CEDAC FINAL RECOMMENDATION

TERIPARATIDE ACP SUBMISSION
(Forteo – Eli Lilly Canada Inc.)
Indication: Severe Osteoporosis in Women

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

Reasons for the Recommendation:

1. Teriparatide costs $15,688 per patient per 18 month course of treatment (the maximum length of time for which teriparatide treatment is recommended by Health Canada) based on its current list price, which is between 15 to 40 times the cost of bisphosphonates. Teriparatide has not been demonstrated to be cost-effective in any subgroup of post-menopausal women with severe osteoporosis.
2. There were no randomized controlled trials meeting the CDR systematic review protocol that evaluated teriparatide in women previously treated with anti-resorptive therapy. The Committee considered the EUROFORS and EFOS studies, both of which included some patients who had received prior anti-resorptive therapy, but interpretation of data from these studies is limited. Although EUROFORS is a randomized controlled trial, the effects of teriparatide in patients previously receiving anti-resorptive therapy were only evaluated in a subgroup analysis that did not include a comparative group, fracture outcomes were not reported, and all patients had previously been exposed to teriparatide for 12 months. Although EFOS enrolled patients who had an insufficient response or who were intolerant to prior anti-resorptive therapy, it was an open-label uncontrolled study and a substantial proportion of patients did not complete the study on treatment.

Background:
Teriparatide is a recombinant human parathyroid hormone (1-34), which has an identical sequence to the 34 N-terminal amino acids of the 84-amino acid human parathyroid hormone. The Health Canada indications for teriparatide are for the treatment of post-menopausal women with severe osteoporosis who are at high risk of fracture, or who have failed or are intolerant to previous osteoporosis therapy; to increase bone mass in men with primary or hypogonadal severe osteoporosis who have failed or are intolerant to previous osteoporosis therapy; and for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men and women who are at increased risk for fracture.

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The focus of this Advisory Committee on Pharmaceuticals (ACP) submission is the use of teriparatide in post-menopausal women with severe osteoporosis who are at high risk of fracture, or who have failed or are intolerant to previous osteoporosis therapy. The recommended dose of teriparatide is 20 mcg injected subcutaneously once daily for a maximum of 18 months. Teriparatide is supplied in a 3 mL (250 mcg/mL) cartridge contained in a pre-filled pen. Each pre-filled pen delivers 20 mcg of teriparatide per dose and can be used for up to 28 days.

Submission History:
Teriparatide was previously reviewed by CEDAC for the treatment of severe osteoporosis. It received a recommendation of "do not list" (see Notice of CEDAC Final Recommendation, December 22, 2004).

The original systematic review of teriparatide by the Common Drug Review (CDR) included two double-blind randomized controlled trials (RCTs) conducted in post-menopausal women with osteoporosis who were at high risk of fracture. One trial, GHAC (N = 1,637), compared teriparatide with placebo, but was terminated early due to concerns related to osteosarcoma in rats. GHAC was not powered to detect changes in hip fracture. Another trial, GHBM (N = 203), compared teriparatide with alendronate over 18 months in post-menopausal women. Both trials excluded patients who had used drugs that alter bone metabolism within the previous two to 24 months before study enrolment and, thus, did not provide evidence to support teriparatide's efficacy for patients with severe osteoporosis who continue to fracture despite adequate anti-resorptive treatment.

A manufacturer resubmission was made in both 2006 and 2008, but it was withdrawn on both occasions. A submission for the indication of glucocorticoid-induced osteoporosis was considered by CEDAC and received a recommendation of "do not list" (see Notice of CEDAC Final Recommendation, July 22, 2009). The manufacturer made another resubmission in 2009 for severe osteoporosis in post-menopausal women, but subsequently withdrew the resubmission.

The basis of this ACP submission for teriparatide for the treatment of post-menopausal women with severe osteoporosis is new publicly available information on teriparatide, particularly studies potentially addressing previous reasons for the CEDAC recommendation on teriparatide.

Summary of CEDAC Considerations:
The Committee considered the following information prepared by CDR: a systematic review of double-blind RCTs of teriparatide in post-menopausal women with severe osteoporosis; additional studies evaluating teriparatide in post-menopausal women who had previously received bone metabolism regulators; and information provided by CDR on the cost-effectiveness of teriparatide based on information in the public domain.

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Clinical Trials

One new trial was identified that met the inclusion criteria for the CDR systematic review. GHCS (N = 159) was a 24-week double-blind RCT comparing the efficacy and harms of three doses of teriparatide (10 mcg, 20 mcg, or 40 mcg daily) with placebo in Japanese post-menopausal women at high risk of fracture. Only the comparison of teriparatide 20 mcg, the Health Canada-approved dose, with placebo was considered.

Two additional studies were identified that reported uncontrolled data evaluating teriparatide in post-menopausal women who had previously received bone metabolism regulators:

- The European Study of Forsteo (EUROFORS) was a two-year study evaluating the effects of teriparatide, raloxifene, and no treatment. All patients received teriparatide for 12 months after which they were randomized to either teriparatide, raloxifene, or no treatment for an additional 12 months. The trial enrolled 868 post-menopausal women at high risk of fracture, the majority of whom (76%) had a history of anti-resorptive use. The CDR review focused on a published subgroup analysis of only teriparatide-treated patients with outcomes stratified by history of previous anti-resorptive use and response. There was no comparator group in this subgroup analysis.
- The European Forsteo Observational Study (EFOS) was a 36-month observational study in which 1,645 patients received teriparatide 20 mcg subcutaneously daily for 18 months and were followed-up for an additional 18 months. Patients were enrolled if they were about to initiate teriparatide therapy. Based on reimbursement criteria for teriparatide in the participating European countries, these were primarily post-menopausal women who were non-responders or intolerant to their prior treatment. Most of the included women were at high risk of fracture and 92% had a history of previous treatment for osteoporosis. The proportion of patients still receiving teriparatide after 17 months was only 62%.

Outcomes

The primary outcome in GHCS and EUROFORS was the change in bone mineral density (BMD) at the lumbar spine. EFOS was designed to look at the incidence of clinical vertebral and non-vertebral fragility fractures.

Other key outcomes were also defined a priori in the CDR systematic review protocol. Of these, the Committee discussed the following: changes in BMD at other sites, serious adverse events, and overall adverse events.

Results

Efficacy or Effectiveness (Systematic Review)

- Fracture data, including hip fractures, were not reported in GHCS and this trial is likely limited in its ability to detect differences in fractures outcomes because of its short duration. Teriparatide compared with placebo resulted in a statistically significantly greater change from baseline in lumbar spine BMD (6.4% versus 0.7%, $P < 0.001$). The change from baseline in total hip BMD was greater for teriparatide compared with placebo (1.9% versus 0.2% respectively), but statistical significance was not reported.

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Efficacy or Effectiveness (Additional Studies)

- In EUROFORS, approximately 50% of teriparatide patients were non-responders to prior anti-resorptive therapy. The subgroup analysis of teriparatide-treated patients showed there was a statistically significant increase in lumbar spine BMD (9.8% change, $P < 0.001$) and total hip BMD (2.3% change, $P = 0.05$) at 24 months compared with baseline in these patients. However, the absence of an appropriate comparator group in this subgroup analysis and the lack of fracture data limit the interpretation of these results.
- In EFOS, which primarily enrolled patients who were non-responders to or intolerant of prior anti-resorptive therapy, the proportion of patients with clinical vertebral fractures significantly decreased from 1.8% between zero to six months to 0.7% between 12 to 18 months. However, the lack of a comparator group and the substantial proportion of patients not completing the study on treatment limits interpretation of the study findings.

Harms (Safety and Tolerability)

- The proportion of patients with a serious adverse event or who withdrew due to an adverse event was low and not statistically significantly different between treatment groups in GHCS. Because of the short trial duration of 24 weeks for GHCS, these data provide limited information on long-term harms.

Cost and Cost-Effectiveness

Based on the current list price of teriparatide ($802.22 per 250 mcg/mL pre-filled pen), at the recommended dose of 20 mcg daily, the average daily cost of treatment is $28.66. This is substantially higher than the daily costs of bisphosphonates (alendronate $0.63 to $0.88; etidronate $1.31; risedronate $1.39 to $1.82; and zoledronic acid $1.84). Teriparatide costs $15,688 per patient per 18 month course of treatment (the maximum length of time for which teriparatide treatment is allowed).

Based on previous CADTH work in osteoporosis, an economic model was used to compare teriparatide with bisphosphonates for the treatment of women with osteoporosis. The data for teriparatide were obtained from a single clinical trial, GHAC, which was included in the original CDR clinical review of teriparatide, and the data for bisphosphonates were obtained from a previously conducted CADTH systematic review of bisphosphonates.

The economic evaluation was a cost-utility analysis of teriparatide compared with bisphosphonates (alendronate, etidronate, risedronate), as well as no treatment. The Markov model was run over the patient's lifetime and reflected the natural history of women with osteoporosis, considering the development of osteoporosis, history of fracture, and residential status. The results of the model suggested that compared with no treatment, or compared with alendronate, teriparatide would not be considered cost-effective.

Other Discussion Points:

- The Committee considered that alternatives exist for patients who cannot tolerate oral bisphosphonates.
- Other published cost per quality-adjusted life-year estimates for teriparatide were discussed, and it was noted that modelling assumptions that were made for these estimates were biased toward teriparatide. Differences in economic models included the underlying rate of

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fractures, utility values used and assumptions around a sustained decrease in quality of life associated with fractures, the modelling of the duration of treatment effects, and the price of teriparatide.
- A population for whom the clinical benefit would improve the cost-effectiveness of teriparatide was not identifiable in clinical trials.
- It was noted that there is variability in the definitions of severe osteoporosis and how patients who are at high risk of fracture are identified.
- The Committee considered that teriparatide is an anabolic agent and acts by a different mechanism of action than bisphosphonates, which are anti-resorptive agents.

CEDAC Members Participating:
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, Dr. Yvonne Shevchuk, and Dr. Kelly Zarnke.

Regrets:
None

Conflicts of Interest:
One CEDAC member reported a conflict of interest and did not participate in the vote.

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.

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

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