PUBLIC SUMMARY DOCUMENT

Product: Teriparatide, solution for injection, in a 3 mL cartridge contained in a pre-filled disposable delivery device (pen), 250 micrograms in 1 mL, Forteo®

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

This resubmission sought an authority required listing for the treatment of osteoporosis in postmenopausal women and men at very high risk of fracture who meet certain criteria.

2. Background

Four previous applications (June 2003, March 2004, July 2005 and March 2006) were rejected by the PBAC.
(See also Public Summary Document for March 2006)

In September 2006, the PBAC's recommendation from March 2006 relating to teriparatide was subject to an independent review. At the November 2006 PBAC meeting, the PBAC considered that the review provided no new basis to warrant reconsideration of its previous recommendation in March 2006.

3. Registration Status

Teriparatide was registered by the TGA on 22 May 2003 for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fracture.

Under the terms of registration the following limitations apply:

1. The maximal lifetime exposure to teriparatide for an individual patient is 18 months.
2. Patients will need to read the Consumer Medicine Information leaflet and pen User Manual before starting therapy with teriparatide and re-read them each time the prescription is renewed.
3. Patients should be made aware that teriparatide caused osteosarcoma in rats and that the clinical relevance of these findings is unknown.
4. Informed consent will need to be obtained from each patient before starting therapy to ensure that the 18-month lifetime limit is understood.

4. Listing Requested and PBAC's View

Authority required

Treatment by a specialist/consulting physician treating osteoporosis for postmenopausal women and men who have received at least 12 months continuous anti-resorptive therapy and have a very high risk of fracture. A very high risk of fracture is defined as:

- The presence of two or more osteoporotic fractures where at least one incident fracture due to minimal trauma has occurred despite at least 12 months continuous therapy with an anti-resorptive agent of proven efficacy and safety for the treatment of osteoporosis; AND

- A bone mineral density (BMD) T-score of -3.0 or less in a patient aged 70 years or older. The initial authority application must state the date, site (femoral neck OR lumbar spine) and score of the qualifying BMD measurement.

The radiological and/or laboratory reports and confirmation of the patient's prior treatment history supporting eligibility must be available for audit by Medicare Australia. Fracture must have been demonstrated radiologically and the year of plain x-ray, or CT-scan or MRI scan, and the year of DEXA must be included in the authority application. A vertebral fracture is defined as a 20% or greater reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, a 20% or greater reduction in any of these heights compared to the vertebral body above or below the affected vertebral body

Anti-resorptive therapies for osteoporosis which will be accepted for the purposes of administering this restriction are alendronate sodium 10mg/day or 70mg QW, risedronate sodium 5mg/day or 35mg QW; raloxifene hydrochloride 60mg/day (women only); etidronate 200mg with calcium carbonite 1.25g/day; strontium ranelate 2g.

If treatment with the above-mentioned drugs is contraindicated according to the relevant TGA-approved Product Information, or intolerance of a severity necessitating permanent treatment withdrawal develops during the relevant period of use, the patient is exempted from the requirement to complete 12 months of therapy with that particular agent or class of agents. Details of the contraindication or intolerance must be provided at the time of application.

Continuing treatment for osteoporosis in postmenopausal women and men with primary osteoporosis with two or more fractures due to minimal trauma and a bone mineral density T score of -3.0 or less where the patient has previously been issued with an authority prescription for this drug.

Teriparatide is available with a lifetime maximum of 18 months teriparatide therapy (18 pens), a maximum of 18 pens will be reimbursed through the PBS.

See Recommendation and Reasons for PBAC's view.

5. Clinical Place for the Proposed Therapy

Osteoporosis affects the skeleton and is characterised by low bone mass and micro-architectural deterioration of bone tissue with a subsequent increase in bone fragility and susceptibility to fracture. Osteoporosis is defined by the measurement of bone mineral density. Established osteoporosis denotes the presence of one of more fragility fractures.

Teriparatide is indicated for the treatment of osteoporosis in postmenopausal women and the treatment of primary osteoporosis in men when other agents are considered unsuitable and when there is a high risk of fractures.

6. Comparator

The submission nominated alendronate as the comparator. This was appropriate as previously advised by the PBAC.

7. Clinical Trials

No changes had been made to the primary trial data that had been presented in the previous submissions. The submission again presented a common comparator analysis of the pivotal clinical trials of teriparatide and alendronate, with the common comparator being placebo, and with fracture as the primary endpoint. These studies have been published as follows:

Trial/first author	Protocol title	Publication citation
Teriparatide		
GHAC/Neer RM	Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis.	New England Journal of Medicine 2001;344:1434-1441.
GHAC/Gallagher JC	Teriparatide reduces the fracture risk associated with increasing number and severity of osteoporotic fractures.	Journal of Clinical Endocrinology and Metabolism 2005;90:1583-7.
Alendronate		
FIT-VFA/Black DM	Randomised trial of alendronate on risk of fracture in women with existing vertebral fractures.	The Lancet 1996; 348: 1535-1541.

The supportive trials presented had been updated to include the results from a head-to-head trial of teriparatide and alendronate in 428 patients with glucocorticoid induced osteoporosis (which is unpublished), as well as two previously submitted trials, one of which was published at the time of submission, as follows:

Trial/First author	Protocol title/Publication title	Publication citation
GHBM/ Arlot M,	Differential Effects of Teriparatide and Alendronate on Bone Remodeling in Postmenopausal Women Assessed by Histomorphometric Parameters.	Journal of Bone & Mineral Research. 20(7):1244-53, 2005 Jul.

The listing requested by the sponsor limits use to after anti-resorptive therapy has failed. However, the proportions of patients in each of the trials who received anti-resorptive therapy was less than 20% and there is no direct data relating to patients previously using antiresorptive therapy.

8. Results of Trials

Comparative effectiveness

The PBAC noted that this application presented a new indirect comparison of teriparatide and alendronate using the full trial population rather than a subgroup as previously and using a new Bayesian analysis in addition to the standard frequentist analysis.

The key results are summarised in the tables below.

Results of rates of patients with one or more new vertebral fractures in the paired radiograph population

Trial/Comparison	Proportion with fracture (%)		Risk results (95% CI)	
	Active drug	Placebo	Risk difference	Relative risk
GHAC Trial				
Teriparatide 20mcg/d vs placebo	22/444 (5.0%)	64/446 (14.3%)	-9.3% (-13.3, -5.6)	0.35 (0.22, 0.55)

BLACK Trial				
Alendronate 10mg/d vs placebo	78/981 (8.0%)	145/965 (15.0%)	-7.1% (-9.9, -4.3)	0.53 (0.41, 0.68)

Results of rates of patients with <u>all</u> new non-vertebral fracture rates in the all randomised population

Trial/Comparison	Proportion with fracture (%)		Risk results (95% CI)	
	Active drug	Placebo	Risk difference	Relative risk
GHAC trial				
Teriparatide 20mcg/d vs placebo	34/541 (6.3%)	53/544 (9.7%)	-3.5% (-6.8, -0.2)	0.65 (0.43, 0.97)
BLACK trial				
Alendronate 10mg/d vs placebo	122/1022 (11.9%)	148/1005 (14.7%)	-2.8% (-5.8, 0.2)	0.81 (0.65, 1.01)

The re-submission provided a Bayesian analysis that was conducted to determine:

- whether there are any differences in treatment effects for teriparatide at the two dosages (20 mcg and 40 mcg)
- the probability that teriparatide treatment effect is as good as, or better than, alendronate (using GHAC and FIT); and
- whether the effects of teriparatide are different when age, BMD and prior fracture sub-groups are considered.

The Bayesian comparison of 20 mcg and 40 mcg teriparatide showed a point estimate of relative risk <1, indicating that each treatment reduced the risk of new vertebral fracture. The probability of efficacy was comparable between the doses. The re-submission stated that these analyses demonstrate that teriparatide 20 mcg and 40 mcg/d doses have equivalent efficacy. The submission also claimed that these analyses demonstrate that the 20 mcg/d and combined 20 mcg/d and 40 mcg/d doses of teriparatide were comparable to or better than alendronate, for which the probability that the relative risk is less than 0.8 was 80%, compared with 93% for the combined teriparatide doses.

The results of Bayesian analysis of teriparatide efficacy by baseline characteristics suggested that teriparatide had comparable efficacy across age groups and had greater or equivalent efficacy in patients with lower BMD or more prior fractures.

See Recommendation and Reasons for PBAC's view of these results.

Comparative toxicity

The submission updated the toxicity data for both teriparatide and for alendronate, but no new major issues arose.

9. Clinical Claim

The submission again claimed teriparatide was significantly more effective than the comparator, alendronate, and could be considered either to have (i) more toxicity due to the possible implications of the preclinical finding of osteosarcoma, or (ii) less toxicity because of the time elapsed since marketing and precautions used. The submission invited the PBAC to consider both options.

The PBAC did not accept this claim, *see Recommendation and Reasons*.

10. Economic Analysis

The re-submission presented an updated preliminary trial-based economic evaluation.

The trial-based incremental cost per extra vertebral fracture avoided over 18 months was estimated by the submission to be between $105,000 - $200,000.

The trial-based incremental cost/extra non-vertebral fracture avoided was estimated by the submission to be > $200,000.

A modelled economic evaluation was presented. As previously, the re-submission presented a cost-utility analysis, using a decision-analytical approach.

The submission estimated that the incremental cost per quality adjusted life year for teriparatide over alendronate felt in the range $15,000 - $45,000.

However, the lack of a demonstrated statistically significant clinical benefit for teriparatide over alendronate, together with doubts about the way the benefit is modelled; contributed to the Committee's continued uncertainty about the incremental cost-effectiveness of teriparatide.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS minus any savings in use of other drugs was estimated to be between $10 - $20 million in Year 3.

12. Recommendation and Reasons

The PBAC, although largely supportive of the intent of the sponsor's new restriction, was concerned that it may not be administrable due to difficulty in establishing whether any new (and often non-clinical vertebral) fracture occurred during or after the 12 months of continuous anti-resorptive treatment, without subjecting a large number of, often ultimately ineligible, patients to repeated X-ray examinations. The PBAC did not accept the proposed exclusion of patients younger than 70 years considering that this would inappropriately exclude some patients and that high fracture risk could be adequately identified using a combination of BMD and fracture, without age.

The Committee noted that this application presented a new indirect comparison of teriparatide and alendronate using the full trial population rather than a subgroup and using a new Bayesian analysis in addition to the standard frequentist analysis. The sponsor argued that teriparatide is a good candidate for a Bayesian analysis because of the wide range of data available.

However, the Committee considered that in light of the continuing debate about the methodological validity of Bayesian analysis it should accept the results of the frequentist analysis of the presented indirect comparison; that there is no statistically significant difference between the teriparatide and alendronate in terms of rates of patients with one or more new vertebral fractures or rates of patients with all new non-vertebral fractures. Even if the Committee accepted that the Bayesian analysis is valid, it is difficult to determine what cut-offs should apply in interpreting its results.

The Committee did acknowledge that there is a trend in the data which suggests that teriparatide may be more effective than alendronate in preventing new vertebral and non-vertebral fractures, and that this has biological plausibility. However the results fail to reach statistical significance. This lack of statistical significance, together with doubts about the way the treatment benefit is modelled; contribute to the Committee's continued uncertainty about the incremental cost-effectiveness of teriparatide.

Additional areas of uncertainty in the model are the estimates of the relative risk of fracture following a previous fracture (the "fracture multiplier") and the utility values.

The economic model continues to assume, in the base case, that all vertebral fractures are associated with the same disutility. As previously concluded, this is unlikely to be the case for the asymptomatic (or non-clinical) vertebral fractures which comprise the majority of new vertebral fractures.

Taken together, these areas of uncertainty led the Committee to conclude that the base case incremental per extra quality adjusted life year (QALY) was substantially underestimated.

The PBAC acknowledged that a small group of patients remain at very high risk of fracture despite the PBS availability of the bisphosphonates, raloxifene and strontium, and that there is a clinical need for effective treatments for this group. The PBAC also agreed that the data from the GHBZ trial which directly compared teriparatide with alendronate in patients with steroid induced osteoporosis indicate teriparatide is clinically more efficacious than alendronate, and that furthermore these patients might comprise up to half of all patients who would become eligible under the sponsor's proposed PBS-restriction. However the cost-effectiveness of using teriparatide to treat glucocorticoid induced osteoporosis is unknown.

The PBAC therefore rejected the submission because of continuing uncertainty about the extent of clinical benefit over the comparator in the total group who would be eligible for treatment under the proposed restriction and because, even if the claimed clinical benefit were accepted, the cost-effectiveness of treatment remains highly uncertain.

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor disagrees with the decision and is considering the options available. Australia remains one of the few countries where teriparatide is not reimbursed through the government formulary for patients with severe osteoporosis. The sponsor refers you to its website (www.lilly.com.au) for further information.