CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

ZOLEDRONIC ACID
(Aclasta™ – Novartis Pharmaceuticals Canada Inc.)

This recommendation is superseded by the CDEC recommendation for this drug and indication dated November 16, 2011.

Description:
Zoledronic acid, an injectable bisphosphonate agent that inhibits osteoclast-mediated bone resorption, is marketed as Aclasta™ and Zometa™. Aclasta is approved for the treatment of osteoporosis in post-menopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and for the treatment of Paget's disease of the bone. Zometa is approved for tumour induced hypercalcemia, bone metastases from solid tumours and osteolytic lesions of multiple myeloma. This submission to the Common Drug Review was for the treatment of osteoporosis in post-menopausal women.

Dosage Forms:
5 mg/100 mL solution for intravenous infusion. The recommended dose is a once-yearly intravenous infusion of 5 mg of zoledronic acid.

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that zoledronic acid not be listed.

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 three times that of generic alendronate.

3. The Committee considered whether zoledronic acid should be listed for the treatment of post-menopausal women with evidence of intolerance, inability to take or inadequate response to an adequate trial of oral bisphosphonate therapy. As zoledronic acid is also a bisphosphonate agent and has not been shown to be more effective or safer, or to improve compliance in this patient

population, the Committee felt there was insufficient evidence to recommend listing in this subgroup of patients.

Summary of Committee Considerations:

The Committee considered a systematic review of double blind randomized controlled trials (RCTs) of zoledronic acid in post-menopausal women with osteoporosis or women >50 years of age. Four RCTs in a total of 10,245 subjects met the inclusion criteria for the systematic review. Patients in all trials also received oral vitamin D and calcium preparations.

One trial compared three years of treatment with zoledronic acid versus placebo in 7,765 post-menopausal women, aged 65 – 89, with osteoporosis. At 3 years, subjects who received zoledronic acid experienced statistically significant reductions in hip fractures (number needed to treat [NNT] = 98), non-vertebral fractures (NNT = 39) and vertebral fractures (NNT = 13).

A second trial in 2,127 patients aged >50, compared zoledronic acid with placebo with the first dose administered within 90 days after surgical repair of a hip fracture. There were 1,619 women and 508 men enrolled in this trial and the median follow-up was 1.9 years. Subjects who received zoledronic acid experienced statistically significant reductions in new clinical fractures (NNT = 19), new non-vertebral fractures (NNT = 33) and new clinical vertebral fractures (NNT = 48).

The other two trials compared the effects of zoledronic acid with alendronate in post-menopausal women with a low bone mineral density. As these trials were smaller (225 and 128 subjects), shorter (12 and six months) and were not designed to assess the effect on fracture rate, they did not influence the Committee's recommendation.

In all four trials, there were no significant differences between study groups in the incidence of serious adverse events, or withdrawal due to adverse events though more patients treated with zoledronic acid experienced at least one adverse event. This was primarily related to transient infusion-related adverse events such as myalgia, arthralgia, bone pain, pyrexia, nausea, chills, headache, influenza-like illness, and fatigue. Significant uncommon adverse events reported in the product monograph for zoledronic acid include renal dysfunction, atrial fibrillation and osteonecrosis of the jaw.

Zoledronic acid costs $645 for a once-yearly IV injection which is more expensive that oral bisphosphonates (alendronate costs $230 per year, risedronate cost $487 per year) and similar in price to oral raloxifene ($652 per year). While the manufacturer indicated that they would cover the infusion related costs for zoledronic acid, the Committee expressed concern that this would not be available in all communities and may be associated with increased public health costs. The manufacturer submitted a cost utility analysis in women with post-menopausal osteoporosis who were intolerant or unresponsive to oral bisphosphonates which reported that, when compared to raloxifene, zoledronic acid is associated with less costs and similar clinical benefits. As raloxifene is in a different therapeutic class, the Committee recognized the rationale for considering it as an alternative in patients unable to take oral bisphosphonate agents but felt that the same rationale could not be substantiated for zoledronic acid, as it is also a bisphosphonate. In an additional economic evaluation, zoledronic acid was not found to be cost-effective when compared to oral bisphosphonate agents.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.

2. There are no high quality data documenting differences in outcomes related to adherence with weekly oral bisphosphonate agents versus yearly zoledronic acid injections.

3. In the placebo-controlled RCT assessing the effectiveness of zoledronic acid in patients with a recent hip fracture, a lower risk of mortality was reported, though this was not a primary study endpoint, and this finding was not noted in the other large placebo-controlled trial. As this trial did not report the vital status of the full patient population at 36 months, it is uncertain whether this mortality effect is due to bias, chance alone, or whether it represents a true benefit of zoledronic acid.

Background:

CEDAC provides formulary listing recommendations to publicly funded drug plans. Recommendations are based on an evidence-based review of the medication's effectiveness and safety and an assessment of its cost-effectiveness in comparison to other available treatment options. For example, if a new medication is more expensive than other treatments, the Committee considers whether any advantages of the new medication justify the higher price. If the recommendation is not to list a drug, the Committee has concerns regarding the balance between benefit and harm for the medication, and/or concerns about whether the medication provides good value for public drug plans.

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