Canadian Expert Drug Advisory Committee
Final Recommendation – Plain Language Version

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

Recommendation:
The Canadian Expert Drug Advisory Committee (CEDAC) recommends that Prolia, which is also called denosumab, be listed by Canada's publicly funded drug plans for 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, either because they have a hypersensitivity to them or because they have an abnormality of the esophagus (problem with the tube that carries food from the mouth to the stomach), and who 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 ≤ –2.5.

Reason for the Recommendation:
In one medical study of women with postmenopausal osteoporosis comparing Prolia with placebo (an injection with no active medication), new spine and hip fractures occurred less often with Prolia than with placebo, in both the total study population and in the group of patients in the study who were at high risk of fractures. Based on an economic evaluation, Prolia may be cost-effective, compared with no treatment, for patients at high risk of fracture.

Of Note:
The Committee considered the studies that the manufacturer used in their economic evaluation of Prolia compared with Evista (which is also called raloxifene). However, the Committee was concerned that the patients in the studies were not similar enough for an accurate comparison of Prolia with Evista.

Background:
Prolia belongs to a class of drugs called fully human monoclonal antibodies. Prolia strengthens the bones by increasing bone mass and lowers the chance of breaking bones of the hip, spine, and non-spinal sites. Health Canada has approved Prolia for treatment of postmenopausal women with osteoporosis who have an increased risk for fractures, or who cannot use other osteoporosis medicines, or for whom other osteoporosis medicines did not work well.

Prolia 60 mg/mL solution for injection is available as a 1.0 mL single-use vial and a 1.0 mL ready-to-use syringe. Health Canada recommends that Prolia be administered as a single subcutaneous (SC) injection (under the skin) of 60 mg once every six months.

Summary of CEDAC Considerations:
To make their decision, the Committee considered the following information prepared by the Common Drug Review (CDR): a review of the medical studies of Prolia and a review of economic information prepared by the manufacturer of Prolia. Also, CEDAC considered information that patient groups submitted about outcomes and issues important to patients who have the condition for which the drug is indicated or who might use the drug.

Clinical Trials
CEDAC reviewed six medical studies conducted in postmenopausal women with osteoporosis. The diagnosis of osteoporosis was made based on patients' BMD T-scores.

- FREEDOM, with 7,808 patients, was a 36-month study that compared Prolia 60 mg SC every six months with placebo. In the FREEDOM study, 45% of the patients were at high risk of a fracture. That is, they met at least two of the following: (i) age greater than 70 years; (ii) BMD T-score of ≤ –3.0 from one of these three bone sites: lumbar (lower) spine, total hip, or femoral neck (part of the hip bone); or (iii) a fracture of the spine that is already present.
- DECIDE, with 1,189 patients, and STAND, with 504 patients, were 12-month studies that compared Prolia 60 mg SC every six months with Fosamax (which is also called alendronate) 70 mg taken by mouth once per week. Both the DECIDE and STAND studies were designed to see if Prolia was not worse than Fosamax, with the option to assess if Prolia was better than Fosamax (if it was not found to be worse than Fosamax).
- DAPS, with 250 patients, was a 24-month study in which the patients received either Prolia 60 mg SC every six months or Fosamax 70 mg by mouth once per week for a year and then switched over to the other medication for the following year. Patients in this study were aware of which medication they were taking.
- Study 20010223, with 406 patients, was a 48-month study that compared various doses of Prolia with placebo and Fosamax. Patients received one of nine treatments; seven of these were with different doses of Prolia, one treatment was with placebo, and the remaining treatment was with Fosamax. Although seven different doses of Prolia were given to patients, CDR looked at only the Prolia results for patients using the Health Canada-recommended dose of 60 mg SC every six months (for four years). Prolia was compared with Fosamax (70 mg by mouth once per week for two years, with two years off treatment) and placebo (injections under the skin every three months for two years, followed by every six months for two years).
- Study 20050179, with 247 patients, was a 12-month study that compared Prolia 60 mg SC every six months with Fosamax 70 mg by mouth once per week, and with placebo.

Approximately 17% of patients stopped taking part during the FREEDOM study, regardless of which treatment they were getting. Of the 7,808 patients in the FREEDOM study, 7,393 (95%) had X-rays of the spine taken at the start of the study and at least once during the study. In the DECIDE and STAND studies, between 4% and 6% of patients stopped taking part in the study, regardless of the treatment they were receiving. In the DAPS study, 8% of Prolia patients, compared with 14% of Fosamax patients, stopped taking part during the study. In study 20010223, 17% of Prolia patients, compared with 37% of placebo patients, stopped taking part in the study. The percentage of patients who stopped participating in study 20050179 was not reported.

Outcomes

The main purpose of each of the studies was to measure the following:

- FREEDOM – occurrence of new spine fractures on X-ray during 36 months
- DECIDE and STAND – percentage change in total hip BMD from study-start to 12 months
- DAPS – proportion of patients who took their assigned doses of Prolia or Fosamax and continued to participate in the study up to 12 months
- Study 20010223 – percentage change in lumbar (lower) spine BMD from study-start to 12 months
- Study 20050179 – percentage change in the thickness of the outer part of the radius bone at the wrist from study-start to 12 months.

The CDR systematic review defined other results of interest in advance. Of these, the Committee discussed the following: hip fracture, mortality (death), quality of life, and side effects.

Four patient groups mentioned that the following results were important to them: lowering of amount of pain, lowering of risk of fracture, and improvement in function (ability to perform everyday tasks such as lifting objects, working, and household duties). Measurement of pain was not the purpose of any of the reviewed studies, but it was measured 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. The lowering of risk of fracture was the main purpose of only one study (FREEDOM). The remaining studies kept track only of fractures as mentioned by patients and were not checked by looking at X-rays.

Results

Efficacy or Effectiveness

- In the FREEDOM study, Prolia patients had a lower occurrence of new fractures of the spine over 36 months compared with placebo patients (2.3% versus 7.2%). This was assessed by looking at X-rays taken at the start of the study and comparing them with those taken during the study. For the high-risk group of patients in the study, Prolia patients also had a lower occurrence of new fractures of the spine on X-ray during the 36 months compared with placebo patients (3.5% versus 10.0%). In addition, there was a lower occurrence of clinical spine fractures (fractures that caused symptoms) in Prolia patients compared with placebo patients, in both the total study population and the high-risk group.

- In the FREEDOM study, Prolia patients had a lower occurrence of hip fractures compared with placebo patients during 36 months, regardless of whether results were for the total study population (0.7% versus 1.1%) or the high-risk group (1.0% versus 1.9%).
- None of the studies comparing Prolia with Fosamax specifically planned to look at the occurrence of fractures. However, in the DECIDE and STAND studies, the occurrence of fractures (reported by patients but not checked with X-ray) was similar for Prolia and Fosamax.
- Both the DECIDE and STAND studies showed that Prolia was not worse than Fosamax for increasing the total hip BMD T-score at 12 months. The results also showed that Prolia was slightly better than Fosamax for increasing BMD T-scores at the lumbar spine, total hip, and femoral neck.
- In the FREEDOM study, Prolia patients and placebo patients had similar quality of life and functional ability (based on the OPAQ-SV and EQ-5D questionnaires), and similar scores on the Disability/Back Pain Questionnaire.
- When data from the DECIDE and STAND studies were combined, they showed that patients were more satisfied with Prolia treatment compared with Fosamax treatment. In the DAPS study, more Prolia patients than Fosamax patients took their assigned medication and completed 12 months of the study (87.3% compared with 76.6%). However, these results may not be accurate for patients who are not participating in medical studies, as the patients in the DAPS study received Prolia during study visits.

Harms (Safety and Tolerability)

- There were a similar number of deaths, serious side effects, side effects, and proportion of patients stopping participation in the study due to side effects between Prolia and placebo in the FREEDOM study, and between Prolia and Fosamax in the STAND and DECIDE studies.
- Two patients who had participated in the FREEDOM study developed osteonecrosis (death of bone tissue) of the jaw after being switched from placebo to Prolia.
- There were similar numbers of gastrointestinal (digestive system) side effects for Prolia, compared with Fosamax and placebo; however, patients who already had gastrointestinal problems were not allowed to participate in the studies.

Cost and Cost-Effectiveness

The manufacturer submitted economic information comparing Prolia with Fosamax, Actonel (which is also called risedronate), and no treatment. The analysis was based on a projection of 25 years into the future after starting treatment.

In its economic evaluation, the manufacturer used information from a number of sources including the FREEDOM study, a review by the National Institute for Health and Clinical Excellence (NICE) of studies of Fosamax and Actonel, and other published information. Based on information provided by the manufacturer, Prolia was not considered to be cost-effective compared with Fosamax, or compared with no treatment in patients unable to take oral bisphosphonates (e.g., Fosamax, Actonel). However, Prolia may be cost-effective, compared with no treatment, for patients at high risk of fracture.

The annual cost of Prolia ($660) is greater than oral bisphosphonates such as Fosamax and Actonel ($131 to $332), and also Evista ($335).

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

- Persons with osteoporosis have reduced mobility (ability to move) and ability to complete day-to-day tasks. For persons with osteoporosis, pain and the need to decrease certain activities due to fear of fractures have an important impact on patients' quality of life.
- For patients taking a bisphosphonate by mouth, either daily or weekly, remembering to take the medication may be difficult.
- Patients feel that bisphosphonates are not very convenient to take (as they have to be taken first thing in the morning on an empty stomach and the patient has to stay upright afterwards) and that they have important side effects (mainly of the digestive system). Patients feel there is a need for another treatment option for patients who cannot take bisphosphonates because of side effects, or for patients who have not received health benefit from them.

Other Discussion Points:

- The Committee noted that although there are studies in which bisphosphonates have been seen to cause gastrointestinal (digestive system) side effects, when the data from studies are carefully reviewed, there does not seem to be much difference between bisphosphonates and placebo in terms of gastrointestinal side effects.
- It was noted that the STAND study, which reported a greater increase in BMD for Prolia compared with Fosamax, included an important patient population. The patients in the STAND study had previously taken Fosamax for at least six months (average of 36 months) and more than 50% had a previous fracture. However, there are no studies specifically designed to determine whether patients who had a fragility fracture while taking a bisphosphonate (e.g., Fosamax) have a lower occurrence of a new fracture if they switch to Prolia compared with continuing their bisphosphonate treatment.
- It was not clear whether mortality data were collected for all patients in the FREEDOM study.
- It was noted that the severity of fractures observed in the studies, both on X-ray and those that caused symptoms, was not known.

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

In making its recommendation, CEDAC 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 CEDAC
CEDAC 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. CEDAC 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, CEDAC 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 CEDAC deliberations.

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