evidence supporting it's use in condition of interest
- It is used within the formal research setting
- It is used for exceptional use, justified by individual clinical circumstances

Adverse events include acute phase reaction, symptomatic or asymptomatic hypocalcaemia and mild intermittent elevations in bilirubin.

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This document was prepared by the following staff at NSW TAG:

- Dr Jocelyn Lowinger, QUM and Publications Manager
- Ms Kate Oliver, Drug Use Evaluation Program Coordinator
- Ms Gill Campbell, Executive Officer

**Review:**

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- Members of the NSW TAG Editorial Committee

**Dualities of interest:**

- Professor John Eisman AO has received research funding and/or served as a consultant for: Amgen, deCode, Eli Lilly, Merck Sharp & Dohme, Novartis, Sanofi-Aventis and Servier.
- Dr Craig Munns is undertaking research studies using Zoledronic acid with provision of medicine and some study funding from Novartis. These studies are co-funded by the National Medical Health and Research Council (NHMRC) and the Australian Paediatric Endocrine Group (APEG).
- There are no other dualities of interest to declare

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## Appendix 1

### Websites searched

#### Australian Websites

- Australasian Paediatric Endocrine Group
- Australian Menopause Society
- Australian & New Zealand Bone & Mineral Society
- Australian Prescriber
- Centre for Clinical Effectiveness (Southern Health)
  
- Clinical Practice Guidelines Portal (NICS)
- Joanna Briggs Institute
- Medical Journal of Australia
- National Health and Medical Research Council
- National Prescribing Service
- Osteoporosis Australia
- Endocrine Society of Australia

[www.apeg.org.au](http://www.apeg.org.au)  
[www.menopause.org.au](http://www.menopause.org.au)  
[www.anzbms.org.au](http://www.anzbms.org.au)  
[www.australianprescriber.com](http://www.australianprescriber.com)  
[http://www.southernhealth.org.au/page/Health\\_Professionals/CCE/](http://www.southernhealth.org.au/page/Health_Professionals/CCE/)  
[www.clinicalguidelines.gov.au/](http://www.clinicalguidelines.gov.au/)  
[www.joannabriggs.edu.au](http://www.joannabriggs.edu.au)  
[www.mja.com.au](http://www.mja.com.au)  
[www.nhmrc.gov.au](http://www.nhmrc.gov.au)  
[www.nps.org.au](http://www.nps.org.au)  
[www.osteoporosis.org.au](http://www.osteoporosis.org.au)  
[www.endocrinesociety.org.au](http://www.endocrinesociety.org.au)

#### International Websites

- Agency for Healthcare Research and Quality
- Canadian Agency for Drugs and Technologies in Health
- Guidelines International Network
- Guidelines Advisory Committee
- International Osteoporosis Foundation
- National Guideline Clearinghouse US
- National Institute for Health and Clinical Excellence UK
- New Zealand Guideline Group
- NHS Evidence
- NHS National Patient Safety Agency
- NIHR Health Technology Assessment programme
- Scottish Intercollegiate Guidelines Network
- TRIP Database

[www.ahrq.gov](http://www.ahrq.gov)  
[www.cadth.ca/index.php/en/home](http://www.cadth.ca/index.php/en/home)  
[www.g-i-n.net](http://www.g-i-n.net)  
[www.gacguidelines.ca](http://www.gacguidelines.ca)  
[www.iofbonehealth.org](http://www.iofbonehealth.org)  
[www.guidelines.gov](http://www.guidelines.gov)  
[www.nice.org.uk](http://www.nice.org.uk)  
[www.nzgg.org.nz](http://www.nzgg.org.nz)  
<http://www.evidence.nhs.uk>  
[www.npsa.nhs.uk](http://www.npsa.nhs.uk)  
<http://www.hta.ac.uk>  
[www.sign.ac.uk](http://www.sign.ac.uk)  
[www.tripdatabase.com](http://www.tripdatabase.com)

## Appendix 2: Response from Novartis Pharmaceuticals Australia



Melissa Mee  
Medical Information

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Kate Oliver  
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Darlinghurst NSW 2010

26 March 2010

**ACLASTA** (zoledronic acid)  
Enquiry No.: 1-243871422

Re: Zoledronic Acid 4 mg vs 5 mg for Fracture Efficacy

Dear Kate

Thank you for your request received on 26 March 2010 for further information on the above subject.

Bone turnover suppression with bone-specific alkaline phosphatase (BSAP) =30% may be needed for antifracture efficacy on hip and other non-vertebral fractures (Bauer et al, 2004). Data from the Fracture Intervention Trial (FIT) was analysed to assess the relationship change in bone turnover after 1 year of alendronate (ALN) or placebo treatment (PBO) and subsequent hip, non-spine, and spine fracture risk among 6186 postmenopausal women. Biochemical markers of bone turnover, including BSAP, were measured and subsequent fractures documented. Each 1 standard deviation reduction in 1-year change in BSAP was associated with a 26% reduction in the risk of spine fractures, 11% reduction in the risk of non-spine fractures, and 39% reduction in the risk of hip fracture. In addition to this, ALN-treated women with =30% reduction in BSAP had a lower risk of non-vertebral and hip fractures, relative to those with reductions <30% (Bauer et al, 2004).

### Fracture Incidence in PBO Group and in ALN Group With and Without =30% 1-Year Reduction in BSAP

Fracture type	PBO group*	ALN group: <30% reduction in BSAP*	ALN group: =30% reduction in BSAP*
Spine	7.3%	4.3%†	3.8%†
Hip	1.0%	0.8%	0.2%†
Non-spine	9.8%	8.7%	6.8%†

\* Proportion of PBO and ALN groups with fracture outcome during the study; †  $P < .01$  vs PBO group.

A one-year, randomised, double-blind, placebo-controlled trial was conducted to study the effects of five regimens of zoledronic acid (0.25 mg, 0.5 mg, or 1 mg at three-month intervals; 2 mg doses at six-month intervals; annual dose of 4 mg) compared with placebo. Although lumbar-spine BMD was the primary end point of the trial (which was met, as the values achieved with all zoledronic acid regimens were significantly higher than those in the placebo group, [ $P < 0.001$ ]), certain bone turnover marker results indicated that the dose of zoledronic acid 4 mg may not have been adequate when given as an annual dose. From 6 months to 1 year, there was an upward trend of BSAP in the group treated with one annual dose of zoledronic acid 4 mg (Reid et al, 2002).

This evidence was one major factor in influencing the decision to use a higher dose of zoledronic acid 5 mg once-yearly in the HORIZON Pivotal Fracture Trial.

External factors also considered were the failed fracture efficacy results from trials in PMO for two other bisphosphonates, ibandronate and tiludronate.

A double-blind, placebo-controlled, randomised study explored the antifracture efficacy and safety of 1 and 0.5 mg iv ibandronate injections, given once every 3 months in 2862 women with PMO. All participants received daily vitamin D (400 IU) and calcium (500 mg) supplementation. The primary endpoint was the incidence of new morphometric vertebral fractures after 3 years. At the end of the study, the magnitude of fracture reduction was suboptimal and insufficient to achieve statistical significance in the ibandronate-treated group compared with placebo. The authors observed a clear dose-response relationship and concluded that higher intravenous doses of ibandronate would be likely to produce proven fracture efficacy of a similar magnitude to other bisphosphonates, including oral ibandronate (Recker et al, 2004). Subsequently, the Dosing IntraVenous Administration (DIVA) study, designed to identify the optimal ibandronate iv injection schedule for the treatment of postmenopausal osteoporosis, demonstrated acceptable antifracture efficacy when using iv ibandronate at a dosage of 2 mg every 2 or 3 months (Eisman et al, 2008).

Two placebo-controlled, randomised, double-blind, multicentre, cyclical, intermittent, dose-ranging studies of tiludronate were conducted involving 1805 women with low vertebral BMD and prevalent vertebral fractures and 488 women with low BMD and no prevalent fracture. Patients were randomized to either tiludronate 50 mg/day, tiludronate 200 mg/day or placebo, given orally for the first 7 days of each month. A supplement of 500 mg elemental calcium was provided daily from day 8 to the end of the month. Tiludronate was found not to be effective in reducing the incidence of vertebral fractures or increasing spinal BMD. The authors concluded that this tiludronate dosage regimen was suboptimal for the treatment of osteoporosis in women (Reginster et al, 2001).

As a result of these failed bisphosphonate antifracture trials due to suboptimal dosing, as well as the evidence of insufficient suppression of BSAP over 12 months with a zoledronic 4 mg iv dose, Novartis selected a 5 mg once yearly iv dose of zoledronic acid for their fracture prevention trials.

The antifracture efficacy of osteoporosis treatments can only be confirmed by well-powered and design studies to investigate this endpoint. To date the only studies of iv zoledronic acid that have been designed and have demonstrated a significant reduction in fractures have used a 5 mg once-yearly regimen (Black et al, 2007; Lyles et al, 2007). The first of these, the 3-year HORIZON-PFT study demonstrated that zoledronic acid 5 mg significantly reduced the risk vertebral, hip, and non-vertebral fracture compared with placebo in postmenopausal women. The second study, the HORIZON-RFT study, showed that zoledronic acid 5 mg reduced the incidence of clinical



fracture and improved survivability compared with placebo in patients who had suffered a recent low-trauma hip fracture

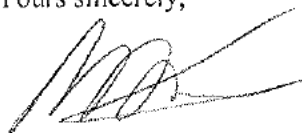
While a 4 mg annual dose of zoledronic has been shown to increase BMD and suppress bone turnover in women with low bone mass, antifracture efficacy has not been demonstrated for this regimen. Moreover, this regimen has not been approved for use in osteoporosis, so cannot be recommended by Novartis.

It would not be possible to conduct a comparative study of iv zoledronic and 4 and 5 mg with a fracture prevention endpoint, because such a study would require an unreasonably large number of patients to meaningfully compare the two groups.

Please find enclosed copies of Bauer et al (2004) and Reid et al (2002) for your reference.

Novartis recommends the use of its products only in accordance with the TGA-approved Product Information (copy available at [http://www.novartis.com.au/healthcare\\_professionals.html](http://www.novartis.com.au/healthcare_professionals.html) or upon request). If you require further information please contact our Medical Information & Communication department on 1800 671 203.

Yours sincerely,



Melissa Mee

#### References

1. Aclasta . TGA-Approved Product Information. Novartis Pharmaceuticals Australia Pty Ltd. 2010;
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#### Enclosures

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