CEDAC FINAL RECOMMENDATION on RECONSIDERATION and REASONS for RECOMMENDATION

TERIPARATIDE
(Forteo™ – Eli Lilly Canada Inc.)
New Indication: Glucocorticoid-Induced Osteoporosis

Description:
Teriparatide is a recombinant human parathyroid hormone (1-34) that has the same physiological activity in bone and kidney as endogenous parathyroid hormone. The basis of the submission is a new Health Canada approved indication for the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men and women who are at increased risk for fracture. Teriparatide has been previously approved by Health Canada for the following:

- The treatment of postmenopausal 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.

Previous CEDAC Recommendation for Teriparatide:
Severe Osteoporosis (see Notice of CEDAC Final Recommendation, December 22, 2004)

Dosage Forms:
Supplied as a 250 µg/mL sterile solution for subcutaneous injection, in prefilled pens. The recommended dose is 20 µg injected subcutaneously once daily for a maximum of 18 months.

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

Reasons for the Recommendation:

1. There was only one double-blind randomized controlled trial (N=428) evaluating the effects of teriparatide on glucocorticoid-induced osteoporosis. No differences were seen between teriparatide and alendronate for incidence of non-vertebral fracture (including hip fracture) or clinical (symptomatic) vertebral fracture. The incidence of radiographic vertebral fractures was statistically significantly lower in the teriparatide group compared with the alendronate group, however, a large proportion of patients were missing radiographic data, reducing confidence in these results.
2. The manufacturer reported that, compared with alendronate, teriparatide is associated with an incremental cost per quality-adjusted life year (QALY) of $35,387 based on the effects of treatment

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on radiographic vertebral fractures and of $121,895 based on the effects of treatment on clinical fractures. Radiographic fractures have prognostic value in predicting clinical fractures but because most radiographic fractures remain asymptomatic, the true cost per QALY is uncertain and most likely lies somewhere between these two estimates.

Summary of Committee Considerations:

The Committee considered the results of one double-blind randomized controlled trial (RCT) evaluating the effects of teriparatide in men and women with glucocorticoid-induced osteoporosis (n=428). Patients received either 20 µg subcutaneous teriparatide daily or 10 mg oral alendronate daily for 36 months and all patients received calcium (1000 mg daily) and vitamin D (800 IU daily). The sample included men (20%), premenopausal (16%) and postmenopausal (64%) women, who had a variety of disorders requiring glucocorticoids (median daily dose of prednisone equivalents ranged from 7.5 mg to 7.8 mg). Cumulative dose exposure to glucocorticoids at baseline was not reported. Patients currently using or having recently used bisphophonates were excluded. The primary endpoint of the trial was the change in bone mineral density (BMD) at the lumbar spine at 18 months. Changes in total hip BMD, femoral neck BMD, markers of bone turnover and the incidence of fractures were also measured at 18 and 36 months.

There was no statistically significant difference between teriparatide and alendronate in the incidence of either clinical (symptomatic) vertebral fractures or nonvertebral fractures (including hip fractures) at either 18 or 36 months. The incidence of radiographic vertebral fractures was statistically significantly lower in the teriparatide group compared with the alendronate group after both 18 months (<1% versus 6%, respectively, P=0.005) and 36 months (2% versus 8%, respectively, P=0.010). However, 20% of patients had missing radiographs and were not included in the analysis, reducing the robustness of these results. Among patients with missing radiographs, baseline characteristics were similar between treatment groups. Although similar between teriparatide and alendronate groups, the high study withdrawal rate (approximately 31% at 18 months and 44% at 36 months), reduced confidence in the results.

Patients in the teriparatide group had a statistically significantly greater increase in percent change from baseline in lumbar spine BMD compared with patients in the alendronate group at 18 months (mean difference= 3.8%, 95% confidence interval 2.6% to 5%) and at 36 months (mean difference= 4.7%, 95% confidence interval 3.1% to 6.3%). These changes are of uncertain clinical importance.

Similar proportions of patients in the teriparatide and alendronate groups experienced a serious adverse event (33% versus 30%, respectively, at 36 months). The most frequently reported serious adverse events were infections, which is consistent with a population receiving long-term glucocorticoid therapy. There were no cases of osteosarcoma observed in the trial. There have been four cases of osteosarcoma reported globally in patients exposed to teriparatide, however, further surveillance is needed to clarify the relationship between teriparatide and osteosarcoma in humans. Withdrawals due to adverse events were statistically significantly higher in the teriparatide group compared with the alendronate group at 18 months (12% versus 6%, respectively), although not at 36 months (14% versus 8%, respectively). Also, the incidence of hypercalcemia (defined as a patient having at least one measurement with serum calcium level > 2.625 mmol/L) was statistically significantly higher in the teriparatide group compared with the alendronate group at both 18 months (18% versus 6%, respectively) and 36 months (21% versus 7%, respectively).

In the cost utility analysis submitted by the manufacturer, teriparatide was compared with alendronate over a 30-year time horizon in women with glucocorticoid-induced osteoporosis. For patients who received active treatment, the duration of therapy was 5 years (1.5 years with teriparatide followed by 3.5 years with alendronate or 5 years of alendronate) after which the manufacturer assumed that the effects of

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treatment would taper off over the next 5 years in the model, i.e., the risk of fractures reverted to the baseline rate at year 11. The manufacturer reported that teriparatide is associated with an incremental cost per quality-adjusted life year (QALY) of $35,387 compared with alendronate. QALY gains were 0.1472 for teriparatide compared with alendronate and their clinical significance is unclear given that there is no RCT evidence of differences between the two therapies on the incidence of non-vertebral and clinical fractures. The results of the manufacturer's analysis were driven largely by the effects of teriparatide on radiographic vertebral fractures. In actual practice, radiographic vertebral fractures frequently remain asymptomatic. Where treatment effects are based on clinical vertebral fractures, the manufacturer reported that the incremental cost per QALY increased to $121,895 compared with alendronate. Since some fractures will be diagnosed radiographically and then treated, the incremental cost per QALY for teriparatide likely lies between these two estimates. The manufacturer also compared teriparatide with no treatment and cost-effectiveness estimates were similar to those comparing teriparatide with alendronate, at $31,511 per QALY based on morphometric fractures and $112,482 per QALY based on clinical fractures.

At an average daily cost of [redacted], teriparatide is substantially more expensive than bisphosphonates: generic alendronate ($0.63 to $0.88), etidronate ($0.22 to $1.31), and risedronate ($1.39 to $1.82). No information on the cost effectiveness of teriparatide in men with glucocorticoid induced osteoporosis was provided by the manufacturer.

Of Note:

1. Both published and unpublished data were reviewed and taken into consideration in making this recommendation.
2. There are no RCTs evaluating teriparatide in patients with glucocorticoid-induced osteoporosis recently failing bisphosphonate therapy.
3. Patients with glucocorticoid-induced osteoporosis often have co-morbidities that may place them at higher risk of negative outcomes, for which the influence of fractures and treatment of fractures, including treatment with teriparatide, is uncertain.
4. This document has been edited to remove confidential information at the manufacturer's request in conformity with the *CDR Confidentiality Guidelines* available on the CADTH website.

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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