

6.05 EXENATIDE

injection, 5 microgram/0.02 mL injection: solution, 60 unit doses, 10 microgram/0.04 mL injection: solution, 60 unit doses;

Byetta®, AstraZeneca Australia Pty Ltd.

1 Purpose of Application

1.1 To request Authority Required (Streamlined) listing for exenatide twice daily (BD) for treatment of Type 2 diabetes mellitus in combination with insulin.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics:

Name, Restriction, Manner of administration and form	Max. Qty	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
EXENATIDE				Byetta®	BQ
<i>exenatide 5mcg/0.02mL per dose, 60, 1 prefilled pens</i>	1	5	\$ [REDACTED]		
<i>exenatide 10mcg/0.04mL per dose, 60, 1 prefilled pens</i>	1	5	\$ [REDACTED]		

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Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type	Authority Required (STREAMLINED)
Condition/PBS indication	Diabetes mellitus type 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria	The treatment must be in combination with insulin AND The treatment must be in combination with metformin: unless contraindicated or not tolerated AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT-2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
Prescribers Instruction	The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor was initiated. Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) Had red cell transfusion within the previous 3 months. The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor, must be documented in the patient's medical records.
Administrative Advice	<i>This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or an SGLT2 inhibitor.</i>

- 2.2 Listing was requested based on a cost-analysis compared to intensification of insulin therapy with rapid- or short-acting insulin.
- 2.3 The requested PBS listing was broader than the TGA-approved indication, as the requested restriction implied that exenatide BD in combination with insulin did not require concurrent use of metformin if there was a contraindication or intolerance to metformin.

3 Background

- 3.1 Exenatide BD is TGA-registered as 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, or a combination of metformin and basal insulin, but who are not achieving adequate glycaemic control. The extension of indications to include use in combination with metformin and basal insulin was approved on 7 September 2012.
- 3.2 The PBAC has not previously considered listing exenatide BD for use in combination with insulin.

4 Clinical place for the proposed therapy

- 4.1 Type 2 diabetes mellitus is a chronic disease characterised by hyperglycaemia (high levels of glucose), as the pancreas is unable to produce enough insulin and/or there is resistance to insulin.
- 4.2 The submission proposed exenatide BD in combination with insulin as an alternative to insulin intensification.

5 Comparator

- 5.1 The comparator proposed in the submission was intensification of insulin therapy using rapid-acting or short-acting insulin. The submission presented clinical data and an economic evaluation comparing exenatide BD in combination with insulin glargine (basal insulin) to the full basal-bolus regimen. The evaluation considered that while insulin intensification is the appropriate comparator, basal-plus regimen and switching to premixed insulin are also alternative insulin intensification regimens.
- 5.2 The ESC noted that the requested place in therapy is the same as dapagliflozin in combination with insulin, recommended for listing at the November 2014 PBAC meeting. The ESC considered dapagliflozin in combination with insulin may also be an appropriate comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted and welcomed the input from individuals (1) and health care professionals (4) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with exenatide including fewer side effects, better administration and increase in therapeutic options. In addition, comments indicated that exenatide may help significantly reduce the potentially major side effects of insulin, such as reducing the amount of weight gain and peripheral oedema.

Clinical trials

6.3 The submission was based on: one head-to-head randomised trial comparing exenatide BD and insulin glargine to insulin lispro three times daily and insulin glargine (basal-bolus regimen) on a background of metformin (Trial GWDM); and one head-to-head randomised trial comparing exenatide BD to placebo on a background of insulin glargine with/without metformin with/without pioglitazone ‘for completeness’ (Trial GWCO).

6.4 Details of the trials presented in the submission are provided in the table below.

Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials		
GWDM	A Randomized Trial Comparing Two Therapies: Basal Insulin Glargine, Exenatide and Metformin Therapy (BET) or Basal Insulin Glargine, Bolus Insulin Lispro and Metformin Therapy (BBT) in Subjects with Type 2 Diabetes who were Previously Treated by Basal Insulin Glargine with either Metformin or Metformin and Sulphonylurea (4B: Basal Insulin Glargine, Exenatide BID, and Metformin Therapy or Basal Insulin Glargine, Bolus Insulin Lispro and Metformin Therapy). Diamant M, Nauck MA, Shaginian R, Malone JK, Cleall S, <i>et al.</i> Glucagon-like peptide-1 receptor agonist or bolus insulin with optimized basal insulin in diabetes.	14 August 2013 <i>Diabetes Care</i> 2014; 37(10): 2763-2773.

GWCO	<p>A Randomized Trial Comparing Exenatide with Placebo in Subjects with Type 2 Diabetes on Insulin Glargine With or Without Oral Antihyperglycemic Medications.</p> <p>Buse JB, Bergenstal RM, Glass LC, Heilmann CR, Lewis MS, <i>et al.</i> Use of twice-daily exenatide in basal insulin-treated patients with type 2 diabetes. <i>Annals of Internal Medicine</i> 2011; 154(2): 103-112.</p> <p>Rosenstock J, Shenouda SK, Bergenstal RM, Buse JB, Glass LC, <i>et al.</i> Baseline factors associated with glycaemic control and weight loss when exenatide twice daily is added to optimized insulin glargine in patients with type 2 diabetes. <i>Diabetes Care</i> 2012; 35(5): 955-958.</p> <p>Buse JB, Han J, Miller S, MacConell L, Pencek R, <i>et al.</i> Addition of exenatide BID to insulin glargine: A post-hoc analysis of the effect on glycemia and weight across a range of insulin titration. <i>Current Medical Research and Opinion</i> 2014; 30(7): 1209-1218.</p>	<p>30 September 2010</p> <p><i>Annals of Internal Medicine</i> 2011; 154(2): 103-112.</p> <p><i>Diabetes Care</i> 2012; 35(5): 955-958.</p> <p><i>Current Medical Research and Opinion</i> 2014; 30(7): 1209-1218.</p>
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6.5 The key features of the randomised trials are summarised in the table below.

Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Comparison	Patient population	Outcome
GWDM	627	R, OL, 12 wks run-in, 30 wks	High	Exenatide BD + glargine vs lispro TDS + glargine (basal-bolus regimen) Background: MET	HbA1c 7.0-10.0% on stable glargine ≥20units/day + MET ± SU (36%) and HbA1c > 7% after run-in titrated glargine	HbA1c
GWCO	261	R, DB, 30 wks	Unclear	Exenatide BD + glargine vs placebo + glargine Background: ± MET ±PIO	HbA1c 7.1-10.5% on stable glargine ≥20units/day ± MET ± PIO	HbA1c

Abbreviations: BD, twice daily; DB, double blind; MET, metformin; OL, open-label; PIO, pioglitazone; R, randomised; SU, sulfonylurea; TDS, three times daily; wk, week

6.6 The ESC considered that trial GWDM has a high risk of bias given that it was an open label study. The Pre-PBAC Response noted that this trial was considered to have a low risk of bias in the evaluation of the November 2014 submission for dapagliflozin (with insulin). The sponsor considered that while the trial was open label, the objective primary outcome reduced the risk of bias.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Comparative effectiveness

Mean change in HbA1c from baseline (or randomisation) in %

	GWDM (PP population) 30 weeks		GWCO (FAS population) 30 weeks	
	Exenatide BD ^a	Insulin lispro TDS ^a	Exenatide BD ^b	Placebo ^b
N	247	263	112	110
Baseline mean HbA1c	8.3 (SD 0.98)	8.2 (SD 0.87)	8.33 (SE 0.08)	8.54 (SE 0.09)
LS mean change (SE)	-1.13 (0.053)	-1.10 (0.051)	-1.71 (0.09)	-1.00 (0.09)
LS mean diff (95% CI)	-0.04 (-0.18, +0.11)		-0.71 (-0.95,-0.47)	

Abbreviations: BD, twice daily; CI, confidence interval; diff, difference; FAS, full analysis set; LS, least squares; PP, per protocol; SD, standard deviation; SE, standard error; TDS, three times daily

Note: Treatment group differences (exenatide BD minus comparator). *There were some differences in the CSR and the identified publication for the GWCO trial; the reasons for these differences are unclear.*

^a background of insulin glargine and metformin

^b background of insulin glargine with/without metformin with/without pioglitazone

6.7 Exenatide BD with insulin glargine was non-inferior to the basal-bolus regimen (on a background of metformin), as the upper limit of the 95% CI of the mean change in

HbA1c from randomisation (+0.11%) was smaller than both the hierarchically tested non-inferiority margins (0.4% and 0.3% respectively) in Trial GWDM.

- 6.8 Exenatide BD resulted in a statistically significantly larger reduction in HbA1c from baseline compared to placebo, on a background of titrated insulin glargine with/without metformin and/or pioglitazone (LS mean difference -0.71%; 95% CI -0.95%, -0.47%). While there were some limitations (e.g. differences in background oral diabetes medicines and HbA1c levels at baseline), the results indicated a clinically relevant benefit of exenatide BD over placebo when added to basal insulin.
- 6.9 Treatment with exenatide BD with insulin glargine was associated with a net improvement in change in body weight, fasting plasma glucose level and systolic blood pressure compared to the basal-bolus regimen (on a background of metformin) in Trial GWDM. There was no statistically significant difference between treatment groups for change in diastolic blood pressure. The ESC considered the changes in body weight, fasting plasma glucose level and systolic blood pressure to be small and of uncertain clinical significance.
- 6.10 The ESC noted that exenatide was also associated with improved 'weight-related quality of life' and treatment satisfaction but considered that these results are subject to bias due to the open label design of the trial.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Comparative harms

- 6.11 The most frequently reported adverse events associated with exenatide BD in both trials were gastrointestinal adverse events including nausea, vomiting, and diarrhoea. In Trial GWDM, the most frequently reported treatment-emergent adverse events in the basal-bolus treatment group were nasopharyngitis, diarrhoea and influenza.
- 6.12 Fewer patients receiving exenatide BD with insulin glargine reported a confirmed episode of hypoglycaemia compared to the basal-bolus treatment group (on a background of metformin) in Trial GWDM. There were statistically significantly lower adjusted annualised rates of confirmed minor and/or major hypoglycaemic events for the exenatide BD treatment group versus the basal-bolus treatment group (rate ratio 0.45; 95% CI 0.36, 0.56). The open-label design of Trial GWDM may bias the reporting of adverse events.
- 6.13 A summary of the comparative harms for exenatide BD versus the main comparator is presented in the table below.

Summary of comparative harms for exenatide BD and insulin lispro TDS (background of insulin glargine and metformin)

Harms						
	Exenatide BD	Insulin lispro	Risk ratio (95% CI)	Event rate/100 patients ^a		RD (95% CI)
				Exenatide BD	Insulin lispro	
Nausea						
GWDM	102/315	5/312	20.21 (8.35, 48.91)	32	2	31% (25%, 36%)
Vomiting						
GWDM	39/315	3/312	12.88 (4.02, 41.23)	12	1	11% (8%, 15%)
Hypoglycaemia (major and/or minor)						
GWDM	93/315	130/312	0.71 (0.57, 0.88)	30	42	-12% (-20%, -5%)

Abbreviations: RD, risk difference;

^aMedian duration of follow-up/ exposure: 30 weeks

- 6.14 On the basis of open label direct evidence presented in the submission, for every 100 patients treated with exenatide BD with insulin glargine in comparison to basal-bolus regimen (on a background of metformin);
- Approximately 31 additional patients would experience nausea over a median duration of follow-up of 30 weeks.
 - Approximately 11 additional patients would experience vomiting over a median duration of follow-up of 30 weeks.
 - Approximately 12 fewer patients would have at least one major and/or minor hypoglycaemic (low blood sugar) episode over a median duration of follow-up of 30 weeks.

Clinical claim

- 6.15 The submission described exenatide BD in combination with titrated insulin as:
- non-inferior in terms of comparative effectiveness and with a different but tolerable safety profile compared to rapid-acting insulin [with basal insulin]; and
 - superior in terms of comparative effectiveness and with a different but tolerable safety profile compared to titrated insulin alone.
- 6.16 The ESC considered that these claims were adequately supported.
- 6.17 The PBAC agreed with the ESC and considered the above claims to be reasonable.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Economic analysis

- 6.18 The submission presented a cost-analysis versus rapid- or short-acting insulin, including drug acquisition costs and costs of healthcare resource consumption. The evaluation considered this was inconsistent with the clinical claim, as additional clinical benefits in terms of efficacy (blood pressure) and safety (hypoglycaemia) were claimed. The Pre-Sub-Committee Response (PSCR) (p2) argued that these additional outcomes should be incorporated in the cost-analysis and that this method was accepted by PBAC for dapagliflozin with insulin in November 2014. However, this approach appears to take account of positive health outcomes (e.g. weight loss and blood pressure) but not negative outcomes such as nausea, and may favour exenatide.
- 6.19 Exenatide 18.6 mcg per day (9.3 mcg twice daily) and main comparator, rapid- and short-acting insulin, 36.8 international unit (IU) per day were estimated to be equi-effective.
- 6.20 The equi-effective doses were based on results from Trial GWDM with a 30 week duration. There was an implicit offset for rapid- or short-acting insulin by basal insulin, as patients in the exenatide BD treatment group received more basal insulin than the basal-bolus treatment group (approximately 5.4 IU per day).
- 6.21 The evaluation considered the insulin doses from Trial GWDM may not be achieved in practice given the complexity of insulin dosing and the potentially less aggressive titration in practice (which may also affect the glycaemic control seen in practice). The dose of exenatide BD from Trial GWDM may be higher than in practice as the up-titration of exenatide BD during the trial was based on tolerability, while the Product Information suggests up-titration to improve glycaemic control. The ESC noted the issue in relation to doses in practice but considered the equi-effective doses to be reasonable and consistent with PBAC Guidelines.
- 6.22 The main driver of the requested price for exenatide 10mcg BD in the submission was the claimed cost-savings from reduced use of blood glucose test strips (\$586.23), insulin drug acquisition costs (\$502.63) and reduced diabetes educator visits (\$253.20). The PSCR (p5) reduced the cost-offset from reduced use of blood glucose test strips to \$449.26 to take account of the weighted average of PBS and National Diabetes Services Scheme (NDSS) test strip prices, as per the pricing negotiations for dapagliflozin in combination with insulin.
- 6.23 The submission proposed that exenatide 5mcg BD be priced at 83.8% of the ex-manufacturer price of exenatide 10mcg BD. The weighting was calculated based on half the insulin drug requisition cost and half the anti-hypertensive medicine cost-offset, with the remaining cost-offsets claimed at 100%. The weighting, calculated at the DMPQ level, was then applied to the ex-manufacturer price.

6.24 The evaluation considered the requested price of exenatide BD was inadequately justified, as the claimed cost-offsets were overestimates:

- During the consideration of the November 2014 dapagliflozin re-submission for the same requested PBS restriction (using a similar methodology), the PBAC disagreed with claimed cost-offsets relating to blood glucose test strips only agreeing to an offset for 1 test strip per day, diabetes (nurse) educator visits for up-titrating insulin doses and reduced anti-hypertensive medicines. The PSCR (p2) argued that, while the sponsor has agreed to the removal of the blood pressure cost offset for dapagliflozin (both in combination with insulin and triple oral therapy), the removal should not be applied to exenatide, which was associated with numerically larger reductions in systolic blood pressure. The ESC disagreed with the PSCR, considering that the difference in systolic blood pressure (of -4.5 mmHg [95% CI: -6.98, -2.02] in Trial GWDM and -4.44 mmHg [95% CI: -7.85, -1.03] in Trial GWCO) was of uncertain clinical significance.
- The PBAC stated that the cost-offset for hypoglycaemia as proposed in the dapagliflozin November 2014 Pre-PBAC Response was reasonable. However, despite sourcing data from the same trial, the claimed hypoglycaemia cost-offset in the submission was approximately four times higher (\$█████ versus ~\$█████). The PSCR (p2) proposed to reduce the cost-offsets for hypoglycaemic events. However, the ESC considered that the offsets remained overly complex.
- The cost-offset from reduced needles use may not be realised, given that needles through the NDSS are required for both exenatide BD and insulin. There is the potential for more needle use should exenatide BD substitute for other insulin intensification regimens. The ESC noted that the PSCR (p2) agreed to halve the cost offset for the number of needles used. The ESC considered that this should also be applied to blood glucose monitoring.
- The assumption that insulin intensification requires referral to an endocrinologist was inadequately justified. The ESC noted that the sponsor had agreed in its PSCR (p2) to omit the cost offset for an endocrinologist consultation. The ESC considered that this was reasonable.

6.25 The ESC noted that the submission based its non-insulin offset calculations on the initial year of treatment and then assumed that the same non-insulin offsets achieved in the first year of therapy will be reproduced in every year of therapy. This is not an appropriate assumption for the costs that are avoided on initiation of treatment, and may also not be an appropriate assumption for some of the offsets that are avoided in the stabilization phase of treatment. The established method of dealing with this issue is to pro rata “one-off” costs over a period of treatment (usually two to three years for chronic therapies).

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Drug cost/patient/year:

Drug	Drug cost/patient/year ^a
Exenatide 5mcg BD	\$█████
Exenatide 10mcg BD	\$█████
Rapid/short-acting insulin in Section D (weighted price assuming 39.6 units/day)	\$502.63
Rapid/short-acting insulin in Section E (weighted price assuming 36.8 units/day)	\$468.13

^a Assumed full compliance and 365.25 days per year

Estimated PBS usage & financial implications

- 6.26 This submission was not considered by DUSC. The submission used a combination of an epidemiological and market share approach.
- 6.27 The PSCR (p6) presented an updated cost-analysis and a resulting revised set of financial implications.
- 6.28 All prices used in the submission are indication specific and exclusive of the special pricing arrangement for exenatide BD. Given the requested weighted price for exenatide BD across indications, the financial impact to the government is likely to be affected by the accuracy of the estimated use across indications (not provided in the submission).

Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
Estimated extent of use					
Initiating pts					
Continuing pts					
Total scripts/packs					
Exenatide BD 5mcg ^b					
Exenatide BD 10mcg ^c					
Estimated net cost to PBS/RPBS/MBS					
<i>Cost of exenatide BD (less co-pay)</i>	\$	\$	\$	\$	\$
Cost-offset rapid/short-acting ins ^d	-\$2,813,538	-\$4,330,123	-\$6,192,375	-\$8,108,900	-\$10,056,698
Cost-offset anti-hypertensive meds ^e	-\$37,092	-\$57,086	-\$81,637	-\$106,903	-\$132,582
<i>Cost-offset glucagon^f</i>	-\$13,589	-\$20,914	-\$29,908	-\$39,165	-\$48,572
<i>Commonwealth gov't cost-offsets</i>	-\$4,461,016	-\$6,865,641	-\$9,818,342	-\$12,857,095	-\$15,945,433
<i>State/territory gov't cost-offsets^g</i>	-\$670,528	-\$1,031,963	-\$1,475,778	-\$1,932,528	-\$2,396,731
Estimated total net cost-savings					
Net cost-savings to gov't budget	\$	\$	\$	\$	\$

^a Estimated number of patients on exenatide BD + insulin outside the current PBS restriction in 2015.

^b Assumed that initiating patients receive 2 scripts/year on average and continuing patients receive 2.435 scripts/year on average year as estimated by the submission.

^c Assumed that initiating patients receive 4.07 scripts/year on average and continuing patients receive 9.74 scripts/year on average year as estimated by the submission.

^d Weighted price across presentations calculated as \$438.64/pt/yr. Half-cycle correction applied to initiating patients.

^e \$5.78/pt/yr. Half-cycle correction applied to initiating patients.

^f \$2.12/pt/yr. Half-cycle correction applied to initiating patients.

^g *Not all States/Territories cover ambulance attendance, but this claimed cost-offset has been attributed in full*

Note: Numbers in italics based on data from the PSCR's accompanying workbook entitled Item 6.05 – exenatide – Byetta Source: Section E amended for PSCR.xlsx. However, the exact values presented in Table 2 of the PSCR and from the workbook could not be replicated, but were broadly similar with independently re-calculated values. There may be very minor differences in rounding due to aggregation/disaggregation of the data.

- 6.29 At year 5, the estimated number of scripts for exenatide 10 mcg was over 200,000 per year and the net cost to the Commonwealth would be a cost savings of \$10 - \$20 million per year.
- 6.30 The claimed cost-savings to government health budgets are unlikely to be realised, mainly due to the overestimation of cost-offsets (see economic analysis) and the potential substitution with other cheaper diabetes medicines.

- 6.31 The estimated extent of use of exenatide BD was uncertain, mainly due the unknown uptake rates in practice and the unclear number of patients with Type 2 diabetes who are inadequately controlled on insulin.
- 6.32 Some of the cost-offsets included in the estimates of financial implications to Government are not costs to the Commonwealth. The ESC requested the sponsor to provide clarification with respect to the breakdown of financial implications for Government Health Budgets to allow a consideration of the costs that only apply to the Commonwealth to facilitate post-PBAC processes.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Quality Use of Medicines

- 6.33 There is the potential for leakage among patients who have not trialed insulin.

Financial Management – Risk Sharing Arrangements

The sponsor claimed that a risk sharing arrangement would not be necessary, as a sensitivity analysis in Section E showed that substitution of basal insulin by exenatide BD in a proportion of patients did not have a large impact on Government health budgets. However, an analysis conducted during the evaluation, correcting for an error in the sensitivity analyses, showed that substitution with other therapies would have an impact on government budgets

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of exenatide twice daily for treatment of Type 2 diabetes mellitus in combination with insulin on a cost analysis basis compared with intensification of insulin therapy to the full basal-bolus regimen. The equi-effective doses are exenatide 18.6 mcg per day (9.3 mcg twice daily) and rapid- and short-acting insulin, 36.8 international unit (IU) per day.
- 7.2 The PBAC accepted that exenatide used in combination with insulin is at least as effective as insulin intensification and has some clinical advantages including reductions in weight gain and small reductions in minor hypoglycaemic episodes. Furthermore, the PBAC acknowledged that exenatide dual therapy has clinical value as patients are able to avoid an increase in dose of insulin.
- 7.3 The PBAC noted that the GWDM trial was considered to have a low risk of bias in the evaluation of the November 2014 dapagliflozin submission and a high risk of bias in the evaluation of this submission. The PBAC considered that the previous assessment was incorrect and that trial GWDM has a high risk of bias given that it was an open label study. The PBAC noted that the primary outcome of GWDM was objective, but considered that the open label nature of the study would result in the rates of hypoglycaemia being biased, for example, as participants on treatment would be more likely to test for hypoglycaemic events.

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- 7.4 The PBAC considered that full basal-bolus insulin regimen was an appropriate comparator, noting that other insulin based comparators would have also been appropriate.
- 7.5 The PBAC provided the following comments as to the suitability of each of the cost-offsets claimed in the submission.

PBAC recommendation on each cost-offset presented in the submission

Cost-offset claimed in the submission	PBAC recommendation
GP consultation of 1 more/year	The PBAC did not accept the claim of one additional GP consultation because the claim was not adequately substantiated.
Endocrinologist visit of 1 less/year	The PBAC did not accept one less endocrinologist consultation. The PBAC considered the assumption that insulin intensification requires referral to an endocrinologist was inadequately justified and noted that the sponsor agreed not to pursue this cost offset in its PSCR.
Diabetes educator visits of 4 less/year	The PBAC did not accept the cost offset of a reduction of 4 visits/year as patients are likely to continue to be referred to a diabetes educator for diabetes related issues other than insulin dose titration. The PBAC noted that the number of diabetes educator visits is derived from a five year old data source (March 2010) which looked at the offsets achieved in the first year of therapy only and which may differ from current practice. However the PBAC considered that a cost offset for one less diabetes educator visit a year would be reasonable.
Glucose test strips of 3 less/day	The PBAC accepted the cost offset for <u>one</u> less glucose indicator strip per day instead of <u>three</u> , as agreed for dapagliflozin and insulin dual therapy in November 2014. The PBAC noted that the sponsor agreed to weight the cost of test strips to account for proportional supply through the PBS and NDSS use for dapagliflozin triple therapy.
Needles of 0.5 less/day	The PBAC did not accept 0.5 less needles/day based on the lack of data presented on the proportion of patients who would avoid a basal bolus insulin regimen and be able to use basal insulin only, and would therefore use fewer needles. The PBAC considered that there is the potential for an increased use of needles/day should exenatide BD substitute for other insulin intensification regimens.
Anti-hypertensive medicines	The PBAC did not accept this cost-offset and considered that the claim of lower dose combinations due to the reduction in systolic blood pressure remained inadequately supported.
Hypoglycaemia- mild, moderate and severe	The PBAC accepted that there may be reductions in minor hypoglycaemic episodes but did not accept the cost offsets claimed for moderate and severe episodes. The PBAC recalled that it had accepted a smaller offset for hypoglycaemia avoided in the context of the dapagliflozin with insulin submission, and considered that that smaller offset would also be reasonable in this setting, as the comparator in both submissions is intensification of insulin therapy.

- 7.6 The PBAC advised that exenatide is not suitable for prescribing by nurse practitioners.
- 7.7 The PBAC recommended that the Safety Net 20 Day Rule should not apply.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

Category/Program	GENERAL – General Schedule (Code GE)
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Restriction type	Authority Required (STREAMLINED)
Condition/PBS indication	Diabetes mellitus type 2
Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined
Clinical criteria	The treatment must be in combination with insulin AND The treatment must be in combination with metformin: unless contraindicated or not tolerated AND Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT-2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

Prescribers Instruction	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor, must be documented in the patient's medical records.</p>
Administrative Advice	<p>This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or an SGLT2 inhibitor.</p>

Flow on restriction change

The Administrative Advice to the existing exenatide listings need to be amended to *"This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or an SGLT2 inhibitor"*, to allow the combination use with insulin.

9 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.

10 Sponsor's Comment

The Sponsor had no comment.