RESPONSE TO THE INDEPENDENT REVIEW
Item 9.1. Teriparatide- FORTEO – Lilly

The sponsor acknowledges the following outcomes of the independent review:

1. Indirect comparison and subgroup analysis

The gold standard for demonstrating superiority is the conduct of a head-to-head randomised controlled trial, however, in the absence of these data the sponsor undertook appropriate statistical measurements to optimize the validity of the indirect comparison. While the design of the GHAC and FIT trials are similar, the validity of the indirect comparison is compromised by the early termination of the GHAC and the subsequent loss to follow-up of patients.

The post-hoc subgroup analysis of the SQ3 patient group is the major deficiency of the submission and as such cannot adequately support the claim of superiority of teriparatide over the comparator in this severe patient group.

Sponsor's response

As stated in the PBAC submissions, there are no clinical trials to exactly match the requested listing. The proposed listing was developed over the course of the submissions in consultation with the scientific and medical community in an effort to make teriparatide available in a cost-effective manner to patients at most need for this therapy. The available clinical data demonstrates that teriparatide is a potent and effective treatment for osteoporosis. However, the cost-effectiveness of this product as a first line treatment cannot be demonstrated at the proposed price. Furthermore, the TGA-approved indication for teripartide stipulates that this product should only be used where other agents are considered unsuitable, that is, alternative should be considered for first-line management of osteoporotic fracture.

Therefore, while the clinical trial was designed for a broader patient group, the sponsor has worked with the clinical community to determine those patients where other agents would be considered unsuitable and where teriparatide would offer the most benefit. The SQ3 fracture group is a small but significant subgroup of patients with osteoporotic fracture. PBAC has previously acknowledged this is a group with a significant clinical need. No clinical trial of any available agent has been conducted specifically in this patient sub-group, all analyses published to date have been post-hoc analyses of existing datasets. These analyses have been conducted by Eli Lilly and Company using both the raloxifene and teriparatide fracture outcomes trials.

The ideal trial for the proposed listing is unlikely to occur for the following reasons:

- The TGA approved indication limiting teriparatide to second-line use is unique to Australia, thus in all other countries where teriparatide is registered this product is available as a first line treatment and this continues to be the case;
- The FDA and other regulatory agents do not require head-to-head comparisons of new bone agents. Therefore, the main objective has been to demonstrate anti-fracture efficacy over "no therapy". Once efficacy was established, head-to-head comparisons have been limited to markers of efficacy – namely bone turnover, BMD etc. These trials have been conducted for teriparatide with and alendronate comparator. The results for BMD are consistent with the results for BMD reported in the GHAC and FIT-VFA trials;
- The clinical trials program for teriparatide has moved into other areas of clinical need including glucocortocoid induced osteoporosis, pain management and fracture healing;

Furthermore, a head-to-head RCT in the SQ3 patient subgroup is technically difficult and has a low probability of being completed in a timely manner at sufficient power. The characteristics of the patient group included under the proposed listing means it would be difficult to recruit required numbers and retain them in study, due to age and increasing co morbidities. The recruitment of patients to fracture endpoint studies is generally slow at best, and in the case of studies involving older age group participants, the disposition from the trial can exceed recruitment. This was the case reported for the study of hip fractures using risedronate. The sponsor is fully supportive of demonstrating the efficacy and safety of a product in head to head clinical trials, however, from a pragmatic and feasibility standpoint, this remains a patient group who are unlikely to be studied in a prospective randomised controlled trial.

2. Biological plausibility of difference between teriparatide and alendronate

The Independent Reviewer has concluded that there is sufficient evidence to support the claim that there is a biologically plausible argument that teriparatide's anabolic mechanism of action could result in a superior therapeutic action in a severe patient subgroup compared with antiresorptive therapies. However, this claim is theoretical and is not adequately supported by the available clinical evidence.

Sponsor's response

Eli Lilly accepts the Independent Reviewer's evaluation of the biological plausibility of the difference between teriparatide and alendronate. This area of research continues to be studied in the scientific literature, mostly in preclinical studies and using surrogate markers. However, for reasons stated above, we are unlikely to be able to confirm this biological hypothesis with a prospective RCt conducted in an SQ3 patient subgroup.

3. Utility values

The principal criticisms of the utility study raised in the PBAC minutes related to the method used to derive the utility weights and the application of these weights in the base case CUA. The Independent Reviewer notes "…the sensitivity analysis, which does allow for the proportion of symptomatic and asymptomatic fractures and the disutility associated with symptomatic fractures, is plausible" (page 6). These sensitivity analyses were described by the reviewer as clinically plausible and reflecting the uncertainty surrounding the method used to derive the utility weights and the final weights themselves. The Independent Reviewer further notes the lack of explicit guidance on the steps required for deriving utilities for CUA analysis.

Sponsor's response

The base case CUA reported in the submission was in the range of $15,000 - $45,000. Under a scenario where the vertebral fracture utilities were adjusted such that 70% of patients have 1/3 the disutility the ICER increases to be in the range of $45,000 - $75,000. In the case where the vertebral fracture utilities are adjusted so that 70% have no disutility (zero disutility if asymptomatic) the ICER increases to be in the range of $75,000 - $105,000. Thus, the ICER is sensitive to the utility values included in the modelled evaluation but our interpretation of the reviewer's comments is that the likely range lies somewhere between $45,000 and $105,000.

In conducting the utility study, we contacted medical specialists treating patients with severe (SQ3 grade) osteoporosis. These practitioners were not asked to determine whether the patients were symptomatic or asymptomatic. The response from specialists has been that these patients with low BMD and multiple fractures would experience symptoms of pain and other functional measures. The clinical trials demonstrated that at least 80% of patients with SQ3 grade fractures report pain associated with the fracture. While pain is a contributory factor to this disutility score, other functions of daily living, physical function, emotional status, and symptoms scores are affected by SQ3 fractures. Furthermore, prospective data collected during most osteoporosis trials have demonstrated that both symptomatic and asymptomatic vertebral fractures are associated with a reduction in QoL.[1] [2]

The sponsor accepts the Independent Reviewer's comments relating to guidance on the measurement of utilities. We have, through various submissions, sought to provide utility values using appropriate methods for deriving utilities and we note the extensive measures that have been taken in the current draft guidelines to address the measurement of utilities. The pivotal trials for both teriparatide and alendronate were conducted during the later half of the 1990's, thus the inclusion of specific measures for derivation of utilities that would be required for a PBAC submission under the draft guidelines are lacking from these trials.

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1 OLEKSIK A, LIPS P, DAWSON A, MINSHALL ME, SHEN W, COOPER C, KANIS J. Health-Related Quality of Life in Postmenopausal Women With Low BMD With or Without Prevalent Vertebral Fractures J Bone Miner Res 2000;15:1384–1392)

2 Oglesby AK. Minshall ME. Shen W. Xie S. Silverman SL. The impact of incident vertebral and non-vertebral fragility fractures on health-related quality of life in established postmenopausal osteoporosis: results from the teriparatide randomized, placebo-controlled trial in postmenopausal women. *Journal of Rheumatology. 30(7):1579-83, 2003 Jul.*

Concluding remarks

Eli Lilly Australia accepts the outcomes of the Independent Review and was aware of the limitations of a sub-group analysis and indirect comparison when the re-submission was lodged and at the time of the request for the independent review. We believe that the approach taken in the submission was valid given the requested positioning for listing and the limitations of the clinical data available. We are encouraged by the confirmation of the claims relating to the biological plausibility of teriparatide superiority, but accept the limitations of the data to support this claim. We concur with the comments made in relation to the utilities and the lack of explicit guidance for measurement of utilities in the PBAC guidelines and advice.

We respectfully request, however, that in considering the outcomes of this independent review on the listing of teriparatide on the PBS, the PBAC provide some guidance on the positioning of products on the PBS for the following areas:

- where the TGA approved indication is not consistent with the clinical data package;
- for high-risk patient sub-groups unlikely to be studied under prospective RCT conditions;
- where clinical practice has advanced since the conduct of the pivotal trial.

We will continue to assess any other options that may lead to subsidised availability of teriparatide in Australia. Should any options appear to have sufficient merit these will be provided in the pre-PBAC response due on October 25th.