Public Summary Document

Product:	Teriparatide, solution for injection, in a 3mL cartridge contained in a pre-filled disposable delivery device (pen), 250 micrograms/mL, Forteo®
Sponsor:	Eli Lilly Australia Pty Ltd
Date of PBAC Consideration:	March 2006

1. Purpose of Application

This application sought listing on the Pharmaceutical Benefits Scheme (PBS) as an authority required benefit for the treatment of severe vertebral osteoporosis in men and postmenopausal women who meet certain criteria.

2. Background

This was the fourth application seeking listing of teriparatide on the PBS. The first two applications (June 2003 and March 2004) were rejected by the Pharmaceutical Benefits Advisory Committee (PBAC) because of doubts about the claims of superior effectiveness over alendronate as the accepted comparator, and the resulting uncertain cost-effectiveness. The PBAC also had concerns about the estimated use of teriparatide and the resulting overall cost to the PBS.

At the July 2005 meeting, the PBAC rejected a third submission requesting an Authority Required listing for initial and continuing treatment of severe established osteoporosis in men and postmenopausal women with evidence of one or more severe painful osteoporotic vertebral fracture because of the inappropriate comparator, placebo, and the resulting uncertain clinical benefit and uncertain cost effectiveness. The PBAC however acknowledged there is a clinical need for an effective treatment for severe established osteoporosis in men and women with evidence of one severe painful osteoporotic vertebral fracture.

3. Registration Status

Teriparatide was registered by the Therapeutic Goods Administration (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 fractures.

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.

Informed consent needs 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

The submission requested the following listing:

Authority required

Treatment by a specialist/consulting physician treating osteoporosis for severe established vertebral osteoporosis in men and postmenopausal women who:

1. have evidence of one or more severe painful osteoporotic vertebral fracture and
2. have received at least 6 continuous months of anti-resorptive therapy of proven efficacy and safety at the time of the [severe] SQ3 vertebral fracture.

A severe vertebral fracture is defined as 40% reduction in height of the anterior or mid portion of a vertebral body relative to the posterior height of that body, or, greater than 40% reduction in any of these heights compared to the vertebral body above or below the affected vertebral body.

Evidence of the fracture/deformity must be demonstrated radiologically and the year of plain x-ray or CT-scan or MRI scan must be included in the authority application.

Antiresorptive therapies for osteoporosis which will be accepted for the purposes of administering this restriction are alendronate sodium 10 mg/day or 70 mg once weekly, risedronate sodium 5 mg/day or 35 mg once weekly; raloxifene hydrochloride 60 mg/day (women only); etidronate 200 mg with calcium carbonate 1.25 g/day. Patients with 6 months continuous prior treatment with strontium ranelate will also be eligible under the administration of this listing.

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 form the requirement to complete 6 continuous 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 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.

For PBAC's view, see Recommendation and Reasons.

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 main comparator. This was appropriate as previously advised by the PBAC.

7. Clinical Trials

The submission 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.

Neither the teriparatide nor the alendronate trials limited enrolments to patients with severe (SQ3) vertebral fractures at baseline. A severe fracture (SQ3) is defined as one in which there is a more than approximately 40% reduction in anterior, mid and/or posterior vertebral height.

The data supporting teriparatide were derived primarily from the GHAC trial. GHAC was a randomised, placebo-controlled trial of two doses of teriparatide (20 micrograms per day and 40 micrograms per day) using morphometric vertebral fracture as the primary outcome. The trial had resulted in a number of peer-reviewed publications at the time of submission: The two main publications cited as supportive evidence are as follows:

Trial/first author	Protocol title	Publication citation
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.

The submission used the results from a post-hoc sub-group of patients from the GHAC study treated with either teriparatide 20 micrograms per day or placebo with severe prevalent vertebral fractures (SQ3) at baseline. This analysis had been published as Gallagher (2005).

The PBAC's did not accept the validity of using this sub-group to assess the therapeutic and economic performance of teriparatide in patients eligible according to the requested restriction. *See Recommendation and Reasons.*

The data supporting alendronate in patients with established osteoporosis were derived from the FIT-VFA, the arm of the Fracture Intervention Trial which included patients with postmenopausal osteoporosis and a prior vertebral fracture.

This trial had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
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 submission used the full trial data for alendronate on the basis of a published report (Ensrud KE et al, Arch Int Med 1997; 157:2617-24) demonstrating a uniform treatment effect across a variety of predefined sub-groups all with p-values for interaction between treatment and sub-group >0.3.

The submission also cited the post-hoc sub-group analysis of the Multiple Outcomes of Raloxifene Evaluation (MORE) trial (Ettinger et al 1999). Like the FIT-VFA, the MORE included patients with osteoporosis and prior vertebral fracture. This trial had been published at the time of submission as follows:

Trial/First author	Protocol title	Publication citation
MORE/Ettinger B	Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial.	JAMA 1999;282:637–45
Delmas PD	Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial	Bone 2003;33:522–32

8. Results of Trials

The key results for the full GHAC trial, the GHAC SQ3 sub-group, the alendronate FIT-VFA trial and the MORE sub-group are presented in the following table.

Indirect analysis of morphometric vertebral fracture rates using placebo as common reference

	Teriparatide data			Alendronate data		
	Active	**Placebo**	**RR (95% CI)**	**Active**	**Placebo**	**RR (95% CI)**
1-Teriparatide & alendronate: all randomised populations						
	22/541	64/544	0.346 (0.22, 0.55)	78/1022	145/1005	0.529 (0.41, 0.69)
Relative risk reduction (indirect comparison) = 0.65 (0.38, 1.12), p=0.1206						
2-Teriparatide & alendronate: paired radiograph populations						
	22/444	64/448	0.347 (0.22, 0.55)	78/981	145/965	0.529 (0.41, 0.69)
Relative risk reduction (indirect comparison) = 0.66 (0.38, 1.12), p=0.1211						
3-Teriparatide: SQ3 sub-group population; alendronate: paired radiograph population						
	5/86	27/95	0.205 (0.08, 0.51)	78/981	145/965	0.529 (0.41, 0.69)
Relative risk reduction (indirect comparison) = 0.39 (0.15, 0.99), p=0.0487						
4-Teriparatide: SQ3 sub-group population; Raloxifene : paired radiograph population						
	5/86	27/95	0.205 (0.08, 0.51)	55/197	75/196	0.74 (0.54, 0.99)
Relative risk reduction (indirect comparison) = 0.28 (0.11, 0.73), p=0.009						

The submission updated the toxicity data for both teriparatide and for alendronate, and the evaluation advised that no major new issues have arisen. With teriparatide, the PBAC remains concerned regarding the findings from rat toxicity studies of osteosarcoma (although no human case has been reported) and, with alendronate, there is concern from case reports of long-term over-remodelling of bone and therefore increased fracture risk and delayed fracture healing, but there is as yet no controlled supportive evidence.

For PBAC's view of these data, see Recommendation and Reasons

9. Clinical Claim

The submission claimed "[t]eriparatide has significant clinical advantages over alendronate: it is significantly more effective than the main competitor,…". Regarding toxicity the re-submission presented both a "more toxicity" and a "less toxicity" option and invited the PBAC to consider both.

For PBAC's view on this claim, see Recommendation and Reasons.

10. Economic Analysis

An updated preliminary economic evaluation was presented in the submission using the treatment effects shown in the indirect comparison, including using the results for the severe fracture (SQ3) sub-group for teriparatide. The trial-based incremental cost per extra new vertebral fracture avoided was in the range of $105,000 - $200,000.

An updated modelled economic evaluation was presented. This was a cost-utility analysis. The modelled evaluation also used the results derived from the severe fracture (SQ3) sub-group for teriparatide. The base case modelled incremental discounted cost per extra (ICER) quality adjusted life year (QALY) gained was calculated in the submission to fall in the range $15,000 - $45,000. Varying some of the key assumptions in the model, including using the teriparatide fracture risk from the ITT population in a multi-way sensitivity analysis, increased the incremental discounted cost per extra discounted life-year to fall in the range in the range $75,000 - $105,000.

For PBAC's view, see recommendation and reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the total number of patients on treatment to be <10 000 in Year 4 of listing. The net cost to the PBS was estimated in the submission to be < $10 million in year 4 of listing.

12. Recommendation and Reasons

The PBAC accepted there is a strong clinical need for an effective treatment for patients with osteoporosis who continue to have symptomatic vertebral fractures whilst receiving a bisphosphonate, with calcium and vitamin D supplementation. The PBAC noted that this re-submission had addressed a number of outstanding issues, including the requested restriction, the appropriate comparator, the toxicity of teriparatide and the uncertainty over the predicted usage. However, some issues remained outstanding, including (a) the reliance on an indirect comparison across placebo-controlled trials to infer the superiority claim for teriparatide over alendronate rather than a head-to-head randomised trial; (b) use of the results of the post hoc sub-group analysis in place of the overall ITT results for teriparatide in the clinical conclusions and the economic model; and (c) the continuing use of the same utilities and disutilities, as previously, in the model where the sensitivity analyses indicate the model is sensitive to the assumptions used to derive the incremental utility estimates from the trial-based outcome measures.

Further, there were still a number of problems with the key randomised trial, as observed in previous submissions, in that, the trial was stopped prematurely, about 20% of patients dropped out and some patients were not x-rayed. Overall, the PBAC was concerned that no further fracture outcome trials have been performed with teriparatide since the conclusion of

the GHAC trial which might otherwise have helped address the important residual uncertainties.

The PBAC noted the submission had appropriately chosen alendronate as the comparator. The Committee further noted that the submission had compared the results of the high risk group for teriparatide with the overall trial population for alendronate, in the absence of the available data for the high risk group for alendronate.

The PBAC noted that although the tests for interaction between baseline fracture severity and treatment effect for the GHAC trial groups indicate that there is a statistically significant difference in absolute risk between the high risk sub-group and the remainder of the trial population, however, as previously, there was no statistically significant difference for the relative risk (which is used in the modelled economic evaluation) across the two sub-groups. The PBAC concluded, as previously, that the relative risk results of the overall trial population applied to the different baseline risk of the high-risk sub-group should form the basis of any clinical or economic evaluation. The PBAC did not accept the statistical arguments presented by the submission to support a claim of a treatment effect modification, which would validate the use of the high-risk sub-group.

Furthermore, no evidence was submitted to suggest any biologically plausible reason that teriparatide is more effective in the high risk sub-group than in the overall trial population. Although a biologically plausible argument could be mounted that alendronate may be less effective in the high risk sub-group because of a lower bone turnover associated with loss of bone architecture in this sub-group, as noted above, the submission did not rely on using the results of a sub-group analysis in place of the overall trial population results for alendronate in its modelled economic evaluation. As noted previously, the submission again sought to base its biological plausibility arguments on the different mechanisms of action of the two alternative drugs. The PBAC concluded that although this might be relevant to the question of differential treatment effects across the drugs, it is irrelevant to the question here of the biological plausibility of the one drug (teriparatide) having an increasing relative treatment effect as baseline fracture severity worsens. The PBAC thus considered that the re-submission therefore provides no new basis that could change the PBAC's previous view concerning the invalidity of adopting the results of this sub-group analysis rather than the results of the overall ITT analysis as the basis for deriving an estimate of the effectiveness of teriparatide to compare with alendronate.

The PBAC therefore rejected the submission because of uncertain clinical benefit and the resulting uncertain and unacceptable cost-effectiveness.

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

Eli Lilly Australia has decided to seek an independent review (IR) of the Pharmaceutical Benefits Advisory Committee's (PBAC's) recent recommendation to not list Forteo on the Pharmaceutical Benefits Scheme (PBS).

Lilly acknowledges and respects the challenging task undertaken by PBAC. However, Lilly also stands by the strength of the clinical evidence in support of this product. Following four PBAC submissions and subsequent meetings with the PBAC and Pharmaceutical Benefits Branch (PBB) there remain fundamental differences between Lilly and the PBAC regarding the strength and interpretation of the relevant data.

Lilly acknowledges the previous PBAC submissions have been complex and some aspects of statistical analysis open to varying interpretation, however, we believe there is sufficient information within the submissions already made to address PBAC concerns regarding uncertainty related to biological plausibility of superiority, clinical effectiveness and cost-effectiveness.

The issues upon which review is sought are:

(a) PBAC concern that the indirect comparison and subgroup analysis does not support the claim of superiority,

(b) PBAC's claim that the submission provides no evidence to suggest any biologically plausible reason to explain the claimed difference between teriparatide and the comparator.

(c) PBAC concern with regard to continuing use of the same utility values in spite of the sponsor's efforts to address these concerns in its responses.

Lilly appreciates the availability of the Independent Review mechanism as a further PBS listing assessment process. The result of the IR will be provided to the PBAC for its consideration in November this year.

For further information on FORTEO®, please see the Consumer Medical Information leaflet available on the sponsor's website. For any other patient or prescriber inquiries please contact the Eli Lilly Australia Medical Information Department by telephone on +61 2 9325 4622.