# Canadian Drug Expert Committee
# Final Recommendation – Plain Language Version

## ZOLEDRONIC ACID – REQUEST FOR ADVICE
## (Aclasta – Novartis Pharmaceuticals Inc.)
## Indication: Osteoporosis (postmenopausal women)

This recommendation replaces the CEDAC recommendation for this drug and indication dated June 25, 2008.

**Recommendation:**
The Canadian Drug Expert Committee (CDEC) recommends that Aclasta, which is also called zoledronic acid, be listed by Canada's publicly funded drug plans for the treatment of women with postmenopausal osteoporosis (thinning and weakening of the bone after menopause) who would be eligible for drug coverage for oral (taken by mouth) bisphosphonates, but who cannot take them because they have an abnormality of the esophagus (problem with the tube that carries food from the mouth to the stomach), and have at least two of the following:

- age > 75 years
- a previous fragility fracture (a broken bone caused by a minor fall or simple activities)
- a bone mineral density (BMD) T-score of ≤ -2.5.

**Reasons for the Recommendation:**

1. There is not enough evidence that Aclasta is better than bisphosphonates taken by mouth, including alendronate (also called Fosamax).
2. The cost of Aclasta is approximately five times that of generic alendronate.
3. The Committee recognized that there may be a small proportion of women who would be eligible for drug coverage for oral bisphosphonates but who are unable to take bisphosphonates by mouth and who may benefit from intravenous (injected into the vein) bisphosphonate therapy, given once per year.

**Background:**
Aclasta belongs to a class of drugs called bisphosphonates. Aclasta works by binding specifically to bone and it does not stay in the blood. Aclasta slows down bone resorption (caused by osteoclasts), which allows the bone-forming cells (osteoblasts) time to rebuild normal bone.

Aclasta has a Health Canada indication for the following:

- Treatment of osteoporosis in postmenopausal women to reduce the risk of hip, spine, and non-spine fractures
- Treatment to increase BMD in men with osteoporosis
- Treatment and prevention of glucocorticoid-induced osteoporosis, to increase BMD
- Prevention of postmenopausal osteoporosis in women with osteopenia (low bone mass)
- Treatment of Paget's disease.

This Request for Advice is specific to treatment of osteoporosis in postmenopausal women.

Aclasta is available as a 5 mg/100 mL solution for intravenous infusion. The Health Canada–recommended dose, for treatment of postmenopausal osteoporosis, is 5 mg by intravenous infusion once a year.

**Submission History:**
Aclasta was previously reviewed by the Canadian Expert Drug Advisory Committee (CEDAC) for postmenopausal osteoporosis and received a recommendation of "do not list" (see Notice of CEDAC Final Recommendation, June 25, 2008). This updated Aclasta recommendation is being made after a Request for Advice from the Common Drug Review (CDR) participating drug plans. The drug plans requested that CDEC provide advice to help the jurisdictions identify differences between the 2008 Aclasta recommendation and the 2011 denosumab (also called Prolia) recommendation, in terms of the evidence for preventing fractures, and the cost and/or cost-effectiveness. The drug plans made this request because, based on previous CEDAC recommendations, Aclasta and denosumab appear to have similar fracture reduction evidence and also have a similar yearly cost.

**Summary of CDEC Considerations:**
The Committee considered a CDR clinical brief that provided information on medical studies that included either Aclasta or denosumab, either compared with each other or placebo (an infusion or injection that contains no active medication), in postmenopausal women, and which reported spine, hip, and other non-spine fractures. Materials included in the CEDAC brief for the 2008 review of Aclasta were available to the Committee.

***Clinical Trials***

CDEC reviewed two studies that met the criteria for the CDR clinical brief (HORIZON PFT and FREEDOM); these studies had been included in the original CDR reports for Aclasta and denosumab, respectively.

- HORIZON PFT, with 7,765 patients, was a 36-month-long study comparing Aclasta 5 mg intravenously at study start, 12 months, and 24 months with placebo. Equal proportions of patients who were already on osteoporosis medication at study start were put in each treatment group. Patients were not allowed to use bisphosphonates other than study medication during the study, but hormone replacement therapy, raloxifene (also called Evista), and calcitonin were allowed.
- FREEDOM, with 7,808 patients, was a 36-month-long study comparing denosumab 60 mg subcutaneously (under the skin) every six months with placebo. Use of other osteoporosis medications was not allowed during the study.

Patients in the HORIZON PFT study seemed to be at a higher risk of fracture compared with patients in the FREEDOM study, because a larger proportion of patients in the HORIZON PFT study had already had fractures before the study started (63% versus 24%, respectively) and also on average had lower BMD T-scores (71% with a score of < -2.5 in HORIZON, compared with an average score of -2.16 in FREEDOM at the hip).

No studies that met the criteria for inclusion in the CDR clinical brief compared Aclasta with denosumab (Prolia). Results from the HORIZON PFT and FREEDOM studies are reported below.

### *Results*

#### *Efficacy or Effectiveness*

- Both Aclasta and denosumab resulted in a smaller percentage of patients having new spine fractures over 36 months, compared with placebo; 3.3% versus 10.9% for Aclasta versus placebo, and 2.3% versus 7.2% for denosumab versus placebo.
- Both Aclasta and denosumab resulted in a smaller percentage of patients having hip fractures over a 36-month period compared with placebo; 1.4% versus 2.5% for Aclasta versus placebo, and 0.7% versus 1.2% for denosumab versus placebo.
- Compared with placebo, both Aclasta and denosumab lowered the chance of the following: more than one new spine fracture, spine fractures with symptoms, and non-spine fractures. However, Aclasta lowered the chance of having more than one spine fracture compared with placebo, even more than denosumab; 0.2% versus 2.3% for Aclasta versus placebo, and 0.6% versus 1.6% for denosumab versus placebo.

#### *Harms (Safety and Tolerability)*

- The percentage of deaths, serious side effects, and stopping taking part in the study due to side effects was similar between Aclasta and placebo, and between denosumab and placebo.
- The percentage of patients reporting a serious side effect of atrial fibrillation (a type of heart palpitation) was higher for Aclasta compared with placebo in the HORIZON PFT study (1.3% versus 0.5%); the FREEDOM study found that the amount of atrial fibrillation was about the same with denosumab as placebo.
- Serious kidney problems occurred in less than 1% of patients in the HORIZON PFT and FREEDOM studies, and was similar for Aclasta and denosumab.
- The frequency of specific types of stomach and bowel side effects was similar for Aclasta and denosumab, and these were found in less than 10% of patients. The most common stomach and bowel side effects from Aclasta and denosumab were nausea and constipation, respectively.

#### *Cost and Cost-Effectiveness*

At current Ontario prices, the yearly cost of Aclasta ($671) is similar to that of denosumab ($660), but both are greater than generic alendronate ($131).

As part of its original submission, the manufacturer submitted a cost analysis in women with postmenopausal osteoporosis who either could not take oral bisphosphonates because of side effects or who did not improve with oral bisphosphonates. The analysis reported that, when compared with raloxifene, Aclasta costs less and has similar benefits. The manufacturer also

compared Aclasta with oral bisphosphonates and found that Aclasta was not cost-effective compared with oral bisphosphonates.

**Other Discussion Points:**

- The Committee discussed that, compared with placebo, Aclasta and denosumab produced a similar lowering of spine and hip fractures, and the yearly costs of treatment were also similar.
- The Committee noted that there is no cost-effectiveness information for the comparison of Aclasta with denosumab.

**CDEC Members:**

Dr. Robert Peterson (Chair), Dr. Lindsay Nicolle (Vice-Chair), Dr. Ahmed Bayoumi, Dr. Bruce Carleton, Ms. Cate Dobhran, Mr. Frank Gavin, Dr. John Hawboldt, Dr. Peter Jamieson, Dr. Julia Lowe, Dr. Kerry Mansell, Dr. Irvin Mayers, Dr. Yvonne Shevchuk, Dr. James Silvius, Dr. Adil Virani

**October 19, 2011 Meeting**

**Regrets:**

One CDEC member did not attend.

**Conflicts of Interest:**

None

**About this Document:**

The information contained within this plain language version of the Canadian Drug Expert Committee (CDEC) Recommendation about this drug is based on the information found within the corresponding technical version of the CDEC Recommendation.

In making its recommendation, CDEC considered the best clinical and pharmacoeconomic evidence available, up to that time. Health care professionals and those requiring more detailed information are advised to refer to the technical version available in the CDR Drug Database on the CADTH website (www.cadth.ca).

**Background on CDEC**

CDEC is a committee of the Canadian Agency for Drugs and Technologies in Health (CADTH). The committee is made up of drug evaluation experts and public members. CDEC provides recommendations about whether or not drugs should be listed for coverage through the participating publicly funded drug plans; however, the individual drug plans make their own decision about whether or not to cover a drug.

In making its recommendations, CDEC decides if the drug under review ought to be covered by the participating public drug plans based on an evidence-informed review of the medication's

effectiveness and safety, and based on an assessment of its cost-effectiveness in comparison with other available treatments. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient, nor is it intended to replace professional advice. CADTH is not legally

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The statements, conclusions, and views expressed herein do not necessarily represent the views of Health Canada, the federal government, any provincial or territorial government, or any pharmaceutical manufacturer.

The manufacturer has reviewed this document and has not requested the deletion of any confidential information.