PUBLIC SUMMARY DOCUMENT
Product: Exenatide, pre-filled injection pen, 5 microgram per dose, 10 microgram per dose, 60 doses, Byetta®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: March 2008

1. Purpose of Application

To seek an Authority Required listing as adjunctive therapy in patients with type 2 diabetes no longer achieving glycaemic control despite optimal therapy with metformin and/or a sulfonylurea.

2. Background

Exenatide was first considered by the PBAC at its July 2007 meeting. The PBAC rejected the submission on the grounds of high and uncertain cost-effectiveness against the comparators in the absence of any evidence of incremental clinical benefit other than the observational finding of weight loss, which has not been shown to be durable or to translate into morbidity or mortality benefits, and because of unresolved safety concerns.

3. Registration Status

Exenatide was TGA registered on 28 June 2007 for adjunctive therapy to improve glycaemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.

4. Listing Requested and PBAC's View

Authority required

Combination therapy with metformin and a sulfonylurea

Initiation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients who have an HbA1c greater than 7% despite maximally tolerated doses of metformin and a sulfonylurea.

The date of the HbA1c measurement, which must be no greater than 4 months old at the time of application, must be provided.

Continuation of therapy, in combination with metformin and a sulfonylurea, in type 2 diabetes mellitus patients where the patient has previously been issued with an authority prescription for exenatide.

Authority required

Combination therapy with metformin or a sulfonylurea

Initiation of therapy, in combination with either metformin or a sulfonylurea, in type 2 diabetes mellitus patients who have an HbA1c greater than 7% and in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date of the HbA1c measurement, which must be no greater than 4 months old at the time of application, must be provided.

Continuation of therapy, in combination with either metformin or a sulfonylurea, in type 2 diabetes mellitus patients where the patient has previously been issued with an authority prescription for exenatide.

5. Clinical Place for the Proposed Therapy

Exenatide provides an alternative class of drug for adjunctive therapy in adults with type 2 diabetes who are taking metformin or a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control.

6. Comparator

The re-submission nominated insulin glargine as the main comparator, with rosiglitazone and insulin aspart as secondary comparators. The PBAC accepted this as appropriate.

7. Clinical Trials

The re-submission presented two direct randomised trials comparing exenatide with insulin glargine (GWAA and GWAO) and four supplementary randomised trials (3 placebo controlled trials: 112, 113 and 115; and 1 trial versus insulin aspart: GWAD). Four randomised trials of rosiglitazone (3 compared with placebo: Fonesca et al 2000, Rosenstock et al 2006 and Daily et al 2004; and one compared with insulin glargine: Rosenstock et al 2006b) were included to enable an indirect comparison.

The table below lists the trials as published at the time of submission.

Trial ID/First author	Publication title	Publication citation
Randomised trials comparing exenatide with placebo		
112 DeFronzo RA	Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes.	*Diabetes Care* 2005; 28:1092-1100.
113 Buse JB	Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes.	*Diabetes Care* 2004 ; 27 :2628-2653.
115 Kendall DM, et al.	Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea.	*Diabetes Care* 2005; 28:1083-1091.
Randomised trials comparing exenatide with insulin glargine		
GWAA Heine RJ	Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial.	*Annals of Internal Medicine* 2005; 143:559-569.
Randomised trials comparing exenatide with insulin aspart		
GWAD Nauck MA	A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study.	*Diabetologia* 2007; 50:259-267.
Randomised trials comparing rosiglitazone with placebo		
Fonseca V	Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial.	*JAMA* 2000; 283:1695-1702.Erratum *JAMA* 2000; 284:1384.
Rosenstock J	Effect of early addition of rosiglitazone to sulfonylurea in older type 2 diabetes mellitus patients (>60 years): the Rosiglitazone Early vs Sulfonylurea Titration (RESULT) study.	*Diabetes, Obesity and Metabolism* 2006; 8:49-57.
Dailey GE	Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial.	*American Journal of Medicine* 2004; 116:223-229.
Randomised trials comparing rosiglitazone with insulin glargine		

Trial ID/First author	Publication title	Publication citation
Rosenstock J	Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naive patients.	*Diabetes Care* 2006; 29:554-559.

8. Results of Trials

Exenatide versus insulin glargine:

The key results from trials GWAO and GWAA showed no statistically significant difference between exenatide and insulin glargine for the HbA1c outcomes with a mean change from baseline and proportion of patients achieving HbA1c ≤7%. Exenatide treatment was associated with a statistically significant reduction in weight; insulin glargine was associated with a statistically significant increase in weight; and the difference between treatments was statistically significant in both the GWAO and GWAA trials, favouring exenatide.

There were no statistically significant differences between exenatide and insulin glargine on any of the quality of life instruments. Quality of life was assessed in the insulin-comparator controlled studies, using the following scales:

- Impact on diabetes symptoms: Diabetes Symptom Checklist Revised (DSC-R)
- Treatment satisfaction: Diabetes Treatment Satisfaction Questionnaire status version (DTSQs – GWAA only)
- Impact on treatment flexibility: Diabetes Treatment Flexibility Scale (DTFS - GWAA and GWAD)
- Impact on psychological well-being: Psychological and Well Being Index (PGWB – GWAO only)
- Health-related quality of life: vitality subscale of SF-36, EQ-5D (index score only – GWAA, index + VAS score – GWAD)
- Fear of hypoglycaemic: Hypoglycaemic Fear Survey (GWAO only)
- Treatment evaluation assessment (GWAO only).

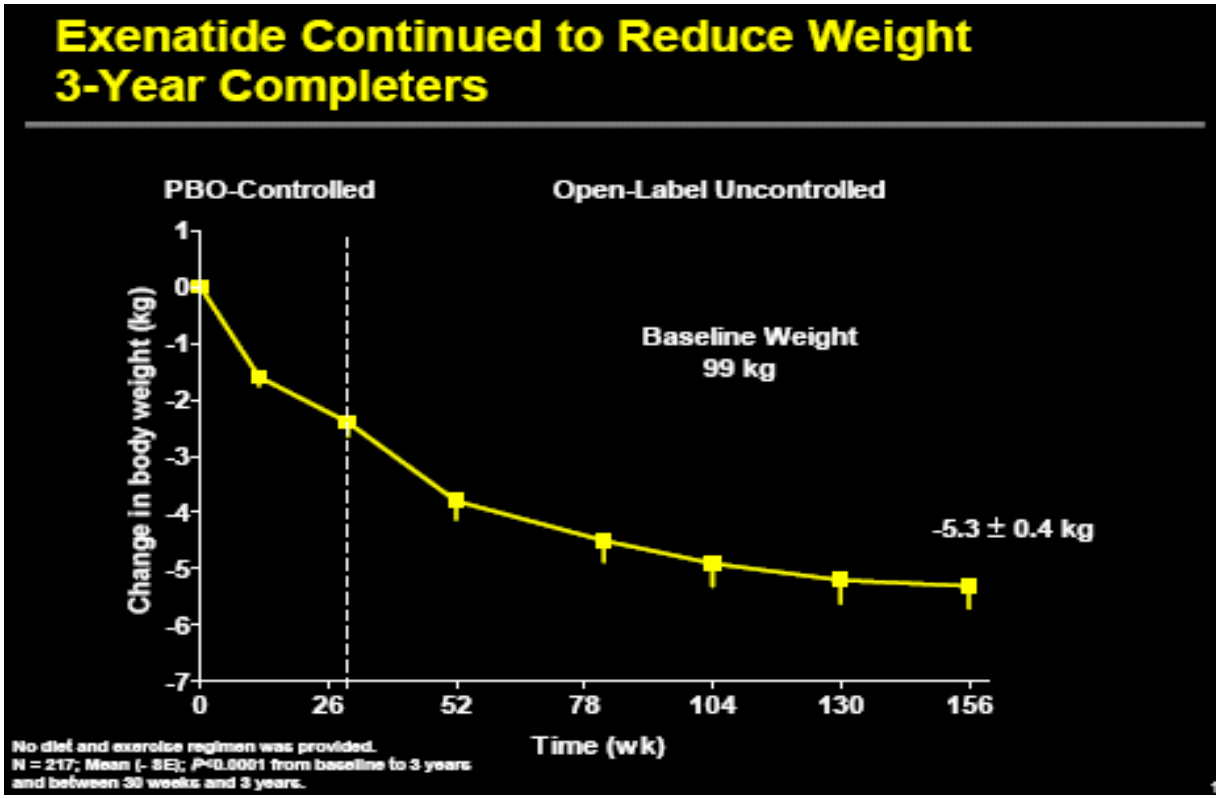
There were higher rates of treatment-emergent adverse events and discontinuations due to adverse events associated with exenatide treatment compared with insulin glargine in the GWAO and GWAA trials. Insulin glargine was associated with higher rates of hypoglycaemia. Exenatide was associated with higher rates of nausea.

Exenatide versus rosiglitazone:

The re-submission claimed that insufficient data are available in the published rosiglitazone trials to enable an indirect comparison of exenatide and rosiglitazone for the outcome mean change from baseline in HbA1c. The results of the indirect comparison for the proportion of patients achieving an HbA1c ≤7% indicated no difference between exenatide and rosiglitazone; and the analysis of mean change from baseline in weight, favoured exenatide.

The figure below shows how the body weight of the completers vary over the course of three years. The PBAC considered the 3-year follow-up data was informative. However, it was not comparative, open-label and may be confounded given it was based on completers only (patients who dropped out were not included). Uncertainty remained over whether the results observed at 3 years are sustained over 35 years, which is the time horizon of the model.

Change in body weight of completers from the placebo-controlled trial 112, 113 and 115



No indirect estimates of the relative safety of exenatide and rosiglitazone were presented. The PBAC was advised longer-term safety, especially in relation to cardiovascular complications, remains uncertain with thiazolidinediones and longer term data with exenatide in this regard would be useful.

9. Clinical Claim

The claim in the re-submission is summarised as follows:

Outcome	Main comparator	Supportive comparators	
	Insulin glargine	Insulin aspart	Rosiglitazone
Clinical effectiveness - Glycaemic control - Weight management	Superior Non-inferior Superior	Superior Non-inferior Superior	Superior Non-inferior Superior
Safety	Equivalent	Superior	Equivalent
Overall conclusion	Superior	Superior	Superior

The PBAC had previously accepted that exenatide is non-inferior to insulin glargine in terms of its effects on HbA1c. However, the PBAC had concerns about whether the previous submission adequately demonstrated that exenatide is non-inferior to rosiglitazone in terms of its effect on HbA1c. The re-submission provided no additional data to support a claim of non-inferiority to rosiglitazone. There were also residual concerns regarding the exclusion of a number of potentially relevant rosiglitazone trials.

In terms of weight changes, the exenatide versus insulin glargine trials showed a statistically significant difference, favouring exenatide. For the comparison with rosiglitazone, no new

data were presented in the re-submission and the PBAC did not accept the claim of greater weight loss in the previous submission. With respect to the previous submission, the PBAC had stated that any weight loss benefit has not been shown to be durable in the longer term.

The PBAC considered that in this re-submission there was no basis for it to change its view that the weight loss benefit associated with exenatide had not been shown to be durable in the longer term.

The Committee further noted that no new data had been provided to alter its previous conclusion that exenatide was associated with a higher incidence of adverse events versus insulin glargine. A difference in hypoglycaemic events between exenatide and insulin glargine was also not convincingly demonstrated. Again, no indirect estimates of the comparative safety of exenatide and rosiglitazone were presented to allow assessment of the comparative safety of exenatide and rosiglitazone.

10. Economic Analysis

A stepped economic evaluation was presented. It included a modelled economic evaluation over a time horizon of one year in addition to an updated modelled evaluation over a time horizon of 35 years.

The inputs of the model were unchanged from the previous submission, in that numerical differences between exenatide and insulin glargine were modelled in the absence of statistically significant differences.

The PBAC noted that the modelled evaluation was driven by the valuation of the weight loss effect of exenatide: changes in body mass index (BMI) which were transformed into changes in utility values.

Results of the short-term economic evaluation produced an incremental cost per extra Quality-Adjusted Life Years (QALY) gained in the range of $15,000 to $45,000. Results of the long-term economic evaluation produced an incremental cost per extra QALY gained in the range of $15,000 to $45,000 in the base case.

The PBAC considered the results of the modelled evaluation to be uncertain.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be between 10,000 and 50,000 in Year 5. The estimated net cost per year to the PBS was in the range of $10-30 million in Year 5.

The re-submission proposed a risk sharing arrangement, in addition to the proposed Authority Required eligibility criteria.

The submission stated that this proposal was intended to reduce the uncertainty in the ICERs in relation to the valuation of the weight reduction associated with exenatide.

12. Recommendation and Reasons

The PBAC agreed that the re-submission's nomination of insulin glargine as the main comparator was appropriate, noting that in clinical practice it is common to exhaust all oral

alternatives before moving onto an injectable alternative and therefore that insulin glargine is the treatment most likely to be replaced in clinical practice. The Committee further agreed that the inclusion of rosiglitazone in a sensitivity analysis in the modelled economic evaluation was reasonable.

The PBAC noted it has previously accepted that exenatide is non-inferior to insulin glargine in terms of its effects on HbA1c. However, the re-submission provided no additional data to address PBAC's previous concern that the claim of non-inferiority to rosiglitazone was inadequately demonstrated.

In terms of weight changes, the Committee agreed that the exenatide versus insulin glargine trials showed a statistically significant difference, favouring exenatide. However, as before the weight loss benefit associated with exenatide had not been verified in a properly designed weight loss or quality of life study. Although the 3 year follow-up data on body weight from studies 112, 113 and 115 was informative, it was open-label and non-comparative and may be confounded as it is based on completers only (patients who dropped out were not included). The increased nausea observed with exenatide may contribute to some patients with weight loss shown in the trials. It was also noted that the pre-PBAC response agrees that "open label data presented beyond the controlled period should be treated with caution" and notes that there are longer term prospective trials that will provide comparative data. The PBAC thus considered there was no basis for it to change its view that the weight loss benefit associated with exenatide has not been shown to be durable in the longer term.

The Committee further noted that no new data had been provided to alter its previous conclusion that exenatide was associated with a higher incidence of adverse events versus insulin glargine. A difference in hypoglycaemic events between exenatide and insulin glargine was also not convincingly demonstrated. Again, no indirect estimates of the comparative safety of exenatide and rosiglitazone are presented to allow assessment of the comparative safety of exenatide and rosiglitazone.

The uncertainties around the clinical benefit of exenatide compared to insulin glargine (eg whether the weight loss is sustained) result in uncertainty in the outputs of the economic model.

Additionally, the lactic acidosis sub-model "work around" which is used to handle changes in body weight, BMI and the associated utilities in the economic model is still associated with an unacceptable lack of clarity, although the Committee acknowledged the pre-subcommittee and pre-PBAC response attempts to provide more detail on this "work-around". This is illustrated by the implausibly large difference in the estimated incremental cost effectiveness ratio (ICER) per life year gained compared with the estimated ICER per quality adjusted life year in a model where weight change is the primary variable driving the outcome.

The PBAC agreed that overall the data show that weight loss is of value to patients. However, uncertainty remains as to the size of the benefit; whether the weight loss is of value in itself or because of impacts on other health outcomes (and what is captured in the modelling); and whether the weight loss is sustained and how the weight loss is modelled.

The PBAC did not accept that the uncertainties described above could be managed by the sponsor's proposed risk-share arrangement. The Committee considered a more acceptable

approach would be for the sponsor to seek listing on a cost-minimisation basis against insulin glargine, taking into account potential differences in the adverse event profiles of the two drugs, and that an insulin glargine dose of 75 IU per day may be able to be justified in the context of such a request. Price increase requests could then be made as the data from the new trials become available for review.

Therefore, as previously the Committee rejected the current application on the grounds of a high and uncertain cost-effectiveness ratio against the comparator, insulin glargine, in the absence of evidence of clinical benefit other than the observational finding of weight loss.

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 will make a further submission to the PBAC, keeping in mind the recommendations for an alternative approach. In regard to the question of the 3 year completers data, the sponsor acknowledges the limitations of such data but argues that for those patients who do tolerate and respond to exenatide, this demonstrates sustained glycaemic control and weight loss. Such patients will have avoided insulin for at least 3 years and the associated weight gain and, if at high doses of insulin, the associated hypoglycaemic episodes. The sponsor also notes that although more treatment-emergent adverse events were reported for exenatide than for insulin glargine in the head to head trials, the actual discontinuation rate for exenatide remained low.