

PUBLIC SUMMARY DOCUMENT

Product: EXENATIDE, injection, 5 microgram per dose, 10 microgram per dose, pre-filled pen, 60 doses, Byetta[®]

Sponsor: Eli Lilly Australia Pty Ltd

Date of PBAC Consideration: July 2007

1. Purpose of Application

The submission sought 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

This drug had not previously been considered by the PBAC.

3. Registration Status

Exenatide was registered by the TGA on 28 June 2007 as an 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

Triple oral 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

Dual oral 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 rosiglitazone maleate or pioglitazone hydrochloride.

NOTE:

Exenatide is not PBS-subsidised as monotherapy or in combination with insulins or a thiazolidinedione.

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.

See Recommendation and Reasons for PBAC's view

5. Clinical Place for the Proposed Therapy

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.

6. Comparator

The submission nominated rosiglitazone as the comparator in its primary analysis and insulin glargine as the comparator in a secondary analysis.

The PBAC agreed that rosiglitazone and insulin glargine were both appropriate comparators.

7. Clinical Trials

The submission presented two analyses of the clinical trial data:

- Primary analysis: The relative clinical efficacy of exenatide and rosiglitazone was evaluated by an indirect comparison of 8 randomised trials using either placebo (6 trials) or insulin glargine (2 trials) as common comparator.
- Secondary analysis: The relative clinical efficacy of exenatide and insulin glargine was evaluated by a single randomised cross-over trial (GWAO). The results of a second comparative study of exenatide and insulin glargine (GWAA) were used in the economic evaluation. However, the submission did not use Study GWAA in a comparison of clinical effectiveness of exenatide and insulin glargine.

The trials forming the basis of the submission and which have been published are tabulated below. Only studies used in the indirect comparison have been published.

Trial ID/First author	Protocol title/ Publication title	Publication citation
Exenatide versus placebo		
T112/ DeFronzo RA et al (2005)	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(5): 1092-1100.
T113/ Buse JB et al (2004)	Exenatide-113 C. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes.	Diabetes Care (2004) 28(5): 1092-1100.
T115/ Kendall DM et al (2005)	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 (5): 1083-1091
Exenatide versus insulin glargine		
GWAA/ Heine RJ et al (2005)	GWAA S. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial.	Annals of Internal Medicine 2005; 143 (8): 559-569.
Rosiglitazone versus placebo in addition to metformin therapy		
49653/094 or Fonseca et al (2000)	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 (11):1384
Rosiglitazone versus placebo in addition to sulfonylurea therapy		
49653/135 or Rosenstock J et al (2006a)	For the RESULT Study Group. 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
Rosiglitazone versus placebo in addition to metformin & sulfonylurea therapy		
Dailey GE et al (2004)	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
Rosiglitazone versus insulin glargine		
Rosenstock J et al (2006b)	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 (3):554-559

8. Results of Trials

Exenatide versus rosiglitazone (primary analysis):

The indirect comparisons presented by the submission are summarised in the table below.

Summary of indirect comparisons presented by the submission for the primary analysis of exenatide versus rosiglitazone

Measures of efficacy	Combination therapy	Trials compared in indirect comparison	Difference in treatment effect (Exenatide – Rosiglitazone) (95% CI)	
			Bucher method	Bayesian method
Change in HbA _{1c} (%)	MET	-	Not performed	Not performed
	SU	-	Not performed	Not performed
	MET & SU	-	Not performed	Not performed
Proportion achieving target HbA _{1c} ≤7% (%)	MET	-	Not performed	Not performed
	SU	-	Not performed	Not performed
	MET & SU	-	Not performed	Not performed
Change in body weight (kg)	MET	-	Not performed	Not performed
	SU	-	Not performed	Not performed
	MET & SU	115 vs Dailey	-2.15 (-2.49 to -1.81)*	-3.77 (-4.79 to -2.76)
		GWAA vs Rosenstock b	-3.47 (-3.99 to -2.96)	-5.32 (-6.36 to -4.31)
		Pooled	-2.15 (-2.49 to -1.81)*	-4.45 (-5.32 to -3.65)
Change in fasting total cholesterol (mg/dL)	MET	112 vs Fonseca	-25.9 (-36.0 to -15.8)	Not performed
	SU	-	Not performed	Not performed
	MET & SU	115 vs Dailey	-17.8 (-26.8 to -8.8)	Not performed
			Pooled	-21.6 (-28.2 to -14.9)
Change in fasting LDL (mg/dL)	MET	112 vs Fonseca	-13.6 (-22.4 to -4.8)	Not performed
	SU	-	Not performed	Not performed
	MET & SU	115 vs Dailey	-10.7 (-18.0 to -3.4)	Not performed
			Pooled	-11.6 (-17.0 to -6.2)
Change in fasting HDL (mg/dL)	MET	112 vs Fonseca	-4.5 (-7.0 to -2.0)	Not performed
	SU	-	Not performed	Not performed
	MET & SU	115 vs Dailey	-3.8 (-5.8 to -1.8)	Not performed
			Pooled	-3.6 (-5.1 to -2.1)
Change in triglycerides (mg/dL)	MET	-	Not performed	Not performed
	SU	-	Not performed	Not performed
	MET & SU	-	Not performed	Not performed

HbA_{1c}=glycosylated haemoglobin; HDL=high-density lipoprotein; MET=metformin; LDL=low-density lipoprotein; SU=sulfonylurea; vs=versus

* These are the results reported in submission but were considered flawed.

The evaluation noted that for Dailey (2004) only the mean change in body weight for the treatment groups was reported in the publication but not the standard error or 95% confidence intervals. To compute the standard error for the between-group difference in treatment effect, the standard errors for the treatment effect of the comparing groups are required. For the standard error for the treatment effect of placebo group, the submission used “the standard error from the comparable placebo arm of trial 115 (SE 0.17)”. For the standard error for the treatment effect of rosiglitazone, the submission used the standard error from the comparable

rosiglitazone arm of Rosenstock 2006b (SE 0.4)”. The validity of indirect comparison results is therefore also dependent on the assumptions that (i) the placebo arm of trial 115 was comparable with Dailey 2004 and (ii) the rosiglitazone arm in Dailey (2004) was comparable to the rosiglitazone arm in Rosenstock (2006b). The placebo groups for Study 115 and Dailey (2004) appeared to be fairly comparable except the placebo group in Study 115 had slightly higher mean BMI (33.8 versus 32 kg/m²), longer history of diabetes (9.4 versus 9 years) and higher mean HbA_{1c} value (8.5 versus 8.1%) at baseline. The rosiglitazone groups for Dailey (2004) and Rosenstock (2006b) appeared to be fairly comparable except the rosiglitazone group in Dailey (2004) had longer history of diabetes (9 versus 8.1 years) and lower mean HbA_{1c} value (8.1 versus 8.7%) at baseline.

The table below shows the proportion of subjects achieving target HbA_{1c} of ≤7% at the end of study. For the three placebo-controlled exenatide studies, the proportion of subjects achieving target HbA_{1c} of ≤7% was statistically significantly greater in both exenatide treatment arms of 5 µg and 10 µg than in placebo. For the GWAA study which compared exenatide with insulin glargine, the between-group difference was not statistically significant. The submission reported that only one rosiglitazone study (Dailey 2004) reported sufficient data to allow the proportion of subjects achieving HbA_{1c} levels ≤7% to be calculated using the full ITT population. In this particular study, the proportion of subjects achieving target HbA_{1c} of ≤7% was statistically significantly greater in rosiglitazone group than in placebo group. The submission did not provide a formal indirect comparison of this outcome.

Although the details of concomitant use with statins were provided for exenatide, such details are not available from the rosiglitazone trials; it is therefore unknown whether the use of concomitant medication was different between the two drugs and this may have affected the therapeutic outcome observed in the trials. The economic model assumes the same proportion of statin use in both treatment arms.

Proportion of subjects achieving target HbA1c levels of ≤ 7% at end of study

	Trial analysis				Report analysis: full ITT population			
	n/N	%	RR (95% CI)	P	n/N	%	RR (95% CI)	P
112								
Placebo	10/77	13	-	-	10/113	8.8	-	-
Exenatide 5 µg	25/79	31.6	2.4 (1.3, 4.7)	0.008	25/110	22.7	2.6 (1.3, 5.1)	0.007
Exenatide 10 µg	39/84	46.4	3.6 (1.9, 6.7)	<0.0001	39/113	34.5	3.9 (2.1, 7.4)	<0.0001
113 ²								
Placebo	6/68	8.8	-	-	6/123	4.9	-	-
Exenatide 5 µg	28/86	32.6	3.7 (1.6, 8.4)	0.002	28/125	22.4	4.6 (2.0, 10.7)	0.0004
Exenatide 10 µg	33/80	41.3	4.7 (2.1, 10.5)	0.0002	33/129	25.6	5.2 (2.3, 12.1)	<0.0001
115 ²								
Placebo	16/174	9.2	-	-	16/247	6.5	-	-
Exenatide 5 µg	54/197	27.4	3.0 (1.8, 5.0)	<0.0001	54/245	22.0	3.4 (2.0, 5.8)	<0.00001
Exenatide 10 µg	60/179	33.5	3.7 (2.2, 6.1)	<0.00001	60/242	24.8	3.8 (2.3, 6.5)	<0.0001
GWAA ³								
Glargine	110/26 7	41.2	-	-	110/26 8	41.0	-	-
Exenatide 10 µg	117/28 2	41.5	1.0 (0.8, 1.2)	0.94	117/28 3	41.3	1.0 (0.8, 1.2)	0.94
Fonesca (2000) ²								
Placebo	NR	7.6	-	-				
Rosiglitaz one 4 mg	NR	NR	NR	NR	NR	NR	-	-
Rosiglitaz one 8 mg	25/89	28.1	3.7	NR	25/113	22.1	NR	NR
Rosenstoc k (2006a) ²								
Placebo	NR	NR	-	-	NR	NR	-	-
Rosiglitaz one 4 mg	NR	NR	NR	NR	NR	NR	NR	NR
Dailey ⁴								
Placebo	24/178	14	-	-	24/184	13.0	-	-
Rosiglitaz one 4 mg	75/177	42	3.1 (2.1, 4.7)	<0.00001	75/181	41.4	3.2 (2.1, 4.8)	<0.00001
Rosenstoc k (2006b)								
Glargine	NR	48	-	-	NR	NR	-	-
Rosiglitaz one 4 mg	NR	49	-	-	NR	NR	NR	NR

EP, evaluable population; HbA1c, Glycosylated haemoglobin specific A1c fraction; ITT, intent-to-treat; PP, per-protocol population; NR, not reported

¹ P-value: placebo or glargine is the reference group;

² Study analysis performed on evaluable population;

³ Study analysis performed on per-protocol population;

⁴ Study analysis performed on the ITT-population

Exenatide versus insulin glargine (secondary analysis):

In Study GWAO, the primary objective of demonstrating the non-inferiority of exenatide to insulin glargine in change in HbA_{1c} was supported by the location of the upper limit of the CI below the pre-specified non-inferiority margin of 0.4%.

Results from Study GWAA were not used in the submission for direct comparison of clinical effectiveness of exenatide and insulin glargine. The least squares (LS) mean change in HbA_{1c} from baseline in the study was -1.00% (SE=0.06) in exenatide group and -1.05% (SE=0.06) in glargine group. The proportion of subjects achieving target HbA_{1c} ≤7% at endpoint was 46.4% (=117/282) in exenatide group and 48.03% (=110/267) in glargine group.

For PBAC's view of these results, see *Recommendations and Reasons*.

9. Clinical Claim

The submission described exenatide as being similar to rosiglitazone and insulin glargine in its effectiveness in lowering HbA_{1c} and in safety but is superior to rosiglitazone and insulin glargine in body weight management. The PBAC partially accepted this claim, see *Recommendations and Reasons*.

10. Economic Analysis

The submission presented a modelled economic evaluation. The choice of the cost-utility approach was considered valid. Total cost included drug costs, patient management costs and costs of management of diabetes-related complications.

The estimated base case incremental cost per extra discounted quality adjusted life year versus either rosiglitazone or insulin glargine fell in the range \$15,000 to \$45,000. The estimated base case incremental cost per extra discounted life year gained versus either rosiglitazone or insulin glargine was > \$200,000.

The PBAC had a number of concerns with the modelled economic evaluation presented, which could result in the incremental cost effectiveness ratio being much higher and less certain than estimated by the submission, see *Recommendations and Reasons*.

11. Estimated PBS Usage and Financial Implications

The financial cost/year to the PBS (excluding co-payments) minus any savings in use of other drugs was estimated by the submission to be between \$10 - \$30 million in Year 5. This is likely to be an underestimate.

12. Recommendation and Reasons

The PBAC agreed that insulin glargine and rosiglitazone were both appropriate comparators and considered that the submission reasonably established that exenatide is non-inferior to insulin glargine in terms of its effects on HbA_{1c}, which remains the most important clinical outcome in the management of diabetes, but that it appears to be associated with a higher incidence of adverse effects.

The PBAC had some residual concerns about whether the submission had adequately demonstrated that exenatide is non-inferior to rosiglitazone in terms of its effect on HbA_{1c}, although acknowledging the difficulties associated with conducting a formal indirect

comparison of the two drugs in terms of this parameter. The Committee was somewhat reassured by the results of the indirect comparison of the proportion of subjects achieving target HbA_{1c} levels $\leq 7\%$. However it was noted that a number of relevant rosiglitazone trials were excluded from the analyses presented. The PBAC also noted that there is an ongoing Phase III randomised trial comparing exenatide, rosiglitazone, and exenatide plus rosiglitazone in metformin treated Type 2 diabetics, and considered that the results of this trial would help inform this issue. It was further noted that no formal indirect comparison of the relative safety and toxicity of exenatide and rosiglitazone had been presented, and the Committee was therefore unable to form a view on this issue.

The Committee did not accept the submission's main therapeutic claim of greater weight loss with exenatide compared with rosiglitazone, noting it is based on data from indirect comparisons of randomised trials of short duration where the apparent advantage of exenatide with respect to weight was an observational outcome. This benefit has not been verified in a properly designed weight loss study or quality of life studies, nor has it been shown to be durable over the long term. Additionally the claimed advantages for exenatide in weight gain have not been shown to result in improved morbidity and mortality outcomes. The Committee did not accept the secondary therapeutic claim of lowered LDL cholesterol levels for similar reasons.

A final area of clinical concern for the Committee was the question of whether exenatide treatment increases the risk of malignancies. However, it is noted in the European Public Assessment Report that a causal relationship between exenatide treatment and cancer is unlikely, although the relatively small number of subjects and short duration of follow-up precluded a definitive conclusion.

The PBAC had a number of concerns with the modelled economic evaluation presented. The model is based on the UKPDS diabetes model which has been validated in terms of the effect of changes in HbA_{1c} on cardiovascular outcomes, but not in terms of incremental weight change as a surrogate outcome which quantitatively predicts a subsequent incremental treatment effect on major cardiovascular events. Additionally the benefit of exenatide in regard to weight gain is unsupported by any long term studies of clinical outcomes. The model is extremely sensitive to the disutility associated with weight gain. If no disutility values for body mass index (BMI) are applied to the primary analysis, the incremental cost effectiveness ratio (ICER) increases from within a range of \$15,000 - \$45,000 to $> \$200,000$. The disutility associated with long-term twice daily injection therapy is not included. The model assumes a constant linear relationship between BMI over 25 and disutility which may not be reasonable. Given that a BMI > 25 is relatively common in the population, this assumption imposes a decrement in QOL (and therefore benefit for exenatide by off-setting this decrement) to people who may have an average BMI.

There is uncertainty regarding the incremental cost effectiveness of using exenatide compared to insulin glargine because special price arrangements apply to insulin glargine.

Therefore 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 has not been shown to be durable or to translate into morbidity or mortality benefits, and because of unresolved safety concerns.

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

The sponsor has since consulted with the PBAC and Department of Health and Ageing and clinical experts to clarify the positioning and the valuation of the claimed benefits and will address these topics in a resubmission. The sponsor disagrees with the statement that study GWAA was not included in the evaluation of outcomes but will address this concern in any resubmission. The sponsor also notes regulatory agencies have generally accepted the product's safety and some international reimbursement agencies have accepted the value of weight loss in a population of patients with Type 2 diabetes. The sponsor refers to its own website (www.lilly.com.au) for more details.