Heritage Information Systems, Inc.

Clinical Edit Proposal

Drug/Drug Class: Forteo (teriparatide injection)/ Parathyroid Hormone

Prepared for: Missouri Medicaid
Prepared by: Heritage Information Systems, Inc.

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, or require prior authorization for use.

Dosage Forms & Manufacturer:

- Each prefilled pen delivery device is filled with 3.3 mL to deliver 3 mL.
- Each mL contains 250 mcg teriparatide.
- Each cartridge pre-assembled into a pen device delivers 20 mcg teriparatide per dose each day for up to 28 days
- Eli Lilly and Company; Indianapolis, IN

Summary of Findings:

Teriparatide (Forteo®) is a recombinant human parathyroid hormone (PTH; 1-34) composed of the first 34 amino acids (the biologically active region) of the 84-amino acid human PTH. It is FDA-approved to treat postmenopausal women with osteoporosis who are at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. Once-daily subcutaneous administration of teriparatide works by a different mechanism than other available osteoporosis therapies, to stimulate new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.

Given the potential risk presented by the finding of osteosarcoma in rats, and the availability of several effective and safe alternative agents for the treatment of osteoporosis, it is recommended that teriparatide be available through a clinical edit.

Status Recommendation:

☐ Prior Authorization (PA) Required
☒ Clinical Edit
☐ Open Access

Type of PA Criteria:

☐ Increased Risk of ADE
☐ Appropriate Indications
☐ Non-Preferred Agent
☐ PA Not Required

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug or not (open access). While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement o f qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Teriparatide (Forteo®) is a recombinant human parathyroid hormone (PTH; 1-34) that is composed of the first 34 amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. It is FDA-approved to treat postmenopausal women with osteoporosis who are at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture.[1] Other available treatments for postmenopausal women with osteoporosis include estrogens, selective estrogen-receptor modulators, bisphosphonates, calcitonin, vitamin D, and calcitriol. These treatments reduce bone resorption (and formation) and moderately increase bone density; some reduce the risk of fracture, but none routinely restore normal bone mass or strength.[2] Once-daily administration of teriparatide works by a different mechanism to stimulate new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.[1]

Dosage Form(s)[1]

A prefilled pen delivery device filled with 3.3 mL to deliver 3 mL

- Each mL contains 250 mcg teriparatide.
- Each cartridge pre-assembled into a pen device delivers 20 mcg teriparatide per dose each day for up to 28 days
- The pen should be stored under refrigeration (36 to 46° F) at all times.

Manufacturer

Eli Lilly and Company; Indianapolis, IN 46285

Indication(s)[1]

Teriparatide is FDA-approved to treat postmenopausal women with osteoporosis who are at high risk for fracture. These include women with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant of previous osteoporosis therapy.

Teriparatide is also FDA-approved to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. These include men with a history of osteoporotic fracture, or who have multiple risk factors for fracture, or who have failed or are intolerant to previous osteoporosis therapy.

Clinical Efficacy (mechanism of action/pharmacology, comparative efficacy)

Mechanism of Action/Pharmacology[1]

Physiologic actions of PTH include regulation of bone metabolism, renal tubular reabsorption of calcium and phosphate, and intestinal calcium absorption. PTH and teriparatide bind to specific high-affinity cell-surface receptors with the same affinity and have the same physiologic actions on bone and kidney. Teriparatide is not expected to accumulate in bone or other tissues.

PTH and teriparatide can increase or decrease bone mass, depending on the pattern of systemic exposure. Once-daily administration of teriparatide stimulates new bone formation on trabecular and cortical (periosteal and/or endosteal) bone surfaces by preferential stimulation of osteoblastic activity over osteoclastic activity. In humans, the anabolic effects of teriparatide are manifest as an increase in skeletal mass, an increase in markers of bone formation and resorption, and an increase in bone strength. By contrast, continuous excess of endogenous PTH, as occurs in hyperparathyroidism, may be detrimental to the skeleton because bone resorption may be stimulated more than bone formation.

Comparative Efficacy in Postmenopausal Women

The efficacy and safety of teriparatide in postmenopausal women with osteoporosis was been assessed in a phase III randomized, placebo-controlled clinical trial, and in a smaller double-blind, randomized trial vs. alendronate.[2,3]

Neer et al., randomly assigned 1637 postmenopausal women with prior vertebral fractures to receive 20 (n=541) or 40 mcg of teriparatide (n=552) or placebo (n=544) daily by subcutaneous self-injection.[2] All women received 1000 mg calcium and at least 400 IU of vitamin D per day. Baseline and endpoint vertebral radiographs were obtained, as were serial measurements of bone mass at the lumbar spine, proximal femur, and radius and total body bone mineral by dual-energy x-ray absorptiometry (DXA). The primary efficacy endpoint was the occurrence of new radiographically diagnosed vertebral fractures.

The mean duration of treatment was 18 months, and treatment compliance ranged from 79 to 83%. Results regarding new vertebral fractures and new nonvertebral fragility fractures are summarized in Table 1. Based on these results, a vertebral fracture was prevented for every 12 patient-years of treatment with teriparatide 20 mcg and for every 10 patient-years of treatment with 40 mcg. Consistent with the above findings, new or worsening back pain was reported by 23% of placebo-treated patients and by 17% and 16% of those in the 20 mcg and 40 mcg teriparatide groups, respectively (P=0.007). The cumulative incidence of one or more new nonvertebral fractures or nonvertebral fragility fractures was lower in women treated with teriparatide than in those treated with placebo (Table 1). This difference became evident after 9 to 12 months of treatment.

Table 1. Effect of teriparatide on risk of fractures in postmenopausal women with osteoporosis

Variable	Placebo	Teriparatide 20 mcg	Teriparatide 40 mcg
% of women with ≥1 vertebral fracture	14%	5%*	4%*
Relative risk (95% CI) vs. placebo	-	0.35 (0.22 to 0.55)	0.31 (0.19 to 0.50)
% reduction in absolute risk	-	9	10
% of women with ≥1 nonvertebral fragility fracture	6%	3%**	3%***
Relative risk (95% CI) vs. placebo	-	0.47 (0.25 to 0.88)	0.46 (0.25 to 0.86)

*P≤0.001 for the comparison with placebo; **P=0.02 for the comparison with placebo; ***P=0.01 for the comparison with placebo

Compared with placebo, the 20 mcg and 40 mcg doses of teriparatide increased bone mineral density (BMD) by 9 and 13 more percentage points in the lumbar spine and by 3 and 6 more percentage points in the femoral neck. Both doses increased total-body bone mineral by 2 to 4 more percentage points than did placebo. The 40 mcg dose decreased BMD at the shaft of the radius by 2 more percentage points compared to placebo.

Bone histology studies in a subset of the study group demonstrated normal mineralization and normal quality new bone formed with teriparatide.[1] Nausea (18%) and headache (13%) occurred more frequently in the high dose teriparatide group compared with placebo or low dose teriparatide; whereas dizziness (9%) and leg cramps (3%) occurred more frequently in the low dose group compared to the two other groups. Not unexpectedly, mild hypercalcemia (defined as a calcium level >10.6 mg/dL) occurred at least once in 2% of placebo-treated women, 11% of those in the 20 mcg group, and in 28% of the 40 mcg group. Persistent hypercalcemia requiring withdrawal from the study occurred in 1 placebo-, 1 teriparatide 20 mcg-, and 9 teriparatide 40 mcg-treated patients.

Body et al.,[3] randomized 146 postmenopausal women with osteoporosis to either once-daily subcutaneous injections of teriparatide 40 mcg plus oral placebo (n=73) or oral alendronate 10 mg plus placebo injection (n=73). The primary study outcome was change in BMD at the lumbar spine, assessed by DXA. Median duration of treatment was 14 months. At month 3, the percentage increase in lumbar spine BMD for the teriparatide group was 2.7% greater than that in the alendronate group (P<0.001). This difference increased to 5.4% at 6 months, and 8.3% at 12 months (P<0.001). From baseline to endpoint, the absolute increases in lumbar spine BMD achieved with teriparatide and alendronate were 15.1% and 6.6%, respectively (P<0.001) Significantly fewer teriparatide-treated patients (5.5%) reported new or worsening back pain compared with those receiving alendronate (19.2%; P=0.012). Teriparatide also increased femoral neck BMD and total body bone mineral significantly more than did alendronate, but BMD at the one-third distal radius decreased with teriparatide vs. alendronate. Nonvertebral fracture incidence was significantly lower in the teriparatide group (4.1%) than in the alendronate group (13.7%; P=0.042).

The only notable difference in adverse effect profiles between the two agents was leg cramps reported by 6 patients (8.2%) in the teriparatide group and none in the alendronate group

(P=0.012). Not unexpectedly, based on its pharmacologic actions, 38.4% of teriparatide-treated patients vs. 3% of alendronate-treated patients had elevated 4-to 6-hour post dose serum calcium at least once in the study. One woman receiving teriparatide discontinued treatment due to the post-dose increased serum calcium level.

No other published trials directly compare the efficacy of teriparatide to other agents for the treatment of osteoporosis, but some general comparisons can be made based on the results of placebo-controlled trials with each of the respective agents. Caution is warranted, however, when drawing conclusions based on such observations, given the differences in study design and populations studied. A recent position statement by the North American Menopause Society on the management of postmenopausal osteoporosis briefly discussed the results of a number of trials with various pharmacologic agents for the treatment of osteoporosis, which are summarized in Table 2.[5]

Table 2. Efficacy results from selected studies of various osteoporosis treatment modalities[2,5]

Drug	Variable			
	Δ in lumbar BMD from baseline	Δ in hip BMD from baseline	RRR in vertebral fractures vs. placebo	RRR in nonvertebral fractures vs. placebo
Teriparatide[2] (20 mcg)	9.7%*	2.6%*	65%*	53%*
Alendronate	1-4% (2-4 yr study) 5-10% (7 yr study)	1-4% (2-4 yr study) 5-10% (7 yr study)	50% (3 yr study)	27% (3 yr study)
Risedronate	4.3%**	2.8%**	41-65%	39%
Raloxifene	2.4%**	2.4%**	35-50%	10%
Estrogens	4-6%	2-3%	40-50%	27-34%
Calcitonin	3%	NS	33%	Data not available

BMD=bone mineral density; NS=not statistically significant; RRR=relative risk reduction
*Statistically significant compared with placebo; **vs. placebo instead of baseline

Comparative Efficacy in Men

Teriparatide has been evaluated in primary (idiopathic) or hypogonadal osteoporosis in men in a phase III double-blind trial described in product labeling that enrolled 437 men.[1,4] Patients were randomized to receive placebo or teriparatide 20 mcg or 40 mcg daily. All patients also received 1000 mg calcium and at least 400 IU vitamin D per day. The primary efficacy endpoint was change in lumbar spine BMD. Mean duration of treatment was approximately 10 months. Treatment with teriparatide resulted in placebo-subtracted increases in lumbar spine bone mineral density of 5.19% at month-12 and 5.35% at endpoint in the 20 mcg group and 8.21% at month-12, and 8.51% at endpoint in the 40 mcg group ($p<0.001$ for within group comparisons vs. baseline). In the teriparatide 20 mcg group, 53% of patients achieved ≥5% increase in spine BMD, and 14% gained ≥10% in BMD at the spine. Among other skeletal sites examined, BMD significantly increased in the teriparatide group only at the femoral neck (1.5% vs. 0.3%; $p<0.05$).

Contraindications[1]

Teriparatide should not be given to patients with hypersensitivity to teriparatide or any of its components.

Warnings[1, 2]

Black Box Warning

In male and female rats, teriparatide caused an increase in the incidence of osteosarcoma (a malignant bone tumor) that was dependent on dose and treatment duration. The effect was observed at systemic exposures ranging from 3 to 60 times the exposure in humans given a 20 mcg dose. Because of the uncertain relevance of the rat osteosarcoma finding to humans, teriparatide should be prescribed only to patients for whom the potential benefits are considered to outweigh the potential risk. The drug should not be prescribed for patients who are at increased baseline risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, open epiphyses, or prior radiation therapy involving the skeleton).

It should be noted that osteosarcomas were not found in monkeys that had undergone bilateral oophorectomy and then given daily doses of teriparatide that were 4 to 10 times the maximal dose in humans over a period of 18 months.[2] No cases of osteosarcoma were reported in clinical trials of teriparatide in humans.[2]

Other Warnings/Precautions

The following categories of patients should be excluded from treatment with teriparatide:

- Bone metastases or a history of skeletal malignancies
- Metabolic bone diseases other than osteoporosis
- Pre-existing hypercalcemia due to the potential of teriparatide to exacerbate this condition

Use of teriparatide for more than 2 years is not recommended due to lack of safety and efficacy data beyond 2 years of treatment.

Teriparatide should be used with caution in patients with active or recent urolithiasis because of the potential to exacerbate this condition.

Transient episodes of symptomatic orthostatic hypotension have been observed infrequently, typically beginning within 4 hours of dosing and spontaneously resolving within a few minutes to a few hours. When they occurred, episodes happened within the first few doses, were relieved by placing the person in a reclining position, and did not preclude continued treatment.

Teriparatide transiently increases serum calcium, with maximal effect observed at 4 to 6 hours post-dose and returning to or near baseline by 16 hours post-dose. Persistent hypercalcemia was not observed in clinical trials; if it is detected, discontinue treatment with teriparatide pending further evaluation of the cause.

Teriparatide increases serum uric acid concentrations. In clinical trials, 2.8% of teriparatide-treated patients had serum uric acid levels above the upper limit of normal compared with 0.7% of placebo-treated patients. However, the hyperuricemia did not result in an increase in gout, arthralgia, or urolithiasis.

Adverse Effects[1]

Overall, teriparatide has been well tolerated in clinical trials. In the 2 phase III trials discussed above, study discontinuation due to adverse events occurred in 5.6% of placebo-treated patients and 7.1% of teriparatide-treated patients. Reported adverse events that appeared to be associated with teriparatide treatment were dizziness (8% vs. 5.4% with placebo) and leg cramps (2.6% vs. 1.3% with placebo).[2,4]

In clinical trials, the frequency of ≥1 episode of transient hypercalcemia in the 4 to 6 hours after teriparatide administration was 11.1% of women and 6.0% of men treated with teriparatide vs. 1.5% of women and none of the men treated with placebo. Transient hypercalcemia was verified on consecutive measurements in 3.0% of women and 1.3% of men treated with teriparatide.

Drug Interactions[1]

Sporadic case reports have suggested that hypercalcemia may predispose patients to digitalis toxicity. Because teriparatide transiently increases serum calcium, the drug should be used with caution in patients taking digitalis.

Dosage and Administration[1]

- Teriparatide is administered as a subcutaneous injection into the thigh or abdominal wall. The recommended dose is 20 mcg once daily.
- The drug should initially be administered under circumstances in which the patient can sit or lie down if symptoms of orthostatic hypotension occur.

Cost Comparison

Table 3. Costs of selected therapies for the treatment of postmenopausal osteoporosis

Drug	Typical dose regimen	Monthly AWP* ($)
Teriparatide (Forteo) 750 mcg/3 mL pen (lasts for 28 days)	20 mcg daily	560.00
Alendronate (Fosamax) 10 mg tab or 70 mg tab	10 mg daily or 70 mg weekly	70.54 65.83
Risedronate (Actonel) 5 mg tab or 35 mg tab	5 mg daily or 35 mg weekly	71.21 66.47
Calcitonin, nasal (Miacalcin)	200 units (1 spray) daily	70.20
Calcitonin salmon injectable (Calcitonin)	50 units daily	156.00
Raloxifene (Evista)	60 mg daily	73.58

*Red Book Update, Montvale, NJ; February 2003.

Conclusion

Teriparatide (Forteo®) is a recombinant human PTH that is composed of the first 34 amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. It is FDA-approved to treat postmenopausal women with osteoporosis who are at high risk for fracture, and to increase bone mass in men with primary or hypogonadal osteoporosis who are at high risk for fracture. Once-daily administration of teriparatide works by a different mechanism than other available osteoporosis therapies, to stimulate new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity.[1]

Teriparatide has demonstrated superiority over alendronate in increasing lumbar spine BMD and decreasing nonvertebral fractures in a small comparative trial.[3] No other studies have directly compared teriparatide to other treatment modalities, but results of similar, placebo-controlled trials with each respective agent allow some general observations regarding comparative efficacy. Keeping in mind the limitations of such comparisons across studies, results suggest superior efficacy of teriparatide over other agents for increasing lumbar BMD and reducing the risk of vertebral and nonvertebral fractures (see Clinical Efficacy, Table 2).

Overall, teriparatide has been well tolerated in clinical trials, with dizziness (8%), leg cramps (2.6%), and transient hypercalcemia (11.1%) being the primary adverse events reported more frequently than with placebo. Teriparatide does carry a black box warning regarding the increase in incidence of osteosarcoma in rats. Because of the uncertain relevance of this finding to humans, the drug should not be used in patients at increased baseline risk for osteosarcoma. Its use should be reserved for patients at high risk for fracture, and in these cases, and should only be used if the potential benefits are considered to outweigh the potential but uncertain risk.

Recommendation(s)

It is recommended Forteo be available through a clinical edit.

Approval Criteria

- Diagnosis of Osteoporosis
- Trial/Failure or intolerance on Bone Reabsorption Inhibitors

References

1. Forteo® (teriparatide injection). Product labeling. Eli Lilly and Company: Indianapolis, IN. 2002.

2. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (134) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. 2001;344:1434-1441.

3. Body JJ, Gaich GE, Scheele WH, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. J Clin Endocrinol and Metab. 2002;87:4528-4535.

4. Schneider BS. Executive summary for advisory committee. NDA 21-318 Center for Drug Evaluation and Research. Food and Drug administration. 27 July 2001. (www.fda.gov)

5. Board of Trustees of the North American Menopause Society. Management of postmenopausal osteoporosis: position statement of the North American Menopause Society. Menopause. 2002;9:84-101.

6. Red Book Update, Montvale, NJ; February 2003.

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