CEDAC FINAL RECOMMENDATION

DENOSUMAB
(Prolia – Amgen Canada Inc.)
Indication: Postmenopausal Osteoporosis

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that denosumab be listed for women with postmenopausal osteoporosis who would otherwise be eligible for jurisdictional funding for oral bisphosphonates, but for whom bisphosphonates are contraindicated due to hypersensitivity or 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.

Reason for the Recommendation:
In one double-blind randomized controlled trial comparing denosumab with placebo in postmenopausal women with low BMD T-scores, denosumab achieved a statistically significantly greater reduction in the incidence of new vertebral and hip fractures, in both the total patient population and a predefined high risk subgroup. A cost-utility analysis based on the high risk subgroup resulted in a cost per quality-adjusted life-year (QALY) of $29,000 for denosumab compared with no treatment. The cost per QALY was higher when the total patient population was considered.

Of Note:
The Committee considered the clinical basis for the manufacturer's economic evaluation of denosumab compared with raloxifene, but had concerns regarding the comparability of the patient populations in the clinical trials that were used to inform the economic evaluation.

Background:
Denosumab is indicated by Health Canada for the treatment of postmenopausal women at high risk for osteoporotic (fragility) fracture, defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other available osteoporosis therapy.

Denosumab is a fully human monoclonal antibody that inhibits osteoclast-mediated bone resorption. Health Canada recommends that denosumab be administered as a single

subcutaneous (SC) injection of 60 mg once every six months. Denosumab 60 mg/mL solution for injection is available as a 1.0 mL single use vial and a 1.0 mL prefilled syringe.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by the Common Drug Review (CDR): a systematic review of randomized controlled trials (RCTs) of denosumab, a critique of the manufacturer's pharmacoeconomic evaluation, and patient group-submitted information about outcomes and issues important to patients.

Clinical Trials
The systematic review included six manufacturer-sponsored RCTs of post-menopausal women with osteoporosis. This diagnosis was based on low BMD as measured by T-scores.

- FREEDOM (N=7,808) was a 36-month double-blind double-dummy parallel-group RCT comparing denosumab 60 mg SC every six months with placebo. FREEDOM predefined a high-risk subgroup (which accounted for 45% of the total patient population); patients in the high-risk subgroup were those who met two of the following: (i) age greater than 70 years; (ii) BMD T-score of ≤ -3.0 at the lumbar spine, total hip, or femoral neck; or (iii) a prevalent vertebral fracture.
- DECIDE (N=1,189) and STAND (N=504) were 12-month double-blind double dummy parallel-group RCTs comparing denosumab 60 mg SC every six months with alendronate 70 mg orally once weekly. Both the DECIDE and STAND trials were designed to test the non-inferiority of denosumab to alendronate, with pre-planned testing for superiority if denosumab was found to be non-inferior.
- DAPS (N=250) was a 24-month, open-label, cross-over RCT. Sequences were one-year in duration and doses were: denosumab 60 mg SC every six months and alendronate 70 mg orally once weekly.
- Study 20010223 (N=406) was a 48-month parallel-group RCT of mixed double-blind (denosumab and placebo) and open-label (alendronate) designs. The trial consisted of nine treatment groups; seven groups employed different doses of denosumab and one group each used alendronate and placebo. Only the denosumab group employing the Health Canada recommended dose (60 mg SC every six months), for four years, was included in the systematic review. Comparator groups consisted of alendronate (70 mg orally once weekly for two years with two years off of treatment) and placebo (SC injections every three months for two years, followed by every six months for two years).
- Study 20050179 (N=247) was a 12-month double-blind, double-dummy, parallel-group RCT that included three treatment groups: denosumab 60 mg SC every six months, alendronate 70 mg orally once weekly, and placebo.

The frequency of withdrawal was approximately 17% in the FREEDOM trial and did not differ substantially between treatment groups. Of the 7,808 patients enrolled in FREEDOM, 7,393 (95%) underwent spinal radiography at baseline and during at least one follow-up visit. In the DECIDE and STAND trials the frequency of withdrawal among treatment groups ranged from 4% to 6% and did not differ substantially between treatment groups within the trials. In the DAPS trial 8% of patients randomized to denosumab withdrew compared with 14% for

alendronate. In study 20010223 17% of patients randomized to denosumab withdrew compared with 37% for placebo. Withdrawals from study 20050179 were not reported.

Outcomes

The primary outcomes in the trials were:

- FREEDOM – incidence of new vertebral fracture on radiograph over 36 months
- DECIDE and STAND – percentage change in total hip BMD from baseline to 12 months
- DAPS – proportion of patients who were adherent to treatment at 12 months
- Study 20010223 – percentage change in lumbar spine BMD from baseline to 12 months
- Study 20050179 – percentage change in cortical thickness at distal radius from baseline to 12 months

Other outcomes were also defined a priori in the CDR systematic review. Of these outcomes the Committee discussed the following: hip fracture, mortality, quality of life, and adverse events. Outcomes of importance mentioned in the four patient group submissions included: reduction in pain, reduction in fracture risk, and function (ability to perform everyday tasks such as lifting objects, working, and household duties). Pain was not a pre-specified outcome in any of the reviewed studies, but was assessed as part of several quality of life and functional scales (e.g., Osteoporosis Assessment Questionnaire Short Version [OPAQ-SV], European Quality of Life – 5 Dimensions [EQ-5D]), and the Disability/Back Pain Questionnaire. Fracture reduction was the primary outcome in only one trial (FREEDOM); the remaining trials recorded fractures only as patient-reported adverse events which were not necessarily confirmed by radiographs.

Results

Efficacy or Effectiveness

- In the FREEDOM trial, among patients having had both a baseline and at least one follow-up spinal radiograph, the 36-month incidence of radiographically confirmed new vertebral fracture was statistically significantly lower for denosumab (2.3%) compared with placebo (7.2%), based on the absolute risk reduction (ARR): 4.8, 95% confidence interval (CI), 3.9 to 5.8. Further, the 36-month incidence of radiographically confirmed new vertebral fracture among the predefined high-risk subgroup was statistically significantly lower for denosumab (3.5%) compared with placebo (10.0%) based on the ARR: 6.5, 95% CI, 4.8 to 8.2. Similarly, the incidence of new clinical fractures was statistically significantly less for denosumab compared with placebo for both the total and high risk patient populations.
- In the FREEDOM trial, the 36-month incidence of hip fracture (a secondary outcome) among the total patient population was not statistically significantly different between denosumab (0.7%) and placebo (1.1%) based on the ARR: 0.3, 95% CI -0.1 to 0.7, but was statistically significant based on the hazard ratio (HR): 0.60, 95% CI, 0.37 to 0.97. The incidence of hip fracture in the predefined high risk subgroup was statistically significantly lower for denosumab (1.0%) compared with placebo (1.9%), based on the HR: 0.52, 95% CI, 0.29 to 0.91.
- None of the active comparator trials were powered to examine fracture. For the two active comparator trials (DECIDE and STAND) that reported on fracture, as patient reported adverse events, the frequency of fracture was similar between denosumab and alendronate.

- Non-inferiority of denosumab compared with alendronate was demonstrated in both the DECIDE and STAND trials, based on the percent change in the total hip BMD T-score at 12 months. Subsequent superiority testing in both STAND and DECIDE identified small but statistically significantly greater increases in BMD T-scores for denosumab compared with alendronate at the lumbar spine, total hip, and femoral neck sites.
- In the FREEDOM trial, there were no statistically significant differences in quality of life or functional ability between denosumab and placebo based on results of the OPAQ-SV and EQ-5D. Further, there were no statistically significant between-treatment differences in scores obtained from the Disability/Back Pain Questionnaire in the FREEDOM trial.
- Pooled data from the DECIDE and STAND trials demonstrated that patient-reported satisfaction with treatment was statistically significantly greater for denosumab compared with alendronate. In the DAPS trial adherence at 12 months was statistically significantly greater for denosumab (87.3%) compared with placebo (76.6%), however the external validity of these data were questionable due to the administration of denosumab at study visits.

Harms (Safety and Tolerability)

- Mortality, serious adverse events, adverse events, and withdrawal due to adverse events were similar between denosumab and placebo in the FREEDOM trial, and between denosumab and alendronate in the STAND and DECIDE trials.
- Two patients in the open-label extension of the FREEDOM trial, developed osteonecrosis of the jaw after being switched from placebo to denosumab.
- The frequency of gastrointestinal events for denosumab treated patients was similar to that observed for placebo and alendronate; however patients with active gastrointestinal disease were excluded.

Cost and Cost-Effectiveness

The manufacturer conducted a cost utility analysis in patients with postmenopausal osteoporosis, with characteristics of patients enrolled in the FREEDOM trial, comparing denosumab with alendronate, risedronate and no treatment over a patient lifetime horizon (~25 years). A Markov model was created based on the following health states: well (no current fracture); hip fracture; vertebral fracture; wrist fracture; other fracture; post vertebral fracture; post hip fracture; and dead. The relative efficacy of fracture reduction was obtained from the placebo-controlled FREEDOM trial for denosumab, and a meta-analysis conducted by the National Institute for Health and Clinical Excellence (NICE) in the UK for alendronate and risedronate compared to placebo. While the point estimates of fracture reduction are numerically lower for denosumab, these are indirect comparisons as no head-to-head studies with active treatments using fractures as primary outcome were provided. The manufacturer assumed a five year treatment period, and a two year offset time in which the risks of fracture return to the baseline levels linearly over two years after active treatment is stopped (to account for continued benefit of the drug on fracture risk for a period of time after the patient has stopped taking the drug). Estimates of the decrease in quality of life associated with the various fractures were incorporated from the literature, rather than the denosumab trials.

The manufacturer suggested that the cost per QALY of denosumab may be around $61,000 varying up as high as ~$110,000 per QALY in sensitivity analysis, when compared to alendronate; and, for patients unable to take oral bisphosphonates, the cost per QALY for

denosumab was $42,915 compared to no treatment, varying as high as $88,935 per QALY. The cost per QALY estimate was less when the manufacturer considered the high risk subgroup from the FREEDOM trial, which was reported as $29,000 per QALY, when comparing denosumab with no treatment.

The annual cost of denosumab ($660) is greater than oral bisphosphonates ($131 to $332) and raloxifene ($335).

Patient Input Information:
The following is a summary of information provided by four patient groups that responded to the CDR Call for Patient Input.

- Persons with osteoporosis reported reduced mobility and ability to complete day-to-day tasks; for persons with osteoporosis, pain, and the curtailing of activities because of the fear of fractures were felt to have an important impact on patients' quality of life.
- Adherence to taking bisphosphonates can be problematic because of forgetfulness related to daily or weekly dosing.
- Bisphosphonates were considered inconvenient to take (related to taking the drug upon waking on an empty stomach and having to remain upright) and were considered to have important adverse effects (mainly gastrointestinal). Patients feel there is a need for an alternative treatment for those who cannot tolerate bisphosphonates or have not responded to them.

Other Discussion Points:

- The Committee noted that while there are observational studies reporting gastrointestinal adverse events with bisphosphonates, systematic reviews of bisphosphonate trials have not reported important differences in gastrointestinal events compared with placebo.
- It was noted that the statistically significant increase in BMD for denosumab compared with alendronate reported in the STAND trial was for a highly relevant patient population; all patients in the STAND trial had previously taken alendronate for a minimum of six months (median 36 months) and more than 50% had a previous fracture. However, there are no RCTs specifically designed to determine if patients who have experienced a fragility fracture while on a bisphosphonate have a lower incidence of fragility fracture if switched to denosumab compared with the continuation of the bisphosphonate.
- It was unclear if mortality data were captured for all patients enrolled in the FREEDOM trial.
- It was noted that the severity of fractures observed in the trials, both morphological and clinical, was unknown.

CEDAC Members Participating:
January 19, 2011
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

March 22, 2011
Dr. Robert Peterson (Chair), Dr. Anne Holbrook (Vice-Chair), Dr. Michael Allan, Dr. Ken Bassett, Dr. Bruce Carleton, Dr. Doug Coyle, Mr. John Deven, Dr. Alan Forster, Dr. Laurie Mallery, Mr. Brad Neubauer, Dr. Lindsay Nicolle, and Dr. Yvonne Shevchuk.

Regrets:
January 19, 2011
Dr. Alan Forster.

March 22, 2011
None

Conflicts of Interest:
None.

About this Document:
CEDAC 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 CEDAC made its recommendation. Patient information submitted by Canadian patient groups is included in the CDR reviews and used in the CEDAC 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 CEDAC 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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