

PUBLIC SUMMARY DOCUMENT

Product: Exenatide, pre-filled injection pen, 5 micrograms per dose, 10 micrograms per dose, Byetta[®],

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: November 2008

1. Purpose of Application

The submission sought an Authority Required listing for use in combination with metformin and/or a sulfonylurea, in patients with type 2 diabetes who no longer achieve glycaemic control despite optimal therapy with metformin and/or a sulfonylurea, or in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

2. Background

The PBAC has considered exenatide on two previous occasions for the indication mentioned above. On the first occasion in July 2007, the PBAC rejected the submission on the grounds of high and uncertain cost-effectiveness against the comparators in the absence of any evidence of clinical benefit other than the observational finding of weight loss which had not been shown to be durable or to translate into morbidity or mortality benefits, and because of unresolved safety concerns. (See also Public Summary Document for July 2007).

At its March 2008 meeting, the PBAC noted that the re-submission provided no additional data to address its 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. 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 at its March 2008 meeting 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. Therefore, like the July 2007 application, the Committee rejected the March 2008 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. (See also Public Summary Document for March 2008).

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.

The PBAC agreed with the Secretariat's suggestion that the restriction wording be consistent with the Restrictions Working Group's (RWG) advice arising from the March 2008 meeting but updated to account for the listing of sitagliptin.

5. Clinical Place for the Proposed Therapy

The submission stated that exenatide provides clinicians with an alternative class of drug for adjunctive third line therapy in adults with type 2 diabetes who are taking metformin, a sulfonylurea, or a combination of metformin and a sulfonylurea but are not achieving adequate glycaemic control, or in whom the addition of metformin or a sulfonylurea is contra-indicated or not tolerated when used in combination.

6. Comparator

The submission nominated insulin glargine as the main comparator. This was considered reasonable. The PBAC noted that the dose of insulin glargine (75 IU/day) selected in the cost-minimisation analysis was the single biggest source of uncertainty within the submission.

7. Clinical Trials

No new trials were presented in the current re-submission. The re-submission presented a direct comparison in one RCT (GWAA) and one randomised cross-over trial (GWAO). Three placebo-controlled randomised trials (112, 113 and 115) and one RCT (GWAD) comparing exenatide with insulin aspart are included as supportive evidence.

At the time of the submission the published studies were:

Trial ID/First author	Protocol title/ Publication title	Publication citation
Direct randomised trials (exenatide versus insulin glargine)		
GWAA Heine RJ	Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial.	Heine RJ. Ann Intern Med 2005; 143:559-569.
GWAO Barnett AH	Tolerability and efficacy of exenatide and titrated insulin glargine in adult patients with type 2 diabetes previously uncontrolled with metformin or a sulfonylurea: A multinational, randomized, open-label, two-period, crossover noninferiority trial.	Barnett AH. Clin Ther 2007; 29(11):2333-2348.
Supplementary randomised trials (exenatide versus 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.	DeFronzo RA. 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.	Buse JB. Diabetes Care 2004 ; 27 :2628-2653.
115 Kendall DM	Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea.	Kendall DM. Diabetes Care 2005; 28:1083-1091.
Supplementary randomised trials (exenatide versus 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.	Nauck MA. Diabetologia 2007; 50:259-267.

8. Results of Trials

No new efficacy data were presented in the current re-submission. The PBAC has previously accepted that exenatide is non-inferior to insulin glargine in terms of its effects on HbA_{1c} and concluded that neither the long-term benefits associated with weight change nor its durability are adequately established.

No new toxicity data was presented except the results of re-analysis of hypoglycaemia event rates and a summary of Periodic Safety Update Report (PSUR06). The PBAC has previously concluded that exenatide was associated with a higher incidence of adverse events versus insulin glargine and that a difference in hypoglycaemic events between exenatide and insulin glargine was not convincingly demonstrated. Based on the new supporting data presented in the current re-submission, exenatide appeared to be associated with statistically significant reductions in rates of overall and nocturnal hypoglycaemic episodes compared to insulin glargine. However, the PBAC noted that:

- Conclusions were based on rates of hypoglycaemic events, not patients with hypoglycaemic events;
- It was unclear that the claimed statistically significant differences represented clinically important differences given the low event rates;
- There were insufficient data to conclude differences between use of exenatide in dual and triple therapy regimens, or differences between concomitant use of metformin or a sulfonylurea.

9. Clinical Claim

The re-submission described exenatide as superior in terms of comparative effectiveness (equivalent glycaemic control but superior in weight management) and equivalent in terms of comparative safety over insulin glargine. The PBAC had previously accepted the non-inferiority of exenatide in glycaemic control. As no new evidence regarding the long-term durability of weight benefits and transformability of weight benefits into long-term morbidity and mortality benefits were presented in the re-submission, the claim of superiority of exenatide in weight management was not established. The PBAC had previously concluded that exenatide was associated with higher incidences of adverse events.

Claims of statistically significant benefits of exenatide over insulin glargine in overall rates and rates of nocturnal hypoglycaemia were new to this submission and were based on numbers of events, not numbers of patients with events. The clinical importance of these differences between exenatide and insulin glargine was unclear.

10. Economic Analysis

In contrast to a modelled economic evaluation considered at the March 2008 PBAC meeting, the current re-submission presented a cost-minimisation analysis (CMA). It was noted that the cost-minimisation analysis presented was not trial-based.

The dosage of drugs used for comparison in the CMA is: exenatide 20 micrograms/day compared with insulin glargine 75 IU/day. Based on an analysis¹ of a random sample of glargine scripts processed by Medicare Australia from October 2006 to September 2007, the re-submission considered it “reasonable to assume that the average dose per day of insulin glargine dispensed through the PBS is between 60IUs and 100IUs per day” and therefore it was reasonable to use a daily glargine dose of 75 IU in CMA. This is much higher than the mean final glargine dose in the head-to-head randomised trials used in the re-submission to establish non-inferiority.

Based on results from the GWAA trial, i.e. when used in triple combination with metformin and a sulfonylurea, the equi-effective doses are estimated as exenatide 9.07 µg twice daily and insulin glargine 24.93 IU/day over 26 weeks. Based on results from the GWAO trial, i.e. when used in dual combination with either metformin or a sulfonylurea, the equi-effective doses are estimated as exenatide 9.35 µg twice daily and insulin glargine 27.30 IU/day over 16 weeks. These estimated equi-effective doses may change as trial results of GWBG become available. Trial GWBG is a phase 3 trial designed to compare the effects of twice daily exenatide plus oral antidiabetic agents (OADs) and once-daily insulin glargine plus OADs with respect to glycaemic control, as measured by hemoglobin A1c, with minimum weight gain, in patients with uncontrolled type 2 diabetes on OADs.

11. Estimated PBS Usage and Financial Implications

The likely number of treated patients per year was estimated to be between 10,000 – 50,000 per year, while the financial cost per year to the PBS (excluding savings on patient co-payments) minus savings in use of insulin glargine and insulin aspart was estimated to be < \$10 million in Year 5.

12. Recommendation and Reasons

¹ Mean average daily dose (ADD) = 101.2 IU for 1,330 patients; ADD = 67.8 IU after 5% of top outliers are removed from the sample.

The PBAC recommended the listing of exenatide on the Pharmaceutical Benefits Scheme on a cost-minimisation basis with insulin glargine taking into account the higher costs associated with the initiation and titration of the dose of insulin glargine. The equi-effective doses were exenatide 9.07 micrograms twice daily and insulin glargine 24.93 international units (IU) per day when these agents were used in triple combination therapy with metformin and a sulfonylurea; and 9.35 exenatide micrograms twice daily and insulin glargine 27.30 IU per day when these agents were used as part of dual combination therapy with either metformin or a sulfonylurea.

The Committee agreed that the clinical trials GWAA and GWAO provided the best available evidence upon which to calculate the equi-effective doses of exenatide and insulin glargine, as these two randomised trials formed the basis for the PBAC's earlier acceptance of the non-inferiority of exenatide compared to insulin glargine in terms of its effects of HbA1c, and as in both trials the dose of insulin glargine could be titrated according to response. The PBAC did not accept the sponsor's claim that it was not valid to calculate equi-effective doses based on these two trials, noting that no substantive arguments invalidating the trial results were made in either the submission or the hearing.

The submission's choice of insulin glargine dose of 75 IU/day to establish equi-effective doses was in contrast not derived from clinical trials and was much higher than the mean final glargine dose (less than 30 IU/day) in the direct randomised trials. Although the PBAC had indicated in March 2008 that a daily dose of 75 IU insulin might be able to be justified, it did not accept that the current submission provided adequate justification for accepting a dose based on a random sample of Medicare Australia prescriptions, which is subject to well known confounders, over the consistent results generated in two rigorous, randomised trials.

The Committee also considered that, as previously, the long term benefits and durability of weight change with exenatide have not been adequately established. PBAC also did not accept the submission's claim that exenatide was equivalent in terms of comparative safety over insulin glargine. The difference in overall hypoglycaemic event rates in study GWAA, although statistically significant in favour of exenatide over insulin glargine were considered clinically immaterial and unlikely to be discernible in practice. On the other hand, treatment with exenatide was associated with more treatment emergent adverse events than insulin glargine. Overall, however, the Committee's safety concerns with exenatide were not sufficient to overturn its cost-minimisation recommendation.

The Committee did not accept the validity of all the claimed cost-offsets for exenatide compared to insulin glargine. Specifically the PBAC considered it only reasonable to offset, on a single occasion, the cost of one diabetes nurse educator visit during treatment initiation as patients would still require training in how to administer exenatide, and of the higher costs associated with treatment titration for glargine. The Committee did not accept that there would be any difference in monitoring costs.

Recommendation

EXENATIDE, injection, 5 micrograms in 20 microlitres, 10 micrograms in 40 microlitres, Byetta[®], Eli Lilly Pty Ltd. (7.2)

Restriction:

Authority Required

Dual combination therapy with metformin or a sulfonylurea

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

NOTE: Exenatide is not PBS-subsidised as monotherapy or in combination with an insulin, a thiazolidinedione (glitazone), or sitagliptin.

Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances:

(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies

and/or

(b) red cell transfusion within the previous 3 months.

Patients in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The date of measurement of the most recent blood glucose level, which must be no greater than 4 months old at the time of application, must be provided.

Authority Required

Triple combination therapy with metformin and a sulfonylurea

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

NOTE: Exenatide is not PBS-subsidised as monotherapy or in combination with an insulin, a thiazolidinedione (glitazone) or sitagliptin.

Blood glucose monitoring as an alternative assessment to HbA1c levels will be accepted in the following circumstances:

(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies

and/or

(b) red cell transfusion within the previous 3 months.

Patients in these circumstances will be eligible for treatment where blood glucose monitoring

over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The date of measurement of the most recent blood glucose level, which must be no greater than 4 months old at the time of application, must be provided.

Maximum quantity: 1

Number of repeats: 5

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 positive recommendation from the PBAC to recommend listing of exenatide on the PBS. Eli Lilly is disappointed that the Committee did not accept the Medicare Australia data used in the submission to determine the insulin glargine dose to establish equi-effective doses. The costs, resources implications, outcomes and increased reporting of adverse events associated with higher dosages of insulin used in the cost minimisation analysis, were supported by observational studies and database analyses but were not considered valid in the current submission.