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 2006

1. Purpose of Application

To consider the findings of the Independent Review Report on teriparatide.

2. Background

The sponsor had submitted four submissions to the PBAC requesting PBS listing for teriparatide. The first (June 2003) and second (March 2004) submissions positioned teriparatide after failure of antiresorptive therapy. The third submission (July 2005) requested teriparatide for patients with severe forms of vertebral fractures (SQ3). The fourth submission (March 2006) combined elements of the three prior submissions in requesting a listing for teriparatide in patients who have suffered an SQ3 vertebral fracture despite at least 6 months of antiresorptive treatment. Following the March 2006 rejection by the PBAC, the sponsor sought an independent review, as reported in the Public Summary Document for this decision, which can be found at http://www.health.gov.au/internet/wcms/publishing.nsf/Content/pbac-psd-teriparatide-mar06

3. Registration Status

Teriparatide was approved by the TGA for marketing in Australia on May 22, 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."

4. Listing Requested

The fourth and most recent submission considered by the PBAC at its March 2006 meeting 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 SQ3 vertebral fracture.

A severe vertebral fracture is defined as (at least) 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 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. 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 from the requirement to complete 6 continuous months of therapy with the 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.

5. Matters for Independent Review

The sponsor nominated the following issues on which review was sought:
a) PBAC concern that the indirect data comparison and subgroup analysis does not support the claim of superiority.
b) PBAC claim that the submission provides no evidence to suggest any biological 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.

6. Findings of the Review

a) Indirect comparison and subgroup analysis
There are two key issues involved in this matter: - (1) the dependence on an indirect data comparison across placebo-controlled trials (rather than head-to-head studies) to infer the superiority of teriparatide over an appropriate comparator treatment, and (2) the scientific validity of using the results of a post hoc subgroup analysis in place of the overall Intention-to-Treat (ITT) results for teriparatide in formulating the clinical conclusion. The two issues are fundamental to the robustness of the sponsor's scientific claim. Although the sponsor has undertaken appropriate statistical measures to optimize the validity of the indirect data comparison, this is a scientifically less rigorous process than the gold standard methodology of head-to-head randomized controlled studies. In particular, the validity of adjusted indirect comparisons depends on the internal validity and similarity of the trials involved in the comparison. Some concerns remain regarding the internal validity and generalisability of the pivotal Fracture Prevention Trial (GHAC study) which include an unanticipated premature termination of the study and the significant loss of evaluable subjects due to various reasons. The result derived from post-hoc subgroup analysis of the GHAC trial indicate an unclear and

arguable benefit with teriparatide treatment in patients with more severe forms of vertebral osteoporosis (SQ3) at baseline. The post-hoc subgroup analysis is a major deficiency in the submissions and lacks several measures of scientific rigor including the potential impact of confounding factors. As such, the hypothesis that teriparatide has a superior treatment effect in patients with severe pre-existing vertebral osteoporosis is not adequately supported by the current submissions. This matter should be regarded as a fundamental requirement to the proposed listing.

b) Biological plausibility of difference between teriparatide and comparator

The key issues involved in this matter relate to the biological plausibility of an increased treatment effect with teriparatide compared with antiresorptive therapy (in particular, alendronate) on the basis of mechanism of action, as well as an increasing treatment effect over the spectrum of osteoporosis severity. There is sufficient evidence to support the sponsor claim of biological plausibility based on the anabolic mechanism of action of teriparatide and how such an action may be disproportionately effective in severe osteoporosis where there is significant alteration in the pathophysiology of osteoporosis favouring such a therapeutic action being effective. However, such a theoretical claim is not adequately supported by the current clinical outcome dataset.

c) Continued use of utility values

The validity of the incremental cost effectiveness ratios (cost per QALY) used in the submissions for teriparatide depend crucially on the validity of the QALY (utility) weights used in the cost utility analysis (CUA). The key issue in this matter is the validity of the continued use of the utility weights used in the CUA. This issue is not sufficiently justified in the submissions. The base case ICER (cost per QALY) should be based on the utility valuation of separate health states (symptomatic versus non-symptomatic) and an appropriate transition probability of entering that state. The principal criticism of the utility analysis is an inability to assess whether the sponsor's base case cost per QALY allows for the proportion of symptomatic versus asymptomatic vertebral fractures because of a flaw in the design of the utility survey. It follows that the sensitivity analysis, which does allow for the proportion of symptomatic and asymptomatic fractures and the disutility associated with symptomatic fractures, is plausible. The Assessment of Quality of Life (AQoL) derived utility weights for vertebral fracture health states are not directly comparable to the utility weights associated with a hip facture as these weights are derived using a different utility measurement technique. A contributory factor to the principal criticism of the utility analysis is the lack of explicit guidelines from the PBAC during the submissions for this drug on the steps to identify, measure and value Quality-of-Life (QoL) outcomes for inclusion in a QALY-based cost utility analysis. However, the PBAC appears to be addressing this deficiency with the recent posting of draft guidelines on this issue which are open to consultation. It is paramount that these guidelines are detailed and clear.

SUMMARY OPINION

The deficiencies in the cost utility analysis are amenable to correction with further work and analysis. However, the correction of the utility analysis will not overcome the inherent problems in the primary clinical outcome analysis, which forms the basis for the cost utility analysis. There is insufficient rigor in the clinical trial data analysis to recommend acceptance of the material presented in the submissions. In particular, the validity and robustness of the

post-hoc subgroup analysis is a major deficiency. This results in an interpretation of unclear therapeutic benefit for teriparatide over comparator therapy.

7. Recommendation and Reasons

The PBAC acknowledged the findings of the independent review. The PBAC considered that the review provided no new basis to warrant reconsideration of the PBAC's previous recommendation in March 2006. The PBAC acknowledged the reviewer's comments regarding the new Guidelines and requested they be referred to the Economic Sub-Committee.

8. 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. In cases such as this, where an independent review of the PBAC decision was conducted, the company may still resubmit to PBAC.

9. Sponsor's Comment

While the Independent Review offered some support to Lilly's arguments regarding the biological basis for Forteo's clinical benefits, the PBAC did not consider the Review's findings warranted a change in its previous decisions. Lilly was satisfied that the process of the Independent Review was transparent and appropriate. However in case of severe patient need where the data is limited and open to interpretation, the Independent Review will not always be the most appropriate mechanism to resolve outstanding barriers to listing a much-needed medicine on the PBS. Nonetheless, Lilly strongly believes that adequate information exists to demonstrate Forteo's clinical and cost effectiveness. Lilly has been investigating all options to table before the PBAC to find ways to make this medicine more accessible, including the provision of emerging additional data.