PUBLIC SUMMARY DOCUMENT
Product: EXENATIDE, powder for injection, 2 mg, Bydureon®
Sponsor: Eli Lilly Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority required listing for the treatment of type 2 diabetes mellitus in combination with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea.

2. Background

This presentation of exenatide had not previously been considered by the PBAC.

At its November 2008 meeting, the PBAC recommended listing exenatide injection solution, 5 micrograms and 10 micrograms per dose in a pre-filled pen (Byetta®, administered twice daily) as an Authority required benefit 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, 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 in used in triple combination therapy with metformin and a sulfonylurea; and exenatide 9.35 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. Details of the PBAC consideration are available in the Public Summary Document available at http://www.health.gov.au/internet/main/publishing.nsf/Content/pbac-psd-exenatide-nov08

Exenatide twice daily was PBS listed from 1 August 2010.

3. Registration Status

Exenatide powder for injection, 2 mg was TGA registered on 20 December 2012 for the treatment of type 2 diabetes mellitus in combination with:

- metformin;
- sulfonylureas;
- metformin and a sulfonylurea;

in patients who have not achieved adequate glycaemic control.

4. Listing Requested and PBAC's View

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 who has an HbA1c greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 and in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date and level of the HbA1c must be documented in the patient's medical records at the time therapy with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c

must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated;

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 results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical record;

Continuation of therapy, in combination with either metformin or a sulfonylurea, in a patient with type 2 diabetes 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 a dipeptidyl peptidase 4 inhibitor (gliptin) or another glucagon-like peptide-1.

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 who has an HbA1c greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite maximally tolerated doses of metformin and a sulfonylurea.

The date and level of the HbA1c must be documented in the patient's medical records at the time therapy with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated;

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 results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical record.

Continuation of therapy, in combination with metformin and a sulfonylurea, in a patient with type 2 diabetes 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 a dipeptidyl peptidase 4 inhibitor (gliptin) or another glucagon-like peptide-1.

Special Pricing Arrangements apply.

The PBAC accepted the requested restriction as appropriate and it is consistent with the PBS restriction for exenatide twice daily.

5. Clinical Place for the Proposed Therapy

Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and exercise are the first steps in managing the disease, followed by the addition of drug therapy with metformin. When diet and exercise modifications and metformin monotherapy is inadequate in controlling blood glucose, current treatment guidelines recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, insulin should preferably be added. Instead of adding insulin, other options include the addition of a glucagon like peptide 1 (GLP-1) receptor agonist, a dipeptidyl peptidase-4 (DPP-4) inhibitor, a thiazolidinedione (e.g. rosiglitazone, pioglitazone), an alpha-glucosidase inhibitor (e.g. acarbose), or a meglitinide (e.g. repaglinide).

Exenatide is a treatment option for adults with type 2 diabetes not achieving adequate glycaemic control when treated with diet and exercise and maximally tolerated doses of either a combination of metformin and a sulfonylurea; or metformin or a sulphonylurea and combination treatment with metformin and a sulfonylurea is contra-indicated or not tolerated.

The submission proposed that exenatide once weekly would substitute for exenatide twice daily. The submission expected the clinical management algorithm for patients with type 2 diabetes mellitus to remain unchanged with the introduction of exenatide once weekly.

6. Comparator

The submission nominated exenatide administered twice daily as the main comparator. Liraglutide was nominated as a secondary comparator. This was accepted by the PBAC.

7. Clinical Trials

The basis of the submission was two pivotal head-to-head trials comparing exenatide 2 mg weekly with exenatide 10 micrograms twice daily (BD) (Studies 105 and 108), and two supportive trials comparing exenatide 2 mg weekly with sitagliptin 100 mg daily or pioglitazone 45 mg daily (Study 106) and insulin glargine (Study GWBR) in patients with type 2 diabetes.

The submission presented an indirect comparison of exenatide 2 mg weekly with the supplementary comparator liraglutide 1.8 mg daily, using exenatide 10 micrograms BD as the common comparator. The indirect comparison was based on two trials comparing exenatide

2 mg weekly with exenatide 10 micrograms BD (Studies 105 and 108) and one trial comparing exenatide 10 micrograms BD with liraglutide 1.8 mg daily (LEAD-6).

Studies 105 and 106 included extension phases where all patients received exenatide weekly. For Study GWBR extension phase (84 week interim analysis of a 130 week study), all patients remain on randomised therapy.

Publication details of the trials presented in the submission are in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Exenatide weekly versus exenatide BD (pivotal)		
Study 105 (includes extension study)	A randomized, open-label, multicenter comparator-controlled study to examine the effects of exenatide long-acting release on glucose control (HbA1c) and safety in subjects with type 2 diabetes mellitus managed with diet modification and exercise and/or oral anti-diabetic medications.	
Drucker *et al.*	Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study.	*Lancet* 2008; 372: 1240-50
Buse *et al.*	DURATION 1: Exenatide one weekly produces sustained glycaemic control and weight loss over 52 weeks.	*Diabetes Care.* published online ahead of print, 9 March 2010
Trautmann *et al.*	Exenatide once weekly treatment elicits sustained glycaemic control and weight loss over 2 years.	European Association for the Study of Diabetes 2009 [abstract].
Study 108	A randomized, open-label, parallel-group, comparator controlled, multicenter study to evaluate the glycaemic effects, safety and tolerability of exenatide once weekly in subjects with type 2 diabetes mellitus.	
Blevins *et al.*	DURATION 5: Exenatide once weekly resulted in greater improvements in glycaemic control compared to exenatide twice daily in patients with type 2 diabetes.	*Journal of Clinical Endocrinology and Metabolism* 2011; 96(5): 1-10 (to be published)
Exenatide weekly versus other comparators (supportive)		
Study 106 (includes extension study)	A randomized, double-blind, parallel-group, multicenter study to compare the glycaemic effects, safety and tolerability of exenatide once weekly to those of sitagliptin and pioglitazone in subjects with type 2 diabetes mellitus treated with metformin.	
Bergenstal *et al*.	Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION 2): a randomised trial.	*Lancet* 2010; 376:9739: 431-439
Wysham C *et al*.	DURATION 2: Effect of switching to once-weekly exenatide from maximum daily doses of sitagliptin or pioglitazone.	American Diabetes Association 2010 [abstract]

Trial ID	Protocol title/ Publication title	Publication citation
Study GWBR (includes extension study) Diamant *et al*.	Efficacy of once-weekly exenatide long-acting release and once-daily insulin glargine in patients with type 2 diabetes treated with metformin alone or in combination with sulfonylurea. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION 3): an open-label randomised trial. GWBR Clinical Study Report 84 week extension	 *Lancet* 2010; 375: 2234-43 Publication in press
Exenatide BD versus liraglutide (used in indirect comparison)		
LEAD-6 Buse *et al*.	Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26 week randomised, parallel-group, multinational, open-label trial (LEAD 6).	*Lancet* 2009; 374: 39-47

Abbreviations: BD, twice daily; met, metformin; QD, once daily; QW, once weekly; SC, subcutaneously; SU, sulfonylurea

8. Results of Trials

The results for the primary outcome of mean change in HbA1c from baseline to endpoint of Studies 105 and 108 are shown in the table below.

Mean change in HbA1c from baseline to endpoint for Studies 105 and 108

	Study 105 (30 weeks)		Study 108 (24 weeks)	
	Exenatide 2mg weekly N=148	**Exenatide 10µg BD N=147**	**Exenatide 2mg weekly N=129**	**Exenatide 10µg BD N=123**
Baseline mean (SE)	8.3 (0.08)	8.3 (0.08)	8.5 (0.10)	8.4 (0.10)
Mean Δ HbA1c (SE)	-1.6 (0.09)	-1.3 (0.08)	-1.4 (0.10)	-0.7 (0.10)
LS mean Δ HbA1c (SE)	-1.9 (0.08)	-1.5 (0.08)	-1.6 (0.10)	-0.9 (0.10)
LS mean difference (95% CI)	-0.33 (-0.54, -0.12) p=0.0023		-0.7 (-0.90, -0.40) p<0.0001	

Abbreviations: Δ, change; BD, twice daily; CI, confidence interval; HbA1c, glycosylated haemoglobin; LS, least squares; SE, standard error
Note: Treatment group difference (exenatide weekly minus comparator).

There were statistically significant larger reductions in HbA1c from baseline to endpoint for exenatide weekly compared to exenatide BD in Studies 105 and 108. The difference was statistically significant from week 10 onwards for Study 105 and from week 8 onwards for Study 108.

There was no evidence to suggest that the magnitude of the reduction of HbA1c varied with baseline treatment of diabetes based on the subgroup analyses (dual therapy with metformin, triple therapy with metformin and a sulfonylurea and sulfonylurea at baseline). Most of the patients in the two studies were taking a combination of metformin and sulfonylurea (triple therapy); only seven patients in the exenatide weekly arm and 18 patients in the exenatide BD arm were on sulfonylurea alone at baseline.

The results from the pivotal trials were pooled for analysis, using data collected at Week 26 for Study 105 and Week 24 for Study 108. The results are presented in the table below.

Pooled analysis of Study 105 (Week 26) and Study 108 (Week 24) for mean change in HbA1c from baseline

	Exenatide 2mg weekly N=277	Exenatide 10µg BD N=270
Baseline LS mean (SE)	8.37 (0.06)	8.35 (0.07)
Mean Δ HbA1c (SD)	*-1.51 (1.11)*	*-0.98 (1.08)*
LS mean Δ HbA1c (SE)	-1.71 (0.07)	-1.18 (0.07)
Without treatment*study interaction term		
LS mean difference (95%CI)	-0.53 (-0.70, -0.36); p<0.001[a]	
With treatment*study interaction term		
LS mean difference (95%CI)	-0.54 (-0.71, -0.37); p<0.001[a]	

Abbreviations: Δ, change; BD, twice daily; CI, confidence interval; HbA1c, glycosylated haemoglobin; LS, least squares; SD, standard deviation; SE, standard error
[a] p-value is based on an ANCOVA model with effects for treatment, study, sulfonylurea usage and HbA1c stratum.

There were statistically significant larger reductions in HbA1c in the exenatide weekly group compared to the exenatide BD group for the pooled results (-0.53% [95% CI -0.70, -0.36] p<0.001). Applying a margin of 0.3%, the additional reductions in HbA1c with exenatide weekly dosing would be considered clinically important, and of borderline clinical importance applying a margin of 0.4%. There were some concerns with pooling the results of Studies 105 and 108 due to the differences in the treatment effect in the two trials.

In the extension arm of Study 105, all patients received exenatide weekly following 30 weeks of randomised treatment. The mean reduction in HbA1c from baseline was maintained with exenatide weekly treatment at 52 and 100 weeks.

The table below summarises the proportions of patients achieving the HbA1c target of ≤7%, <7% or ≤6.5% for Studies 105 and 108, as well as the pooled results of these trials.

Individual trial and pooled results of the proportion of patients achieving target HbA1c of ≤7%, <7% or 6.5% for Studies 105 and 108

HbA1c target	% achieving target		Exenatide weekly vs exenatide BD		
	Exen QW n/N (%)	Exen BD n/N (%)	Crude risk difference (95% CI)	Crude odds ratio (95% CI)	Adjusted odds ratio[a] (95% CI)
Study 105 (Week 30)					
≤7.0%[b]	104/142 (73.2)	80/140 (57.1)	**0.16 (0.05, 0.27)**	**2.05 (1.25, 3.38)**	**2.17 (1.27, 3.72)**
≤6.5%	67/148 (45.3)	56/147 (38.1)	0.07 (-0.04, 0.18)	1.34 (0.84, 2.14)	1.34 (0.82, 2.20) p=0.2042
Study 108 (Week 24)					
<7.0%	75/129 (58.1)	37/123 (30.1)	**0.28 (0.16, 0.40)**	**3.23 (1.92, 5.43)**	**3.68 (2.10, 6.45)**
≤6.5%	53/129 (41.1)	20/123 (16.3)	**0.25 (0.14, 0.36)**	**3.59 (1.98, 6.50)**	NR
Pooled results (Study 105 at Week 26 and Study 108 at Week 24 week)					
<7.0%	170/267 (63.7)	109/250 (43.6)	**0.20 (0.12, 0.29)**	**2.27 (1.59, 3.23)**	**2.65 (1.80, 3.90)**

Abbreviation: BD, twice daily; Exen, exenatide; CI, confidence interval; HbA1c, glycosylated haemoglobin; NR, not reported; QW, weekly
[a] Adjusted for baseline HbA1c stratum and concomitant sulfonylurea use at screening
[b] only patients with a baseline HbA1c >7% included
Bolded results are statistically significantly different.

Individual trial and pooled results of the proportion of patients achieving target HbA1c of ≤7%, <7% or ≤6.5% for studies 105 and 108 showed that statistically significantly higher proportions of patients achieved HbA1c targets of <7% or ≤7% with exenatide weekly compared to exenatide BD for study 105 (adjusted odds ratio (OR) 2.17 [95% CI: 1.27, 3.72]), study 108 (adjusted OR 3.68 [95% CI: 2.10, 6.45]) and the pooled results (adjusted OR 2.65 [95% CI 1.80, 3.90]).

There were statistically significant larger reductions in fasting blood glucose (FPG) for exenatide weekly compared to exenatide BD in Studies 105 and 108 and the pooled results.

There were no statistically significant differences between exenatide weekly and exenatide BD in quality of life measures.

The results for the mean change in HbA1c from baseline to endpoint of Studies 106 and GWBR are shown in the table below.

Mean change in HbA1c from baseline to endpoint Study 106 and GWBR

	Study 106 (26 wks)			Study GWBR (26 wks)	
	Exenatide 2mg QW N=160	**Sitagliptin 100mg N=166**	**Pioglitazone 45mg N=165**	**Exenatide QW N=233**	**Insulin glargine N=223**
Baseline mean (SE)	8.6 (0.09)	8.5 (0.09)	8.5 (0.08)	8.3 (1.10)[a]	8.3 (1.02)[a]
Mean Δ HbA1c (SE)	-1.4 (0.11)	-0.8 (0.09)	-1.1 (0.09)	-1.4 (1.02)[a]	-1.3 (0.92)[a]
LSM Δ HbA1c (SE)	-1.6 (0.10)	-0.9 (0.10)	-1.2 (0.10)	-1.4 (0.06)	-1.3 (0.06)
LSM difference (95% CI)		-0.63 (-0.89, -0.37) p<0.0001	-0.32 (-0.57, -0.06) p=0.0165	-0.16 (-0.31,-0.02) p=0.027	

Abbreviations: Δ, change; BD, twice daily; CI, confidence interval; HbA1c, glycosylated haemoglobin; LSM, least squares mean; QW, once weekly; SE, standard error; wks, weeks
Note: Treatment group difference (exenatide weekly minus comparator), results from Study 106 appropriately adjusted to reflect this.
[a] mean and SD reported

There were statistically significant greater reductions in HbA1c for exenatide weekly compared to sitagliptin, pioglitazone and insulin glargine. The results suggest that exenatide weekly may be clinically superior to sitagliptin, as the additional reductions in HbA1c with exenatide weekly would be considered clinically important applying a margin of 0.3 %, and of borderline clinical importance applying a margin of 0.4 %. However, the difference between exenatide weekly and pioglitazone is of uncertain clinical importance as the 95 % CI include values that are not clinically important. The difference between exenatide weekly and insulin glargine is unlikely to be clinically important.

The submission concluded that there was no difference between exenatide weekly and liraglutide daily based on an indirect comparison using exenatide BD as the common comparator. However, the preliminary results of the head-to-head trial of exenatide weekly versus liraglutide (DURATION-6) available in the public domain indicate that exenatide weekly did not meet the pre-specified primary endpoint of non-inferiority to liraglutide. In light of the availability of the preliminary results from DURATION-6 (see table below), the sponsor stated that as exenatide once weekly did not meet the pre-specified primary endpoint of non-inferiority to liraglutide, the clinical claim of non-inferiority of exenatide once weekly with liraglutide 1.8mg presented in the submission was no longer supported.

LS mean change in HbA1c from baseline to endpoint: DURATION 6

	Exenatide 2mg QW	Liraglutide 1.8 mg QD
LS Mean change from baseline in HbA1c(SE)	-1.28 (0.05)	-1.48 (0.05)
pvalue	<0.001	<0.001
LS Mean difference (SE)	0.21 (0.07)	
95%CI (for difference)	(0.08,0.34)	
p value	0.002	

The most frequent adverse events reported with exenatide weekly were gastrointestinal events (mainly nausea, vomiting, and diarrhoea), injection site reactions, nasopharyngitis, hypoglycaemia and headache. When compared to exenatide BD (pooled results of Studies 105 and 108), there were statistically significantly more patients treated with exenatide weekly reporting injection site reactions (pruritus, erythema, induration, and nodule); whereas there were statistically significantly more exenatide BD patients reporting nausea, and vomiting. Differences in the rates of nausea and injection site reactions are carried into the economic model.

The submission presented additional data beyond the duration of the trials discussing pancreatitis, acute renal failure, rapid weight loss, anti-exenatide antibodies (anaphylactic-type reactions), cardiovascular events and malignant neoplasm (particularly pancreatic and thyroid cancers). The PBAC noted that the FDA has requested a thorough QT study with exposures of exenatide higher than typical therapeutic levels of exenatide weekly.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission described exenatide weekly as superior in terms of comparative effectiveness and equivalent in terms of comparative safety over exenatide BD.

The submission described exenatide weekly as superior in terms of comparative effectiveness and equivalent in terms of comparative safety to sitagliptin, pioglitazone, and insulin glargine.

For PBAC's view, see recommendation and reasons.

10. Economic Analysis

A stepped economic evaluation was presented. The type of economic evaluation presented was a cost-utility analysis. The individual-patient simulation model compared treatment with exenatide weekly and treatment with exenatide BD in patients with type 2 diabetic patients who have failed first line therapy (metformin/and or sulfonylurea therapy). The model had three health states: 'alive, no complications,' 'alive, complications,' and dead. The complications included in the model were ischaemic heart disease (IHD), congestive heart failure (CHF), myocardial infarction (MI), stroke, amputation and blindness. The time horizon in the modelled economic evaluation was a patient's lifetime (until death or aged 100 years). The model's cycle length was one year. HbA1c was the only clinical parameter that differed significantly between patients receiving exenatide weekly and exenatide BD, and was updated annually in the model.

It was assumed that patients switch to insulin glargine after a period of time on treatment with exenatide (weekly or BD) and remain on insulin glargine for the remainder of the model. It

was also assumed that the difference in HbA1c observed at the end of the trial was maintained for the duration of the model in patients who were initially treated with exenatide compared with those initially treated with insulin glargine.

The incremental cost per quality adjusted life year (QALY) gained was less than $15,000 in the base case.

The model was sensitive to disutilities associated with differing administration schedule (weekly versus daily), the time horizon, and the difference between treatment arms in HbA1c after switching from exenatide (weekly and BD) to insulin glargine.

During the evaluation, a multi-variate sensitivity analysis testing all three assumptions resulted in an incremental cost per QALY gained of between $105,000 and $200,000.

The PBAC considered there were several uncertainties with the economic model.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission's estimate of the net cost per year to the PBS/RPBS was less than $10 million in Year 5.

12. Recommendation and Reasons

The PBAC accepted the requested restriction as appropriate and it is consistent with the PBS restriction for exenatide twice daily.

The PBAC noted the comparator nominated for this submission was exenatide twice daily (BD) injection with a higher price requested for the exenatide once weekly (QW) injection than that of the comparator.

The basis of the higher price was an overall 0.53 % reduction in HbA1c based on the pooled results from studies 105 and 108. This difference in HbA1c was statistically significant and the PBAC agreed it would represent a clinically meaningful difference. However, there was some uncertainty about this pooled result. The clinical importance of the HbA1c reduction in Study 105 is uncertain as the 95 % CI includes values that are not clinically important (0.12 %). In Study 108, the difference between treatment arms exceeded the non-inferiority margin of 0.4 %, consistent with exenatide weekly being clinically superior to exenatide BD with respect to diabetes control. There were substantially larger reductions in HbA1c in the exenatide BD arm of Study 105 than Study 108 (LS mean reduction of -1.5 % versus -0.9 %). The reasons for these differences between trials are unclear.

The claim of non-inferior safety to the BD injection is uncertain, as the long-term safety of exenatide QW is unknown. This is of particular concern given the dose of the weekly injection (2000 microgram) is over tenfold higher than the dose of the BD injections over an equivalent period (140 microgram/week).

The PBAC considered there were several uncertainties with the economic model.

The PBAC considered that the assumed continuation of a treatment effect (i.e. 0.53% difference in HbA1c) unchanged for a lifetime, regardless of subsequent treatment, is inappropriate. HbA1c is unlikely to be different once patients are switched to insulin and the progression of HbA1c over 10 years in the model was considered implausible.

The PBAC recognised there were statistically significantly more exenatide BD patients reporting nausea, and vomiting than exenatide QW patients. However, the inclusion of disutilities for these events in the model may have lead to double counting, as patients would discontinue treatment if these events are of concern, given there are other treatment options available. The disutilities for fewer injections were notably not supported in the quality of life data collected during Study 105. The PBAC considered that these disutilities are likely to be overestimated. The PBAC noted that injection site reactions are more common with exenatide QW.

The use of some of the risk equations from the UKPDS Outcomes model may not be valid. An Australian study found that the UKPDS risk equations overestimated the number of coronary heart disease (CHD) events in Australian type 2 diabetics (Davis et al, 2009). The authors concluded that UKPDS CHD equations are not suitable for predicting the risk in Australians with type 2 diabetes. The model is therefore likely to significantly overestimate the reductions in CHD events associated with exenatide weekly versus exenatide BD.

The PBAC therefore rejected the submission on the basis of uncertain cost-effectiveness, with particular concern over the model assumptions regarding duration of treatment benefit, timing of the switch to insulin, disutilities associated with GI events and injections, and overestimation of cardiovascular benefits.

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 no comment.