CDEC FINAL RECOMMENDATION

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

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

Recommendation:
The Canadian Drug Expert Committee (CDEC) recommends that zoledronic acid be listed for women with postmenopausal osteoporosis who would otherwise be eligible for jurisdictional funding for oral bisphosphonates, but for whom oral bisphosphonates are contraindicated due to abnormalities of the esophagus (e.g., esophageal stricture or achalasia), and have at least two of the following:

- age > 75 years
- a prior fragility fracture
- a bone mineral density (BMD) T-score ≤ –2.5.

Reasons for the Recommendation:

1. There is insufficient evidence that zoledronic acid offers a therapeutic advantage over oral bisphosphonates, including alendronate.
2. The cost of zoledronic acid is approximately five times that of generic alendronate.
3. The Committee recognized that there may be a small proportion of women who are otherwise eligible for jurisdictional funding of oral bisphosphonates but who are unable to take oral bisphosphonates and who may benefit from annual intravenous (IV) bisphosphonate therapy.

Background:
Zoledronic acid (marketed as Aclasta) has a Health Canada indication for:

- Treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral 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
- Treatment of Paget's disease.

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

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

Submission History:
Zoledronic acid 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 zoledronic acid recommendation is being made subsequent to a Request for Advice from the Common Drug Review (CDR) participating drug plans. The drug plans requested that CDEC provide advice to assist the jurisdictions in distinguishing the 2008 zoledronic acid recommendation from the 2011 denosumab (Prolia) recommendation, with respect to the fracture data and the cost and/or cost-effectiveness. The context for the request was that, based on previous CEDAC recommendations, zoledronic acid and denosumab appear to have similar evidence related to fracture reduction and similar annual cost.

Summary of CDEC Considerations:
The Committee considered a CDR clinical brief that provided information on double-blind randomized controlled trials (RCTs) that included either zoledronic acid or denosumab, compared with either each other or placebo, in postmenopausal women, and which reported vertebral, hip, and other non-vertebral fractures. Materials included in the CEDAC brief for the 2008 review of zoledronic acid were available to the Committee.

Clinical Trials
Two trials met the inclusion criteria for the CDR clinical brief. Both trials (HORIZON PFT and FREEDOM) had been included in the original CDR reports for zoledronic acid and denosumab, respectively:

- HORIZON PFT (N = 7,765) was a 36-month double-blind RCT comparing zoledronic acid 5 mg intravenously at baseline, 12 months, and 24 months with placebo. Randomization was stratified by use of osteoporosis medication at baseline; users and non-users. Bisphosphonate use, other than study medication, was disallowed during the trial; however, concomitant use of hormone replacement therapy, raloxifene, and calcitonin was allowed.
- FREEDOM (N = 7,808) was a 36-month double-blind RCT comparing denosumab 60 mg subcutaneously every six months with placebo. Use of other osteoporosis medications was disallowed during the trial.

Patients in the HORIZON PFT trial appeared to be at higher risk of fracture compared with patients in the FREEDOM trial, based on the higher prevalence of fractures at baseline (63% versus 24%, respectively) and lower BMD T-scores (71% with a score of < –2.5 in HORIZON, compared with a mean score of –2.16 in FREEDOM at the femoral neck).

No trials that met the criteria for inclusion in the CDR clinical brief compared zoledronic acid with denosumab. Results from the HORIZON PFT and FREEDOM trials are reported below.

Results

Efficacy or Effectiveness

- Both zoledronic acid and denosumab produced a statistically significantly lower 36-month incidence of new vertebral fracture compared with placebo; 3.3% versus 10.9% (relative risk [RR]: 0.30, 95% confidence interval [CI] 0.24 to 0.38) for zoledronic acid, and 2.3% versus 7.2% (RR: 0.32, 95% CI: 0.26 to 0.41) for denosumab.
- Both zoledronic acid and denosumab produced a statistically significantly lower 36-month incidence of hip fracture compared with placebo; 1.4% versus 2.5% (hazard ratio [HR]: 0.59, 95% CI: 0.42 to 0.83) for zoledronic acid, and 0.7% versus 1.2% (HR: 0.60, 95% CI: 0.37 to 0.97) for denosumab.
- Compared with placebo, both zoledronic acid and denosumab produced a statistically significantly lower incidence of the following: multiple new vertebral fractures, clinical vertebral fractures, and non-vertebral fractures. However, zoledronic acid reduced the incidence of multiple vertebral fractures compared with placebo to a greater degree than observed with denosumab; 0.2% versus 2.3% (RR: 0.11, 95% CI: 0.05 to 0.23) for zoledronic acid, and 0.6% versus 1.6% (RR: 0.39, 95% CI: 0.24 to 0.63) for denosumab.

Harms (Safety and Tolerability)

- The percentages of deaths, serious adverse events, and withdrawal due to adverse events were not statistically significantly different between zoledronic acid and placebo, or between denosumab and placebo.
- The percentage of patients reporting a serious adverse event of atrial fibrillation was statistically significantly higher for zoledronic acid compared with placebo in the HORIZON PFT trial (1.3% versus 0.5%); the FREEDOM trial reported no statistically significant difference in serious adverse events of atrial fibrillation between denosumab and placebo.
- Serious renal toxicity (impairment or failure) occurred in less than 1% of patients in the HORIZON PFT and FREEDOM trials and was similar for zoledronic acid and denosumab.
- The incidence of individual gastrointestinal adverse events was similar for zoledronic acid and denosumab, and these were reported in less than 10% of patients. The most common gastrointestinal adverse events associated with zoledronic acid and denosumab were nausea and constipation, respectively.

Cost and Cost-Effectiveness

At current Ontario prices, the annual cost of zoledronic acid ($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-utility analysis in women with postmenopausal osteoporosis who were intolerant of or unresponsive to oral bisphosphonates; the analysis reported that, when compared with raloxifene, zoledronic acid is associated with less costs and similar clinical benefits. A comparison to oral bisphosphonates was also considered by the manufacturer, in which they reported that zoledronic acid yields an incremental cost per quality-adjusted life-year estimate in excess of $360,000.

Other Discussion Points:

- The Committee discussed that, compared with placebo, zoledronic acid and denosumab produced similar reductions in the incidence of vertebral and hip fractures, and that annual costs of treatment were also similar.
- The Committee noted that no cost-effectiveness information regarding the comparison of zoledronic acid with denosumab was available.

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, and Dr. Adil Virani.

October 19, 2011 Meeting

Regrets:

One CDEC member did not attend

Conflicts of Interest:

None

About this Document:

CDEC provides formulary listing recommendations to publicly funded drug plans. Both a technical recommendation and plain language version of the recommendation are posted on the CADTH website when available.

CDR clinical and pharmacoeconomic reviews are based on published and unpublished information available up to the time that CDEC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CDEC deliberations.

The manufacturer has reviewed this document and has not requested the removal of confidential information in conformity with the *CDR Confidentiality Guidelines*.

The Final CDEC Recommendation neither takes the place of a medical professional providing care to a particular patient nor is it intended to replace professional advice.

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