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: November 2008

1. Purpose of Application

To request a PBS listing for teriparatide as a Section 85 Authority required benefit for the treatment of glucocorticoid induced osteoporosis (GIOP) and as a second line treatment for patients at high risk of fracture due to severe established osteoporosis (SEVERE).

2. Background

This was the sixth application seeking listing of teriparatide on the PBS. Five previous applications (June 2003, March 2004, July 2005 March 2006 and July 2007) were rejected by the PBAC. *(See Public Summary Documents for July 2005, March 2006 and July 2007)*

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.

In July 2007, the PBAC again rejected a 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 remained highly uncertain.

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.

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.

The indication "*treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in women and men at high risk for fracture"* was not TGA registered at the time of writing.

4. Listing Requested and PBAC's View

The submission proposed two listing restrictions, one for the GIOP indication and one for the SEVERE established osteoporosis indication, as follows:

2ND LINE SEVERE OSTEOPOROSIS (SEVERE)

Authority Required

Treatment as the sole PBS-subsidised agent for patients with severe, established osteoporosis who have a *very high risk* of fracture *where other agents would be considered unsuitable*. Treatment must be initiated by a specialist/consulting physician treating osteoporosis.

A very high risk of fracture is defined as:

- The presence of *two or more* fractures AND A bone mineral density (BMD) T-score of -3.0 in postmenopausal women or men with idiopathic or hypogonadic osteoporosis.

Other agents would be considered unsuitable in the following circumstances:

- The patient has demonstrated at least one new fracture despite at least 12 months continuous therapy with an anti-resorptive. Antiresorptive 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 carbonate 1.25g/day; strontium ranelate 2g.
- Treatment with anti-resorptive therapy 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. Details of the contraindication or intolerance must be provided at the time of application.

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

Authority Required

Continuing treatment for severe established osteoporosis 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.

GLUCOCORTICOID INDUCED OSTEOPOROSIS (GIOP)

Authority Required
Treatment as the sole PBS-subsidised agent for patients with steroid-induced osteoporosis who have a *very high risk* of fracture. Treatment must be initiated by a specialist/consulting physician treating osteoporosis.

A very high risk of fracture in patients with steroid induced osteoporosis is defined as:

- The presence of *one or more* fractures in patients who have received glucocorticoid therapy at an average dose of ≥5 mg/day of prednisone or its equivalent for ≥3 consecutive months immediately preceding initial of teriparatide.

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

Authority Required
Continuing treatment for steroid-induced osteoporosis 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.

SEVERE ESTABLISHED OSTEOPOROSIS

6. Comparator

The submission nominated alendronate as the comparator for SEVERE established osteoporosis. The PBAC had previously accepted alendronate as the appropriate comparator in the population targeted by the SEVERE listing.

7. Clinical Trials

No changes were made to the trial data presented in the previous submission. During the evaluation the indirect analysis was conducted using both the frequentist and Bayesian approaches.

The trials published at the time of the submission are as follows:

Trial/First author	Protocol title/Publication 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

8. Results of Trials

The primary outcome of the indirect analysis is summarised in the table below.

Trial	Teriparatide (20mcg/day)	Placebo	Alendronate (10mg/day)	Treatment effect RR (95% CI)[a]
Proportion of patients with new vertebral fractures (paired radiograph population) [n/N (%)]				
GHAC	22/444 (5.0)	64/448 (14.3)	-	0.35 (0.22. 0.55) $p < 0.0001$
FIT-VFA	-	145/965 (15.0)	78/981 (8.0)	0.53 (0.41, 0.69) $p < 0.0001$
Frequentist indirect estimate of effect [RR (95% CI)]				0.66 (0.38, 1.12) $p = 0.1211$
Bayesian indirect estimate of effect [median RR (95% CrI)]				0.66 (0.38, 1.11)

Abbreviations: CI, confidence interval; CrI, credible interval; RR, relative risk
[a] Calculated using a random effects model

The re-submission presented an indirect analysis of gastrointestinal adverse events. The indirect analysis did not identify any additional safety issues. The re-submission has also identified recent concerns regarding a possible association between atrial fibrillation and alendronate treatment.

For PBAC's comments on these results see Recommendation and Reasons.

9. Clinical Claim

The re-submission claimed, "teriparatide is therapeutically superior to alendronate for the treatment of severe established osteoporosis and has a comparable safety profile".

For PBAC's view see Recommendation and Reasons.

10. Economic Analysis

The submission presented an updated modelled economic evaluation based on an indirect comparison of randomised studies. The type of economic evaluation presented is a cost-utility analysis.

The results of the sensitivity analyses indicated that the model is most sensitive to: the relative risk of vertebral fractures, the use of 'fracture multipliers', assumptions regarding any

extended treatment effect, and the application of disutility values associated with the vertebral fractures. The submission estimated the incremental cost-effectiveness ratio (ICER) per Quality Adjusted Life Year (QALY) gained to be less than $15,000. However, the PBAC noted that changing this assumption so that only 30 % of vertebral fractures are associated with disutility had been shown in a univariate sensitivity analysis to substantially increase the ICER per QALY to the range of $45,000-$75,000.

For PBAC's view see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients was estimated in the submission to be less than 10,000 per year for both severe established osteoporosis and steroid-induced osteoporosis.

The financial cost/year to the PBS was estimated in the submission to be less than $10 million per year. The PBAC considered this uncertain, and likely that the financial impact of teriparatide would exceed $10 million per year if listed for both indications.

12. Recommendation and Reasons

PART A: SEVERE ESTABLISHED OSTEOPOROSIS

The PBAC recommended the listing of teriparatide on the Pharmaceutical Benefits Scheme as a Section 85 authority required benefit for the treatment of severe established osteoporosis on the basis of acceptable cost-effectiveness over the comparator, alendronate, in the context of a very high clinical need.

The Committee considered that the restriction proposed by the sponsor should be amended to specify that at least one new symptomatic fracture to have occurred after 12 months of continuous anti-resorptive therapy with an anti-resorptive agent at appropriate doses. The PBAC's recommendation to limit treatment to patients whose new fracture is symptomatic reflects its conviction that the disutility associated with a fracture is related to symptoms, or in other words, that an asymptomatic fracture is very unlikely to be associated with any disutility. The anti-resorptives and doses which will be accepted for the purposes of administering this restriction are: alendronate sodium 10 mg/day or 70 mg QW, risedronate sodium 5 mg/day or 35 mg QW; zoledronic acid 5 mg per annum; raloxifene hydrochloride 60 mg/day (women only); etidronate 200 mg with calcium carbonate 1.25 g/day; and strontium ranelate 2 g/day.

In making this recommendation, the Committee noted that the most significant change since it last rejected an application to list teriparatide for this indication has been a substantial price reduction. There were also some minor changes to the modelled economic evaluation, and the data from a study in corticosteroid induced osteoporosis (GHBZ) had been presented in support of the efficacy of teriparatide in severe osteoporosis (and as the key evidence in support of a listing request for Glucocorticoid Induced Osteoporosis).

Although there have been no changes to the trial data for the severe population, which shows that there is no statistically significant difference in efficacy between teriparatide and alendronate at TGA-approved doses, the Committee noted that it had previously accepted that there is a trend in these data which suggest that teriparatide may be more effective than alendronate in preventing new vertebral and non-vertebral fractures, and that this has biological plausibility. The data from study GHBZ provided further reassurance on this

issue, and overall, the Committee was prepared to accept the submission's approach to modelling the difference between the two agents.

The Committee further considered that the submission's assumption that non-clinical (asymptomatic) fractures have the same disutility as clinical (symptomatic) fractures is not reasonable, and that a more reasonable approach would have been to assume that only a proportion of vertebral fractures are symptomatic. The Committee noted that changing this assumption so that only 30 % of vertebral fractures are associated with disutility had been shown in a univariate sensitivity analysis to substantially increase the incremental cost-effectiveness ratio (ICER) per Quality Adjusted Life Year (QALY) gained.

Taking into account the substantial reduction in price offered by the sponsor prior to the meeting, the Committee considered the ICER per QALY gained over alendronate to represent acceptable cost-effectiveness, in the context of a high clinical need for a treatment for the group of patients who continue to fracture despite treatment with the currently available anti-resorptives or who have a true contraindication or intolerance to these agents.

Recommendation
TERIPARATIDE, injection 150 micrograms per mL, Forteo®, Eli Lilly Pty Ltd.

SEVERE ESTABLISHED OSTEOPOROSIS

Restriction: To be finalised

NOTE:
Any queries concerning the arrangements to prescribe teriparatide may be directed to Medicare Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. EST Monday to Friday).

Written applications for authority to prescribe teriparatide should be forwarded to:

Medicare Australia
Prior Written Approval of Specialised Drugs
Reply Paid 9826
GPO Box 9826
HOBART TAS 7001

Further prescribing information is on the Medicare Australia website at www.medicareaustralia.gov.au.

Authority Required
Initial treatment, by a specialist or consulting physician treating osteoporosis, as the sole PBS-subsidised agent for severe, established osteoporosis in a patient with a very high risk of fracture who:
a) has a bone mineral density (BMD) T-score of -3.0 or less, and
b) has two or more fractures due to minimal trauma, and
c) has experienced at least one new symptomatic fracture after at least 12 months continuous therapy with an anti-resorptive agent at adequate doses, or

d) treatment with anti-resorptive therapy 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. Details of the contraindication or intolerance must be provided at the time of application.

A very high risk of fracture is defined as the presence of two or more minimal trauma fractures AND a bone mineral density (BMD) T-score of -3.0 in postmenopausal women or men with idiopathic or hypogonadic osteoporosis.

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 and their adequate doses, 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 carbonate 1.25g/day; strontium ranelate 2g/day and zoledronic acid 5 mg per annum.

Authority applications must be made in writing and must include: Details of prior anti-resorptive therapy, fracture history and the date, site (femoral neck or lumbar spine) and score of the qualifying BMD measurement.

Authority Required
Continuing treatment for severe established osteoporosis where the patient has previously been issued with an authority prescription for this drug.

Teriparatide must only be used for a lifetime maximum of 18 months therapy (18 pens). A maximum of 18 pens will be reimbursed through the PBS.

Maximum quantity: 1
Number of repeats: 5

GLUCOCORTICOID INDUCED OSTEOPOROSIS

6. Comparator

The submission nominated alendronate as the comparator. The PBAC accepted this as appropriate, adding that risedronate would also be an appropriate comparator for teriparatide in this indication.

7. Clinical Trials

The submission presented one randomised trial (GHBZ) that compares teriparatide (20 mcg/day) with alendronate (10 mg/day) in patients with steroid-induced osteoporosis.

The trial published at the time of the submission is as follows:

Trial ID	Protocol title/ Publication title	Publication citation
Teriparatide vs alendronate		
GHBZ	Teriparatide or alendronate in glucocorticoid-induced osteoporosis	Saag et al (2007) New England Journal of Medicine, Vol 357 p2028–2039

8. Results of Trials

The primary outcome of the GHBZ trial was the change in BMD at the lumbar spine. At the last measurement (at 18 months), patients in the teriparatide group had a significantly greater increase in mean (± standard error [SE]) BMD at the lumbar spine from baseline than patients in the alendronate group (7.2 ± 0.7% vs. 3.4 ±0.7%, p<0.001).

The key secondary outcomes of the GHBZ trial are presented in the following table.

Outcome	Teriparatide (20 mcg/day)	Alendronate (10 mg/day)	RD (95% CI)	RR (95% CI)	p value[a]
Proportion of patients with new radiographic vertebral fractures (paired radiograph population) [n/N (%)]					
-	1/171 (0.6)	10/165 (6.1)	-0.06 (-0.09, -0.02)	0.10 (0.01, 0.75)	0.004
Proportion of patients with new clinical vertebral fractures (ITT population) [n/N (%)]					
Any fracture	0/214 (0.0)	3/214 (1.4)	-0.01 (-0.03, 0.00)	*0.14 (0.01, 2.75)*	0.086
Proportion of patients with new clinical non-vertebral fractures (ITT population) [n/N (%)]					
Any fracture	12/214 (5.6)	8/214 (3.7)	0.02 (-0.02, 0.06)	1.50 (0.63, 3.60)	0.362

Abbreviations: CI, confidence interval; ITT, intention-to-treat; RD, risk difference; RR, relative risk

[a] Percentages compared between treatment groups using a region stratified Cochran Mantel Haenszel test

The GHBZ study indicated that teriparatide was superior to alendronate in terms of BMD and radiographic vertebral fractures. However no statistically significant difference was reported for clinical vertebral and non-vertebral fractures (patient-relevant outcomes).

A comparison of safety outcomes in the GHBZ trial indicated that teriparatide treatment was associated with a significantly higher incidence of pharyngitis, viral infection, nausea, and psychiatric disorders (including insomnia). Alendronate treatment was associated with a significantly higher incidence of sciatica, asthma, rash, and weight loss. There were no significant differences in total adverse events or events leading to discontinuation, hospitalisation or death.

The extended assessment of harm did not identify any additional safety issues for teriparatide.

9. Clinical Claim

The submission describes teriparatide as superior in terms of comparative effectiveness over alendronate and comparable in terms of safety.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a modelled economic evaluation based on the direct comparison of teriparatide and alendronate in the GHBZ trial. The type of economic evaluation presented was a cost-utility analysis.

The results of the sensitivity analyses indicated that the model is most sensitive to: the relative risk of vertebral fractures, the use of 'fracture multipliers', assumptions regarding any extended treatment effect, and the application of disutility values associated with vertebral fractures. The PBAC considered that the evidence to support the assumptions used in the base case analysis was weak and considered that equally plausible scenarios could be generated with substantially higher costs per QALY.

The PBAC noted that the base case ICER per QALY fell in the range $15,000-$45,000. When this was recalculated to set the fracture multiplier at one and to assume only 30 % of vertebral fractures are associated with disutility, the ICER per QALY increased to > $200,000. If only the disutility assumption is altered as described above, the ICER per QALY was $75,000-$105,000. If only the fracture multiplier assumption is altered as described above, the ICER per QALY was $75,000-$105,000.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The likely number of patients was estimated in the submission to be < 10,000 per year in Year 4 (based on both severe established osteoporosis and steroid-induced osteoporosis).

The financial cost/year to the PBS was estimated in the submission to be < $10 million in Year 4. The PBAC considered the estimates presented in the submission to be highly uncertain, and it is likely that the financial impact of teriparatide would exceed $10 million if listed for both indications.

The PBAC considered that the estimation of the eligible population based on the incidence rather than the prevalence of glucocorticosteroid-induced osteoporosis was inappropriate and underestimated usage.

12. Recommendation and Reasons

GLUCOCORTICOID INDUCED OSTEOPOROSIS

The PBAC agreed that alendronate or risedronate were both appropriate comparators for teriparatide in this indication, recognising that under the restriction proposed by the submission alendronate was the therapy most likely to be replaced in practice, but that with the Committee's recent recommendation to list risedronate for glucocorticoid induced osteoporosis, albeit in patients without a prevalent fracture, risedronate may also be an appropriate comparator. The Committee however considered that, overall; the clinical place of teriparatide in the treatment of this condition remains unclear.

The Committee agreed that the evidence from the key trial, GHBZ, supports the claim that teriparatide is superior to alendronate in terms of radiographic vertebral fractures, which PBAC has previously accepted as an appropriate endpoint in these small trials. The Committee also considered that in terms of safety, teriparatide and alendronate appear to have different but comparable safety profiles, but that the long-term safety of teriparatide in steroid induced osteoporosis is unclear.

The Committee noted that the sponsor was requesting a higher price for teriparatide for this indication compared to that requested for the severe population, and furthermore that, as acknowledged by the submission, the baseline risk of fracture in the glucocorticoid treated population targeted by the requested listing is lower than in the population with severe osteoporosis, although uncertainties remain as to how this difference in pre-treatment risk of fracture has been incorporated into the economic model.

The Committee noted that the economic model for this indication uses the same disutility values for fracture as the model for the severe indication, and again applies these disutility values to all fractures irrespective of whether they are symptomatic or asymptomatic. The Committee considered that a more reasonable approach would have been to assume that only a proportion of vertebral fractures are symptomatic. The Committee further noted that changing this assumption so that only 30 % of vertebral fractures are associated with disutility had been shown in a univariate sensitivity analysis to substantially increase the incremental cost-effectiveness ratio (ICER) per Quality Adjusted Life Year (QALY) gained.

The PBAC noted that the base case ICER per QALY is $15,000-$45,000. If this is recalculated to set the fracture multiplier at one and to assume only 30 % of vertebral fractures are associated with disutility, the ICER per QALY increases to >$200,000. If only the disutility assumption is altered as described above, the ICER per QALY is $75,000-$105,000. If only the fracture multiplier assumption is altered as described above, the ICER per QALY is $75,000-$105,000. Thus, the Committee rejected the application for subsidy of teriparatide for glucocorticoid-induced osteoporosis on the basis of a high and uncertain incremental cost effectiveness ratio.

Recommendation
Reject

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 welcomes the PBAC's decision to recommend PBS listing for teriparatide. Eli Lilly will address issues and uncertainties related to the assumptions used in the economic modelling for GIOP and looks forward to the opportunity to address issues related to the "fracture multiplier" and disutilities associated with fracture.