

6.03 DULAGLUTIDE, Injection 1.5 mg in 0.5 mL single dose pre-filled pen, Trulicity®, Eli Lilly Australia Pty Ltd.

1 Purpose of Application

- 1.1 The major submission requested an Authority Required (STREAMLINED) listing for dulaglutide 1.5 mg once weekly (QW) for the treatment of type 2 diabetes mellitus (T2DM) in combination with insulin and metformin unless contraindicated or not tolerated.
- 1.2 The requested listing was based on a cost-minimisation analysis against exenatide 10 mcg twice daily (BID).

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Adults with type 2 diabetes mellitus inadequately controlled with insulin (and metformin, if not contraindicated or intolerant)
Intervention	Dulaglutide 1.5 mg once weekly single use pen injection, in combination with insulin (and metformin, if not contraindicated or intolerant)
Comparator	Exenatide 10 mcg twice daily, in combination with insulin (and metformin, if not contraindicated or intolerant)
Outcomes	Change from baseline to week 28/30 in HbA1c; proportion of patients achieving target HbA1c <7% or ≤6.5% at week 28/30; change from baseline to week 28/30 in fasting blood glucose, body weight; safety outcomes
Clinical claim	In patients with type 2 diabetes mellitus who have inadequate glycaemic control with insulin treatment, dulaglutide 1.5 mg once weekly is non-inferior in terms of glycaemic control (HbA1c) and safety compared to exenatide 10 mcg twice daily, when used in combination with insulin.

Source: Table 1.1-2, p17 of the submission
Abbreviations: HbA1c, glycosylated haemoglobin

2 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (Units)	No.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
Dulaglutide 1.5 mg per 0.5 mL solution for injection, 4 x 1.5 mg single use pen (auto-injector)	4	5	\$131.15 (Published) \$ [REDACTED] (Effective)	Trulicity®, Eli Lilly Australia
Category/Program:	Authority Required (STREAMLINED)			
PBS indication:	Diabetes mellitus type 2			

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Clinical criteria:	<p>The treatment must be in combination with insulin, AND</p> <p>The treatment must be in combination with metformin unless contraindicated or not tolerated, AND</p> <p>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 (SGLT2) inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR</p> <p>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 SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.</p>
Prescriber Instructions:	<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 SGLT2 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 SGLT2 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 SGLT2 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>

- 2.1 A Special Pricing Arrangement (SPA) is currently in place for the dual and triple therapy listings for dulaglutide with metformin, and with metformin and a sulfonylurea. The submission proposed that the same SPA for dulaglutide be applied to the requested listing.
- 2.2 The requested restriction for use with insulin was consistent with the PBS listings of exenatide 5 mcg and 10 mcg BID. The requested restriction was narrower than the approved TGA indication as dulaglutide must be used with insulin in combination with metformin (unless contraindicated or not tolerated), and patients must meet qualifying HbA1c or blood glucose levels. The Economics Sub-Committee (ESC) and the PBAC noted that the current restriction of exenatide BID for treatment of T2DM in combination with insulin and metformin (unless contraindicated), and therefore the proposed restriction, do not allow combination use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) with sodium-glucose co-transporter-2 (SGLT2) inhibitors (see paragraph 4.4).

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

3 Background

Registration status

- 3.1 Dulaglutide was first registered with the TGA on 19 January 2015 for the treatment of T2DM as monotherapy or in combination with metformin, metformin and a sulfonyleurea, metformin and thiazolidinedione, or prandial insulin, with or without metformin. The submission for use in combination with basal insulin was made under TGA/PBAC Parallel Process. The updated indication of dulaglutide was registered on the ARTG on 23 July 2019 for use as monotherapy or in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Previous PBAC consideration

- 3.2 The PBAC recommended dulaglutide 1.5 mg QW in November 2017 for the treatment of T2DM as dual therapy in combination with metformin, and triple therapy in combination with metformin or a sulfonyleurea.

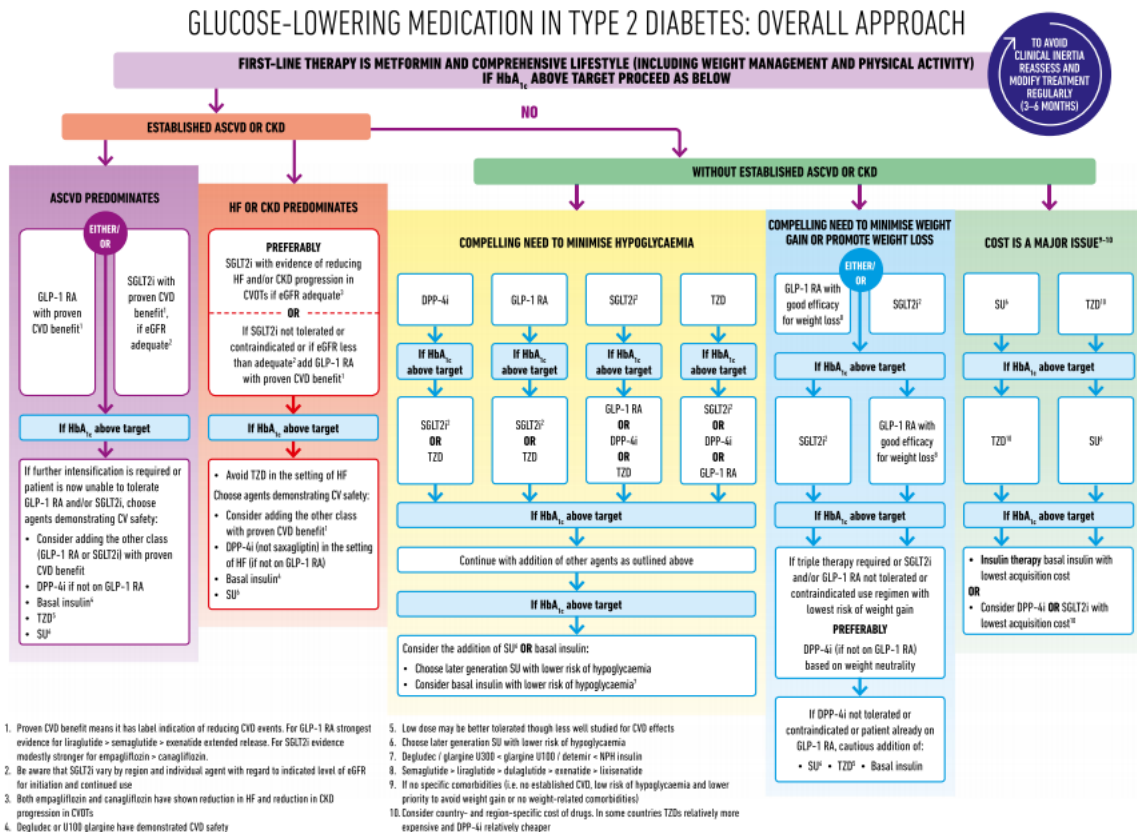
For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 Type 2 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, impaired insulin secretion or both. Complications such as cardiovascular disease and renal disease are the leading cause of morbidity and mortality in patients with T2DM, with cardiovascular disease accounting for approximately half of all mortality and disability associated with diabetes. The main goals of treatment for T2DM are to prevent or delay complications and maintain quality of life in current practice.
- 4.2 The recently published international consensus guidance on the management of diabetes from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) is shown in Figure 1. The EASD and ADA 2018 consensus statement concluded that *"the management of hyperglycaemia in type 2 diabetes has become extraordinarily complex with the number of glucose-lowering medications now available. Patient-centred decision making and support and consistent efforts to improve diet and exercise remain the foundation of all glycaemic management. Initial use of metformin, followed by addition of glucose-lowering medications based on patient comorbidities and concerns is recommended as we await answers to the many questions that remain."*
- 4.3 The submission positioned dulaglutide as an alternative to exenatide (BID formulation) for use in combination with insulin (and metformin, if not contraindicated or not tolerated) to treat T2DM in patients with inadequate glycaemic

control despite treatment with insulin (and metformin). This was broadly consistent with current PBS listings of GLP-1 analogues.

Figure 1: Management of hyperglycaemia in T2DM by the ADA and the EASD



Source: Davies M.J, et al., (2018), Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), Diabetologia vol 61, issue 12, pp2461-2498.

4.4 The PBAC noted that the recent guidance from EASD and ADA recommends earlier use of GLP-1 RAs or SGLT2 inhibitors, and use of GLP-1 RAs and SGLT2 inhibitors in combination due to cardiovascular benefits, lower risk of hypoglycaemia and weight loss benefits. Updated Australian guidelines for the management of type 2 diabetes are expected to be published by the Australian Diabetes Society (ADS) and the Royal Australian College of General Practitioners (RACGP) in 2020. The PBAC considered that the use of GLP-1 RAs in combination with SGLT2 inhibitors outside PBS restrictions was likely.

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

5 Comparator

5.1 The submission nominated exenatide 10 mcg BID as the comparator, as it was the only GLP-1 RA that was listed on the PBS for use in combination with insulin. The ESC considered exenatide BID as the most appropriate comparator, while use of insulin in

combination with other diabetes medicines (i.e. SGLT2 inhibitors and gliptins) was permitted in current PBS restrictions, exenatide BID is the existing pharmacological analogue of dulaglutide that is already listed for use with insulin, and it is administered in a similar manner.

- 5.2 In addition to injection frequency, the following clinical differences between dulaglutide and exenatide were noted:
- dulaglutide can be given to patients with severe renal impairment (creatinine clearance ≥ 15 mL/min not requiring dialysis) while exenatide is recommended for use in patients with mild or moderate renal impairment (creatinine clearance ≥ 30 mL/min).
 - the REWIND trial for dulaglutide showed a significant reduction in the primary 3-point MACE outcomes (major adverse cardiovascular events; non-fatal MI, stroke or CV-specific death) while EXSCEL trial for exenatide resulted in a non-significant reduction in MACE outcomes.

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 health care professionals (3) and organisations (1) via the Consumer Comments facility on the PBS website. The comments were supportive of the use of dulaglutide in combination with insulin, and described a range of benefits of treatment with dulaglutide QW including sustained glycaemic control, weight loss, and reduction in risk of major adverse cardiovascular events. The comments also emphasised the ease of administration of dulaglutide QW noting the fewer injections compared with exenatide BID.
- 6.3 Diabetes Queensland supported changing the existing listing of dulaglutide to include use in combination with insulin. Diabetes Queensland indicated that the hidden needle would significantly reduce fear of self-injection and therefore allow greater adherence and persistence of use. Diabetes Queensland considered that for some patients, dulaglutide QW provides effective diabetes management, resulting in fewer complications and a reduction in diabetes related hospitalisation.

Clinical trials

- 6.4 The submission was based on an indirect comparison of one dulaglutide with insulin trial (AWARD-9, n=300) and one exenatide BID with insulin trial (GWCO, n=261), with placebo with insulin as the common reference.

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

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
AWARD-9	A Randomized, Double-Blind Trial Comparing the Effect of Dulaglutide 1.5 mg with Placebo on Glycemic Control in Patients with Type 2 Diabetes on Basal Insulin Glargine (AWARD-9: Assessment of Weekly Administration of LY2189265 in Diabetes - 9)	24 February 2016
	A Randomized, Double-Blind Trial Comparing the Effect of Dulaglutide 1.5 mg with Placebo on Glycemic Control in Patients with Type 2 Diabetes on Basal Insulin Glargine (AWARD-9: Assessment of Weekly Administration of LY2189265 in Diabetes - 9)	30 January 2014
	Pozzilli et al. Placebo-controlled, randomized trial of the addition of once weekly glucagon-like peptide-1 receptor agonist dulaglutide to titrated daily insulin glargine in patients with type 2 diabetes (AWARD-9)	Diabetes Obes Metab 2017; 19: 1024-1031.
	Yu et al. Patient-reported Outcomes in Patients with Type 2 Diabetes Treated with Dulaglutide Added to Titrated Insulin Glargine (AWARD-9)	Clin Ther 2017; 39 (11): 2284-2295.
	Pantalone et al. Dulaglutide 1.5 mg as an add-on option for patients uncontrolled on insulin: Subgroup analysis by age, duration of diabetes and baseline glycated haemoglobin concentration	Diabetes Obes Metab 2018; 20: 1461-1469.
GWCO	Buse et al. Use of Twice-Daily Exenatide in Basal Insulin-Treated Patients With Type 2 Diabetes: A Randomized, Controlled Trial	Ann Intern Med 2011; 154: 103-112.
	Rosenstock et al. Baseline Factors Associated With Glycemic Control and Weight Loss When Exenatide Twice Daily Is Added to Optimized Insulin Glargine in Patients With Type 2 Diabetes	Diabetes Care 2012; 35: 955-958.
	Buse et al. Addition of exenatide twice daily to insulin glargine: a post-hoc analysis of the effect on glycemia and weight across a range of insulin titration	Curr Med Res Opin 2014; 30 (7): 1209-1218.

Source: Table 2.2-3, p47 of the submission.

6.6 The key features of the randomised trials are summarised in the table below.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Dulaglutide 1.5 mg once weekly with insulin vs placebo with insulin					
AWARD-9	300	Phase 3, multicentre, double blind, placebo-controlled, parallel group RCT (28 weeks)	Low	Type 2 diabetes with uncontrolled HbA1c on basal insulin (with or without metformin)	Change from baseline in HbA1c, FSG, body weight; HbA1c responders
Exenatide 10 mcg twice daily with insulin vs placebo with insulin					
GWCO	261	Phase 3, double blind, placebo-controlled, parallel group RCT (30 weeks)	Low	Type 2 diabetes with uncontrolled HbA1c on basal insulin (with or without metformin and/or pioglitazone)	Change from baseline in HbA1c, FPG, body weight; HbA1c responders

Source: Table 2.2-4, pp49-51 of the submission.

Abbreviations: FPG, fasting plasma glucose; FSG, fasting serum glucose; HbA1c, glycosylated haemoglobin

6.7 The trials were generally comparable, with similar design and inclusion and exclusion criteria. The AWARD-9 trial allowed metformin as background therapy, but the GWCO trial allowed the use of pioglitazone, metformin, or both as background therapy. Randomisation imbalance resulting from block randomisation by study site caused between-group differences in baseline HbA1c, sex and concomitant diabetes medications within the different treatment arms of the GWCO trial, but the trial authors noted that adjustment for these variables in the analysis of the primary outcome did not alter the results. There were some differences in the baseline treatment and patient characteristics between the two trials, including differences in baseline insulin use, which may have the potential to affect the outcome of the indirect analysis.

Comparative effectiveness

Dulaglutide + insulin versus placebo + insulin

6.8 Results for the ITT population from the AWARD-9 dulaglutide trial, for the primary outcome of least squares mean change from baseline to Week 28 in HbA1c, are presented in Table 4.

Table 4: Results of change from baseline to Week 28 in HbA1c, ITT population

AWARD-9	Dulaglutide 1.5 mg + insulin			Placebo + insulin			LS Mean difference (95% CI)
	Baseline, mean (SD) N=150	Week 28, mean (SD) N=138	Change from baseline, LSM (SE)	Baseline, mean (SD) N=150	Week 28, mean (SD) N=132	Change from baseline, LSM (SE)	
HbA1c %	8.41 (0.85)	6.66 (0.93)	-1.44 (0.09)	8.32 (0.84)	7.39 (1.00)	-0.67 (0.09)	-0.77 (-0.97,-0.56)

Source: Table 2.5-1, p74 of the submission; AWARD-9 Clinical Study Report

Abbreviations: HbA1c, glycosylated haemoglobin; LSM, least-squares mean; MRMM, mixed effect model repeat measures; SD, standard deviation; SE, standard error

Note: Treatment differences were analysed using MMRM with treatment, pooled country, metformin use, visit and treatment-by-visit interaction as fixed effects, baseline HbA1c as a covariate and patient as a random effect.

6.9 The reduction in HbA1c from baseline to Week 28 was statistically significantly greater in the dulaglutide + insulin arm compared to the placebo + insulin arm.

6.10 The proportion of patients achieving target HbA1c levels (< 7.0% or ≤ 6.5%) at week 28 are presented in Table 5.

Table 5: Proportion of HbA1c responders at week 28

HbA1c target	Dulaglutide 1.5 mg + insulin N=150	Placebo + insulin N=150	OR (95% CI)
< 7.0%, n (%)	100 (66.7)	50 (33.3)	6.42 (3.66, 11.28)
≤ 6.5%, n (%)	75 (50.0)	25 (16.7)	6.63 (3.70, 11.90)

Source: Table 2.5-2, p75 of the submission

Abbreviations: HbA1c, glycosylated haemoglobin.

6.11 The proportion of treatment responders at both HbA1c thresholds was statistically significantly higher in the dulaglutide + insulin treatment group compared with the placebo + insulin group.

6.12 Change in fasting serum glucose (FSG) levels from baseline to week 28 was also reported in the submission. The reduction in FSG was statistically significantly greater in the dulaglutide + insulin arm (LSM -2.48 (SE 0.23) mmol/L) than in the placebo + insulin arm (LSM -1.55 (SE 0.23) mmol/L; LSM difference -0.93; 95% CI -1.44, -0.41).

6.13 Patients in the dulaglutide + insulin arm experienced a mean reduction in bodyweight from baseline to week 28 (LSM -1.91 kg), while those in the placebo + insulin arm had a mean increase in bodyweight (LSM +0.50 kg), a statistically significant difference (LSM -2.41; 95%CI -3.19, -1.64).

6.14 Patient-reported outcomes (pp 67-68, 79 of the submission) were pre-specified in AWARD-9. Quality of life was measured using the Impact of Weight on Self-Perceptions (IW-SP), EuroQol 5-Dimension 5-Level (EQ-5D-5L) and EQ visual analogue scale (EQ VAS), Diabetes Health Profile (DHP-18), and the Medication Device Delivery Assessment Battery (MDDAB) questionnaires. Overall, there were no statistically significant within or between-group changes for most of the measures across the different questionnaires. There was a statistically significant difference in change from

baseline to Week 28 in IW-SP scores (Impact of Weight on Self-Perception) and the DHP-18 Disinhibited eating domain, both favouring patients in the dulaglutide arm of the trial. These results were consistent with the reduction in bodyweight observed in patients in the dulaglutide treatment arm compared with the placebo treatment arm.

Indirect comparison of dulaglutide once weekly and exenatide twice daily

6.15 Results of the indirect comparison of dulaglutide and exenatide BID for change from baseline in HbA1c at Week 28/30 are presented in Table 6.

Table 6: Results of the indirect comparison for change from baseline in HbA1c at Week 28/30

Trial	Change from baseline in HbA1c LSM (SE)			LSM (95% CI) ^a
	Dulaglutide + insulin (28 weeks)	Placebo + insulin	Exenatide + insulin (30 weeks)	
AWARD-9	N=150 -1.44 (0.09)	N=150 -0.67 (0.09)	-	-0.77 (-1.02, -0.52)
GWCO	-	N=122 -1.04 (0.09)	N=137 -1.74 (0.09)	-0.70 (-0.95, -0.45)
Indirect mean difference (95% CI)				-0.07 (-0.42, 0.28);

^a Results used in the indirect comparison were calculated using R version 3.4.2 with meta and metaphor packages for the purpose of the submission.

Source: Table 2.6-2, p93 of the submission.

Abbreviations: CI, confidence interval; LSM, least square mean; SE, standard error

6.16 There was no statistically significant difference between dulaglutide 1.5 mg QW with insulin and exenatide 10 mcg BID with insulin in reduction of HbA1c levels from baseline, with an indirect mean difference of -0.07 (95% CI -0.42, 0.28). The upper limit of the 95% confidence interval did not exceed the non-inferiority margin of 0.3%. There was a difference in HbA1c change in the placebo arms of the trials, with a smaller change from baseline noted in the AWARD-9 trial compared with the GWCO trial. The ESC considered the nominated non-inferiority margin to be appropriate.

6.17 Results of the supportive indirect comparison of dulaglutide and exenatide BID for percentage of patients achieving HbA1c targets at week 28/30 are presented in Table 7.

Table 7: Summary of results of the indirect comparison for proportion of patients reaching HbA1c targets

Trial ID	Dulaglutide + insulin (28 weeks)	Placebo + insulin	Exenatide + insulin (30 weeks)	Treatment Effect		
				RD (95% CI)	RR (95% CI)	OR (95% CI)
Percentage of patients who achieved HbA1c <7.0% at Week 28/30						
AWARD-9	100/150 (66.7)	50/150 (33.3)	-	0.33 (0.23, 0.44)	2.00 (1.55, 2.58)	4.00 (2.47, 6.46)
GWCO	-	43/122 (35.2)	82/137 (59.9)	0.25 (0.13, 0.36)	1.70 (1.29, 2.24)	2.74 (1.65, 4.54)
Indirect comparison dulaglutide 1.5 mg once weekly vs exenatide 10 mcg twice daily (all in combination with insulin)				0.09 (-0.07, 0.25)	1.18 (0.81, 1.71)	1.46 (0.73, 2.93)
Percentage of patients who achieved HbA1c ≤6.5% at Week 28/30						
AWARD-9	75/150 (50.0)	25/150 (16.7)	-	0.33 (0.23, 0.43)	3.00 (2.03, 4.44)	5.00 (2.93, 8.54)
GWCO	-	15/122 (12.3)	55/137 (40.1)	0.28 (0.18, 0.38)	3.27 (1.95, 5.47)	4.78 (2.52, 9.07)
Indirect comparison dulaglutide 1.5 mg once weekly vs exenatide 10 mcg twice daily (all in combination with insulin)				0.05 (-0.09, 0.20)	0.92 (0.48, 1.76)	1.05 (0.45, 2.41)

Note: AWARD-9 trial assessed proportion of patients with HbA1c <7.0%, while GWCO reported proportion with HbA1c ≤7.0%

Source: Table 2.6-3, p95 of the submission.

Abbreviation: RD, risk difference; RR, relative risk; OR, odds ratio

6.18 There were no statistically significant differences between dulaglutide 1.5 mg QW with insulin and exenatide 10 mcg BID with insulin in the percentage of patients who achieved HbA1c levels of < 7.0% or ≤6.5%.

6.19 The submission also presented indirect comparisons of change from baseline to Week 28/30 in fasting glucose levels and body weight. There was a statistically significantly greater reduction in fasting glucose levels in patients treated with dulaglutide 1.5 mg QW with insulin compared to exenatide 10 mcg BID with insulin (mean difference -0.83; 95% CI -1.60, -0.06). There was no statistically significant difference between treatment arms in the indirect comparison of change in body weight from baseline to Week 28/30 (mean difference 0.33; 95% CI -0.98, 1.64).

Comparative harms

6.20 Key adverse events from the AWARD-9 and GWCO trials are summarised in Table 8.

Table 8: Summary of key adverse events in the AWARD-9 and GWCO trials

	AWARD-9, 28 weeks		GWCO, 30 weeks	
	Dulaglutide + insulin N=150	Placebo + insulin N=150	Placebo + insulin N=122	Exenatide + insulin N=137
Treatment-emergent AEs, n (%)	96 (64.0)	75 (50.0)	86 (70.5)	109 (79.6)
Study drug related AEs, n (%)	36 (24.0)	8 (5.3)	NR	NR
Serious AEs, n (%)	9 (6.0)	7 (4.7)	11 (9.0)	8 (5.8)
Deaths, n (%)	0 (0)	0 (0)	1 (0.8)	0 (0)
Discontinuations due to AEs	6 (4.0)	2 (1.3)	1 (0.8)	13 (9.5)
Treatment-emergent adverse events				
Nausea	18 (12.0)	2 (1.3)	10 (8.2)	56 (40.9)
Diarrhoea	17 (11.3)	6 (4.0)	10 (8.2)	25 (18.2)
Vomiting	9 (6.0)	0	5 (4.1)	25 (18.2)
Headache	6 (4.0)	6 (4.0)	5 (4.1)	19 (13.9)
Constipation	5 (3.3)	1 (0.7)	2 (1.6)	14 (10.2)
Hypoglycaemic adverse events (FPG ≤ 3.0 mmol/L)				
Symptomatic hypoglycaemia	18 (12.0)	13 (8.7)	35 (28.7)	34 (24.8)
Nocturnal hypoglycaemia	12 (8.0)	9 (6.0)	32 (26.2)	23 (16.8)

Source: Table 2.5-14, p85; Table 2.5-15, p86; Table 2.5-16, p88 of the submission; relevant trial publications and reports
Abbreviations: AE, adverse events; CI, confidence interval; FPG, fasting plasma glucose; NR, not reported.

6.21 The submission presented an indirect comparison of safety outcomes, including overall adverse events, and GLP-1 receptor agonist-related gastrointestinal adverse events. There were no statistically significant differences in the indirect comparison of safety outcomes for dulaglutide and exenatide BID. The only exception was nausea, which was statistically significant for risk difference (RD -0.22; 95% CI -0.33, -0.11) but not for relative risk (RR 1.80; 95% CI 0.37, 8.71) or odds ratio (OR 1.30; 95% CI 0.25, 6.79). There were differences in occurrence of nausea (AWARD-9, 1.3%; GWCO, 8.2%) and other gastrointestinal adverse events in the placebo arms of the trials. There were also differences between the placebo arms of the trials for hypoglycaemic outcomes therefore, the results of the indirect comparison of safety must be interpreted with caution. The PSCR claimed that the difference in rates of nausea and hypoglycaemia could be due to the difference in the mean baseline insulin dose in the placebo arms (AWARD-9 (36.6 U/day) vs GWCO (47.4 U/day) and the time point when the two trials were performed (GWCO spanned October 2008 to January 2010 while AWARD-9 spanned May 2014 to October 2015 respectively) as the knowledge and management of nausea among people with T2DM has improved in recent years. The PSCR noted there was no difference in terms of other gastrointestinal adverse events or serious adverse events and therefore considered that the indirect comparison of safety

outcomes presented in the submission supported the clinical claim of non-inferiority safety. The ESC considered that overall, the indirect comparison across the trials; AWARD-9 and GWCO provided support for a conclusion of non-inferior safety.

Clinical claim

- 6.22 The submission described dulaglutide 1.5 mg QW as non-inferior in terms of efficacy and safety compared with exenatide 10 mcg BID, both in combination with insulin.
- 6.23 The clinical claim of non-inferiority in efficacy and safety for dulaglutide versus exenatide BID was adequately supported by the evidence in the submission. The indirect comparison of change from baseline to week 28/30 in HbA1c between dulaglutide and exenatide BID met the condition for non-inferiority. There were no non-inferiority margins specified for other outcomes, but there were no statistically significant differences between the treatment arms for proportion of HbA1c responders or change from baseline in body weight, and results were numerically in favour of dulaglutide (pp93, 94 of the submission). Change from baseline in fasting blood glucose was statistically significantly in favour of dulaglutide (mean difference -0.83; 95% CI -1.60, -0.06). There were also no statistically significant differences in the indirect comparison of key safety outcomes, including treatment-emergent adverse events, discontinuations, hypoglycaemia, and gastrointestinal adverse events. However, the results of the indirect safety comparison were difficult to interpret due to differences in event rates between the comparator arms of the trials.
- 6.24 The sponsor argued that the once-weekly formulation of dulaglutide would be particularly beneficial for patients with high clinical needs, such as Indigenous people and the elderly due to likely improved adherence. However, the submission did not present any evidence that the once-weekly formulation will result in better efficacy and safety outcomes for these patient subgroups.
- 6.25 The ESC considered there may be potential health benefits from dulaglutide QW for high clinical need patients based on improved adherence compared with exenatide BID. The ESC considered that there may be difficulty for some patients to adhere to exenatide BID due to the injection frequency, dosing schedule (60 minutes prior to morning and evening meals) and requirement for needle handling.
- 6.26 The PBAC considered that the claim of non-inferior comparative effectiveness and safety was reasonable and adequately supported by the available data.

Economic analysis

- 6.27 The submission presented a cost-minimisation analysis (CMA) comparing dulaglutide 1.5 mg QW to exenatide 10 mcg, based on a claim of non-inferior efficacy and safety of dulaglutide to exenatide BID, both in combination with insulin. Results of the cost-minimisation analysis are presented in Table 9.

- 6.28 The equi-effective doses proposed in the submission were dulaglutide 1.5 mg QW and exenatide 10 mcg BID as observed in the trials, noting that exenatide was titrated from 5 mcg BID after 4 weeks to 10 mcg BID in the GWCO trial, which aligned with the currently approved TGA dosing regimen to improve tolerability and glycaemic control.
- 6.29 The CMA was performed on a cost per week basis. The submission estimated a cost-minimised price for dulaglutide (AEMP equivalent to \$ [REDACTED] per week), calculated based on the direct cost per week for exenatide BID (AEMP equivalent to \$17.02 per week), a cost offset from reduced needle use (\$ [REDACTED]), and a price premium for improved adherence (\$ [REDACTED]). This approach assumed that the simplified dosing regimen of dulaglutide would likely translate into improved adherence, and result in better health outcomes in patients with high clinical needs (such as the elderly, indigenous people, and people with mental health disorders). Despite its claim that the once-weekly formulation of dulaglutide is particularly beneficial for these patient subgroups, the submission requested a price premium related to improved adherence be applied across all patient populations.
- 6.30 The cost offset of \$ [REDACTED] for improved adherence was pragmatically determined as the difference between the current dulaglutide AEMP and the exenatide BID AEMP and the cost offset of reduced needles per week. The submission argued that exenatide 2 mg QW was recommended with a small price advantage over exenatide 10 mcg BID, and the same circumstance should apply for dulaglutide QW with insulin (paragraph 7.4, exenatide once weekly public summary document (PSD), July 2015). The ESC considered that dulaglutide QW may improve adherence for some patients with high clinical needs due to its less frequent injections, flexible dosing schedule and ease of administration (pre-attached hidden needle) compared with exenatide BID.
- 6.31 The amount of the cost-offset for reduced needle use was calculated based on the cost of 50% of the needles required for one week's supply (equivalent to the cost of 7 needles). The submission stated that this cost was in line with previous PBAC's recommendations regarding needle use (paragraph 6.29, exenatide once weekly PSD, July 2015).

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Table 9: Results of the cost-minimisation analysis

Component	Dulaglutide	Exenatide
Cost per dose (AEMP)	\$ [REDACTED]	\$1.22
Dose frequency	Once weekly	Twice daily
Administrations per week	1	14
Total medicine cost per week	\$ [REDACTED]	\$17.02
Cost offset – needle use per week ^a	-	\$ [REDACTED]
Cost offset – adherence per week ^b	-	\$ [REDACTED]
Total health care costs per week	\$ [REDACTED]	\$ [REDACTED]

^a cost-offset for needle use per week was calculated based on the cost of 50% of the needles required for one week's supply (equivalent to the cost of 7 needles). The average cost for one needle was estimated at \$ [REDACTED], based on the average cost of needles from several Australian online diabetes supply stores (See Attachment A6.1 of the submission).

^b calculated as the difference between the cost (AEMP) of one week's treatment for exenatide 10 mcg twice daily and dulaglutide, minus the cost offset for needle use per week.

Source: Table 3.4.2, Table 3.4.3, p125 of the submission

Abbreviations: AEMP, approved ex-manufacturer price

Drug cost/patient/year

6.32 The cost per patient per year for dulaglutide 1.5 mg weekly is \$1,712.15 (published) or \$ [REDACTED] (effective). Treatment is ongoing. In comparison, the cost per patient per year for exenatide 10 mcg BID is \$1,095.35.

Table 10: Drug cost per patient for dulaglutide and exenatide twice daily

	Dulaglutide			Exenatide twice daily		
	Trial dose and duration	Cost-min	Financial estimates	Trial dose and duration	Cost-min	Financial estimates
Mean dose/week	1.5 mg	1.5 mg	1.5 mg	140 mcg ^a	140 mcg	124.6 mcg ^b
Mean duration (SD), weeks ^c	26.2 (5.5)	ongoing	ongoing	NR, trial duration 30 weeks	ongoing	ongoing
Cost/patient/year (calculated for published and effective prices for dulaglutide)^d						
Published	-	\$1,712.15	\$1,712.15	-	\$1,095.35	\$1,032.27
Effective	-	[REDACTED]	[REDACTED]	NA	NA	NA

^a The trial included a dose titration period of 4 weeks at 5 mcg / twice daily, and the remaining 26 weeks at 10 mcg/ twice daily.

^b Assumed market share of 22% exenatide 5 mcg and 78% exenatide 10 mcg; i.e. 0.22 x \$808.63 + 0.78 x \$1095.35 = \$1032.27

^c Cost-minimisation analysis and financial estimates assumed 100% compliance with both treatments.

^d Dulaglutide DPMQ published \$131.30; effective \$ [REDACTED] x 13.04 scripts/patient/year. Exenatide 5 mcg DPMQ \$66.39; 10mcg \$89.93 x 12.18 scripts/patient/year.

Source: Attachment A6.1, A7.1 of the submission; relevant trial publications and clinical study reports.

Abbreviations: Cost-min, cost-minimisation analysis; NA, not applicable; NR, not reported; SD, standard deviation

Estimated PBS usage & financial implications

- 6.33 This submission was not considered by DUSC.
- 6.34 The submission adopted a market share approach to estimate the potential utilisation and financial implications of listing dulaglutide for use with insulin. In order to derive the estimate of the market size for dulaglutide in combination with insulin, the submission estimated the number of patients for exenatide 5 mcg and 10 mcg BID with insulin in the absence of a dulaglutide listing, using a 10% Medicare sample extrapolated over the 6 years of listing.
- 6.35 Uptake of dulaglutide was assumed to come only from the exenatide 5 mcg and 10 mcg BID market, with uptake rates extrapolated from uptake of exenatide QW in the dual/triple therapy market with metformin and/or a sulfonylurea. The submission did not consider uptake from patients who would otherwise be treated with other diabetes medicines in combination with insulin (such as gliptins, SGLT2 inhibitors or alternative insulin regimens).
- 6.36 The analysis considered patients to be on treatment if a script was refilled within a 6 month period. The PSCR presented results of sensitivity analyses (Table 11 and Table 12) assuming that a lapse in treatment of 3, 9, and 12 months represented a gap in treatment, and claimed that based on these analyses, the length of the period used to estimate a gap in treatment has minimal impact on the financial estimates. The PBAC considered the use of a 6 month gap to represent a gap in treatment to be uncertain, noting that there is wide variation in average units of insulin use reported in the literature.

Table 11: Sensitivity Analysis: Patient estimates by allowance period for repurchasing insulin or EBID

Allowance period for repurchasing Insulin or EBID					
	3 months	6 months	9 months	12 months	DUSC
June 2016	EBID with insulin	EBID with insulin	EBID with insulin	EBID with insulin	EBID with insulin
Number of patients	████	████	████	████	████
Increase compared to 6 months	-22.8%	-	21.8 %	36.2%	- 6.7%

EBID = exenatide twice daily;

Note: The number of patients reflects exenatide BID in combination with any insulin (i.e. basal and bolus)

Table 12: Net cost for the health budget by allowance period (3, 6, 9 and 12 months)

Net cost (effective) excluding copayments	2020	2021	2022	2023	2024	2025
3 months	████	████	████	████	████	████
6 months	████	████	████	████	████	████
9 months	████	████	████	████	████	████
12 months	████	████	████	████	████	████

- 6.37 Estimated use and financial implications are presented in Table 13.

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Table 13: Estimated use and financial implications

	Year 1 (2020)	Year 2 (2021)	Year 3 (2022)	Year 4 (2023)	Year 5 (2024)	Year 6 (2025)
Extrapolated utilisation of exenatide 5 mcg and 10 mcg twice daily (with insulin) in absence of dulaglutide						
Total exenatide patients	████	████	████	████	████	████
Uptake of dulaglutide (with insulin) from exenatide 5 mcg and 10 mcg (13.04 scripts/patient/year)						
Estimated uptake rate of dulaglutide	██%	██%	██%	██%	██%	██%
Total dulaglutide patients	████	████	████	████	████	████
Total dulaglutide scripts	████	████	████	████	████	████
Cost of dulaglutide scripts (effective) ^a	████████	████████	████████	████████	████████	████████
Patient copayments	████	████	████	████	████	████
Total cost (effective) excluding copayments	████	████	████	████	████	████
Change in number of exenatide 5 mcg and 10 mcg twice daily scripts (12.18 scripts/patient/year)						
Total exenatide scripts	████	████	████	████	████	████
Total cost of substituted exenatide ^b	████████	████████	████████	████████	████████	████████
Total patient copayments	████	████	████	████	████	████
Total cost (excluding copay)	████	████	████	████	████	████
Net cost to the PBS/RPBS						
Net cost (effective) excluding copayments	████	████	████	████	████	████

Note: Scripts per patient per year for dulaglutide and exenatide were based on the script duration (28 days for dulaglutide, 30 days for exenatide) and assuming 100% compliance.

^a Dulaglutide DPMQ effective \$████

^b Exenatide 5 mcg DPMQ \$66.39; 10 mcg DPMQ \$89.93

Source: Attachment A7.1_Dulaglutide Section 4 Model.xlsx of the submission.

6.38 The net cost of listing dulaglutide was less than \$10 million at year 1, increasing to less than \$10 million at year 6, a cumulative total of \$less than \$10 million in the first 6 years of listing. The net increase in costs to the PBS/RPBS was due to the proposed price advantage for dulaglutide over exenatide BID.

6.39 Overall, the submission's calculations of budget impact were substantially underestimated for the following reasons:

- The submission's estimates of the size of the dulaglutide QW with insulin market were based on the size of the existing market for exenatide BID with insulin. This approach would most likely lead to the significant underestimation of market share and utilisation given that the market size for dulaglutide with

insulin is expected to be substantially larger than that of exenatide BID with insulin.

- The submission estimated the number of patients for dulaglutide with insulin, based on the projected number of patients for exenatide BID (both 5 mcg and 10 mcg strengths) in the existing market. However, among 422,101 patients with diabetes who were registered with the National Diabetes Services Scheme (NDSS) as insulin users (Diabetes data snapshots, September 2019¹), 281,419 patients with T2DM required insulin in Australia. This implicitly indicated the potential for greater patient numbers due to higher than predicted number of eligible patients with T2DM where insulin treatment is necessary.
- The submission estimated uptake rate of ■% at year 1, increasing to ■% at year 6, based on the assumption that the same pattern of uptake for exenatide once weekly in dual/triple therapy with metformin and/or sulfonylurea will be observed for dulaglutide with insulin. However, most clinicians may prefer to add dulaglutide to the treatment regimens for patients with inadequate glycaemic control on insulin (and metformin), or switch to dulaglutide for patients already receiving exenatide BID due to the simplified dosing regimen of dulaglutide compared with exenatide BID. The PBAC therefore considered that the majority of patients receiving treatment with exenatide BID and insulin would likely be switched to dulaglutide QW and insulin following extension of the current dulaglutide restriction to include combination use with insulin.
- The submission did not consider uptake of dulaglutide by patients who would otherwise be treated with other diabetes medicines in combination with insulin (such as gliptins, SGLT2 inhibitors or alternative insulin regimens). Since its PBS listing in June 2018, use of dulaglutide in the dual/triple therapy market with metformin or metformin and a sulfonylurea has rapidly increased and overtaken utilisation of exenatide BID and exenatide QW, while the overall use of exenatide has remained relatively stable over that same time period, suggesting that dulaglutide substitutes for other diabetes therapies as well as exenatide. As such, it is possible that uptake of dulaglutide in combination with insulin will also come from patients currently using other oral therapies with PBS restrictions permitting use with insulin. Overall, the PBAC considered the market growth rate from listing dulaglutide for use with insulin to be significantly higher than the predicted in the submission (approximately ■% per annum).

Quality Use of Medicines

¹ <https://www.ndss.com.au/about-the-ndss/diabetes-facts-and-figures/diabetes-data-snapshots/>

- 6.40 The submission detailed a number of quality use of medicines activities supporting the appropriate use of dulaglutide, tailored towards endocrinologists, GPs and credentialed diabetes educators. The submission suggested there would likely be a focus on recent changes to treatment guidelines including the role of GLP-1 receptor agonists in place of therapy, and individualisation of care to account for important phenotypic, behavioural and clinical characteristics.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making a recommendation to extend the existing listing of dulaglutide 1.5 mg once weekly (QW) to include the treatment of type 2 diabetes mellitus (T2DM) in combination with insulin and metformin unless contraindicated or not tolerated. This was to request revision of the financial estimates that the PBAC considered to be uncertain and likely to be significantly underestimated.
- 7.2 The PBAC considered exenatide BID was the appropriate main comparator.
- 7.3 The PBAC noted the benefits of dulaglutide QW described in the consumer comments and emphasis on ease of administration compared with exenatide BID. The PBAC considered there were potential health benefits associated with the simplified QW dosing regimen of dulaglutide based on improved adherence compared with exenatide BID, for some patients with high clinical needs such as the elderly, indigenous people, and people with mental health disorders. The PBAC also noted that dulaglutide can be used in patients with severe renal impairment, which may make it a more appropriate choice for some high clinical need populations.
- 7.4 The PBAC noted the submission was based on an indirect comparison of one dulaglutide with insulin trial (AWARD-9, n=300) and one exenatide BID with insulin trial (GWCO, n=261), with placebo with insulin as the common reference. The PBAC considered the claim of non-inferior effectiveness for dulaglutide QW versus exenatide BID was adequately supported, noting there was no significant difference in reduction of HbA1c levels HR -0.07, 95% CI -0.42, 0.28 at Week 28/30, and the upper limit of the 95% confidence interval did not exceed the non-inferiority margin of 0.3%.
- 7.5 The PBAC noted there were no significant differences in the indirect comparison of safety outcomes with the exception of a higher incidence of nausea in the exenatide BID + insulin arm of the GWCO trial. The PBAC noted there was some uncertainty in the interpretation of the indirect comparison of safety due to differences in occurrence of nausea, other gastrointestinal adverse events and hypoglycaemia in the placebo arms of the trials. However overall, the PBAC was satisfied that the safety of dulaglutide QW is likely similar to exenatide BID.
- 7.6 The PBAC considered the equi-effective doses are dulaglutide 1.5 mg QW and exenatide 10 mcg BID.

- 7.7 The PBAC considered it was reasonable to incorporate a cost-offset for reduced needle use in the cost-minimisation analysis against exenatide BID. The PBAC noted the cost-offset was calculated based on the cost of 50% of the needles required for one week's supply, which is consistent with the Committee's previous advice around a reasonable basis for a claimed offset in its consideration of exenatide (Exenatide PSD, November 2013).
- 7.8 The PBAC noted that the submission requested a price advantage of \$ [REDACTED] per week on the basis of potential health benefits from likely improved adherence in a small number of patient populations with high clinical needs. The PBAC considered that a small price advantage for high clinical need populations was appropriate, however the PBAC considered that any price advantage applied should only account for the proportion of patients with high clinical needs who are likely to benefit from the simplified dosing regimen of dulaglutide QW. Noting that the price advantage requested was not determined based on the proportion of patients with high clinical needs, the PBAC considered that the price advantage for dulaglutide QW requested over exenatide BID was not warranted.
- 7.9 The PBAC considered the estimated financial impact of extending the current listing of dulaglutide to include use in combination with insulin was substantially underestimated due to underestimates in patient numbers, market share and market growth. The PBAC noted the estimated number of patients utilising dulaglutide was less than 10,000 in Year 1 increasing to less than 10,000 in Year 6. Noting there are 281,419 patients with T2DM requiring insulin therapy registered with the National Diabetes Services Scheme in 2019, and considering the uptake of dulaglutide QW was likely to be high, the PBAC considered that utilisation would be substantially higher than estimated. The PBAC considered that a majority of prescribers would likely substitute exenatide BID with dulaglutide QW in patients currently treated with exenatide BID in combination with insulin given the more convenient dosing schedule. Further, the PBAC considered that the dulaglutide market would likely grow beyond estimated in the submission, noting the changes in clinical place for GLP-1 RA therapies (see paragraph below).
- 7.10 The PBAC agreed with the view of the EASD and ADA in the 2018 consensus statement that the management for type 2 diabetes has become increasingly complex due to the vast number of diabetes medicines available and continuous change in guidelines overseas. The PBAC noted that the new Australian guidelines for the management of type 2 diabetes to be published in 2020 are likely to be similar to the ADA/EASD guidelines. The PBAC considered that it may be appropriate to review the listings of medicines for type 2 diabetes once the guidelines are updated. The PBAC considered that use of dulaglutide in combination with SGLT2 inhibitors (i.e. outside the PBS restrictions), which is recommended by EASD and ADA due to cardiovascular benefits, lower risk of hypoglycaemia and weight loss benefits was likely.

7.11 In deferring making its decision on whether to extend the current listing of dulaglutide to include use in combination with insulin, the PBAC considered the following issues would need to be addressed:

- Any requested price advantage over exenatide BID should be proportionate to the small number of high clinical need populations who may experience health benefits from likely improved adherence with dulaglutide QW.
- Revised financial estimates would be required to address the issues around the estimates outline in paragraph 7.9.

Outcome:

Deferred

8 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

9 Sponsor's Comment

The sponsor had no comment.