

## 5.06 DULAGLUTIDE, Solution for injection 1.5 mg in 0.5 mL, Trulicity®, Eli Lilly Australia Pty Ltd

### 1 Purpose of application

- 1.1 To request an Authority required (STREAMLINED) listing for dulaglutide 1.5mg once weekly for the treatment of type 2 diabetes mellitus as dual therapy in combination with metformin and triple therapy in combination with metformin and sulfonylurea.
- 1.2 The submission was based on cost-minimisation analyses to a main comparator exenatide once weekly (QW) and a supplementary comparator exenatide twice daily (BID).

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

Component	Description
Population	Patients with T2DM who are not achieving adequate glycaemic control with metformin or metformin and a sulfonylurea (dual therapy with metformin only if the patient is contraindicated/intolerant to a combination of metformin and a sulfonylurea).
Intervention	Dulaglutide, 1.5mg injection in a single use pre-filled pen (autoinjector), administered once weekly in combination with metformin (dual therapy) and in combination with metformin and a sulfonylurea (triple therapy).
Comparator	Primary: Exenatide 2mg injection, administered once weekly. Supplementary: Exenatide 10µg injection, administered twice daily.
Outcomes	Change in HbA1c% from baseline to week 26; change in fasting blood glucose baseline to week 26; patients achieving target HbA1c <7% at week 26; patients achieving target HbA1c ≤6.5% at week 26; change in bodyweight from baseline to week 26; safety outcomes.
Clinical claim	<u>vs. exenatide QW</u> : Dulaglutide, as part of a triple therapy with metformin and sulfonylurea is statistically significantly better than exenatide QW for reduction in HbA1c at 26 weeks. As part of a dual therapy with metformin, there is no difference in HbA1c reduction profiles between dulaglutide and exenatide QW. The Pre-Sub Committee Response (PSCR) (p4) adjusted the clinical claim to non-inferior efficacy and safety in both triple and dual therapy settings. <u>vs. exenatide BID</u> : Dulaglutide, as part of triple therapy with metformin and sulfonylurea is statistically significantly better than exenatide BID for reduction in HbA1c at 26 weeks. As part of dual therapy with metformin, dulaglutide is statistically significantly better than exenatide BID for HbA1c reduction at 26 weeks. Dulaglutide has a similar safety profile to exenatide QW and exenatide BID.

BID=twice daily; QW=once weekly

Source: Table 1.1.1 p2-3 of the submission.

## 2 Requested listing

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
DULAGLUTIDE Solution for injection 1.5 mg in 0.5mL	1	4 single use pen (auto-injector)	5	\$ [REDACTED] <sup>a,b</sup>	Trulicity®, Eli Lilly Australia Pty Ltd

<sup>a</sup> The requested DPMQ was \$ [REDACTED] in the submission, which matched the published PBS price for exenatide QW at the time of submission lodgement. The DPMQ has been updated based on the current DPMQ for exenatide QW.

<sup>b</sup> The submission requests a special pricing arrangement. Exenatide QW has a special pricing arrangement.

### (Abbreviated version)

<b>Category / Program</b>	General Schedule Authority Required (STREAMLINED)
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS indication:</b>	Diabetes mellitus type 2
<b>Treatment phase:</b>	N/A
<b>Restriction:</b>	<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
<b>Treatment criteria:</b>	N/A
<b>Dual combination therapy with metformin</b>	
<b>Clinical criteria:</b>	The treatment must be in combination with metformin AND Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR Patient must not have tolerated a combination of metformin and a sulfonylurea, 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 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea
<b>Triple combination therapy with metformin and a sulfonylurea</b>	
<b>Clinical criteria:</b>	The treatment must be in combination with metformin AND The treatment must be in combination with a sulfonylurea 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 (SGLT2) inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea

## 3 Background

### Registration status

3.1 Dulaglutide was registered by the TGA on 19 January 2015. The TGA indication is as follows:

- Dulaglutide is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus:
  - As monotherapy.

- In combination with the following oral glucose-lowering medications: metformin, metformin and sulfonylurea; metformin and thiazolidinedione.
  - In combination with prandial insulin, with or without metformin.
- 3.2 The submission requested PBS listing for only a portion of the approved TGA indication, specifically for use in combination with metformin or in combination with metformin and a sulfonylurea.

## **4 Population and disease**

- 4.1 Diabetes mellitus is a group of complex metabolic disorders characterised by impaired insulin secretion and variable degrees of peripheral insulin resistance leading to hyperglycaemia. In type 2 diabetes, insulin resistance is typically accompanied by inadequate insulin secretion. Complications such as cardiovascular disease and renal disease are substantial contributors to overall mortality, with cardiovascular disease accounting for approximately half of all mortality and disability associated with diabetes.
- 4.2 If dulaglutide is listed on the PBS as proposed, the submission considered it would be another treatment option when a glucagon-like peptide 1 receptor agonist (GLP-1 RA) is deemed appropriate. The submission described the treatment algorithm for type 2 diabetes as developed by the Australian Diabetes Society (ADS). In this algorithm, metformin should be considered for first-line therapy unless contraindicated or not tolerated; second-line treatment adds a sulfonylurea to metformin; and for third-line treatment, triple oral therapy or addition of a GLP-1 RA or insulin is recommended.

## **5 Comparator**

- 5.1 The submission nominated exenatide once weekly (QW) as the main comparator. Exenatide QW is a once weekly pharmacological analogue of dulaglutide that also has the same mode and frequency of administration. The main reason provided for this nomination was that exenatide QW is considered to be the closest analogue and is the therapy that prescribers would most likely replace with dulaglutide. The submission also nominated exenatide twice daily (BID) as a supplementary comparator.
- 5.2 The evaluation and ESC considered that the nomination of exenatide QW and BID as comparators was reasonable. The PBAC did not accept the sponsor's approach to making exenatide QW and exenatide BID a main and a supplementary comparator, rather considering that they were different dosing regimens of the same comparator. The PBAC recalled that, in July 2015, it had recommended exenatide 2 mg once weekly for dual combination therapy with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea in patients with T2DM, on a cost-minimisation basis with exenatide 10 mcg twice daily with a cost offset for reduced needle use and a further small price advantage on the basis of potential health benefits from likely improved adherence by a small number of high clinical need populations. At that time, the PBAC considered that the data available for exenatide supported exenatide 2 mg once weekly being at least non-inferior to

exenatide 10 mcg twice daily in terms of efficacy (based on mean change in HbA1c from baseline) and non-inferior in terms of safety.

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 a health care professional (1) via the Consumer Comments facility on the PBS website. The comment described a range of benefits of treatment with dulaglutide including the smaller bore needle and the lack of mixing requirements.

### Clinical trials

6.3 The submission was based on a total of four dulaglutide trials and seven exenatide trials, with four comparisons made, in dual therapy versus exenatide QW and versus exenatide BID; and in triple therapy versus each comparator.

6.4 The submission presented four complete clinical sections; one for each of the comparisons identified above. Three of the comparisons were based on indirect comparisons (versus exenatide QW in triple therapy; versus exenatide QW in dual therapy; versus exenatide BID in dual therapy) while the fourth (versus exenatide BID in triple therapy) was based on a head-to-head trial. A fifth clinical section was presented as an attachment to the submission, providing an indirect comparison versus exenatide BID in triple therapy.

6.5 Details of the trials presented in the submission are provided in the table below. For the dulaglutide trials, only the key publications of the trial are included in this table.

**Table 2: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>Direct randomised trial</b>		
AWARD-1	A Randomized, Placebo-Controlled Comparison of the Effects of Two Doses of LY2189265 or Exenatide on Glycemic Control in Patients with Type 2 Diabetes on Stable Doses of Metformin and Pioglitazone (AWARD-1: Assessment of Weekly Administration of LY2189265 in Diabetes-1). Wysham C, et al. Efficacy and safety of dulaglutide added onto pioglitazone and metformin versus exenatide in Type 2 Diabetes in a randomized controlled trial (AWARD-1)	15 July 2013  Diabetes Care 2014;37: 2159–2167
<b>Trials included in the indirect comparisons</b>		
AWARD-2	Phase 3, open-label comparator (double-blind with respect to LY2189265 dose assignment), multicentre, parallel-arm, randomized, 78-week treatment study to compare the safety and efficacy of 2 doses of LY2189265 to insulin glargine in patients with type 2 diabetes mellitus who were on stable doses of metformin and glimepiride Giorgino et al., Efficacy and safety of once-weekly dulaglutide versus insulin glargine in patients with type 2 diabetes on metformin and glimepiride (AWARD-2)	6 September 2013  Diabetes Care 2015; 38:2241–2249
AWARD-5	Phase 2/3, multicentre, randomized, placebo- controlled, 24-month,	9 July 2013

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Trial ID	Protocol title/ Publication title	Publication citation
	double-blind, parallel study comparing once weekly dulaglutide (0.25 to 3.0 mg) to once-daily sitagliptin (100 mg) in patients with type 2 diabetes mellitus on metformin Nauck et al., Efficacy and safety of dulaglutide versus sitagliptin after 52 weeks in type 2 diabetes in a randomised controlled trial (AWARD-5)	Diabetes Care 2014; 37: 2149-2158
GBDK	The efficacy and safety of once-weekly, subcutaneous dulaglutide compared to once-daily insulin glargine in patients with type 2 diabetes mellitus on metformin and/or a sulphonylurea.	29 March 2017
DURATION-2	Bergenstal et al., 2010, 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, 376: 431-439
DURATION-3	Diamant M, Van Gaal L, Stranks S, Northrup J, Cao D, Taylor K and Trautmann M. Once weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes (DURATION-3): an open-label randomised trial. Buse JB, Peters A, Russell-Jones D, Furber S, Donsmark M, Han J, Macconell L, Maggs D, Diamant M. Is insulin the most effective injectable antihyperglycaemic therapy? Diamant M, Van Gaal L, Guerci B, Stranks S, Han J, Malloy J, Boardman MK, Trautmann ME. Exenatide once weekly versus insulin glargine for type 2 diabetes (DURATION-3): 3-year results of an open-label randomised trial.	The Lancet 2010; 375 (9733):2234-2243 Diabetes, Obesity and Metabolism 2015; 17 (2):145-151 The Lancet Diabetes and Endocrinology 2014; 2 (6):464-473
Apovian 2010	Apovian CM, Bergenstal RM, Cuddihy RM, Qu Y, Lenox S, Lewis MS and Glass LC. Effects of Exenatide Combined with Lifestyle Modification in Patients with Type 2.	Diabetes American Journal of Medicine 2010; 123 (5):468.e9-468.e17
Derosa 2013	Derosa G, Franzetti I, Querci G, Carbone A, Ciccarelli L, Piccinni M, Fogari E, Maffioli P. Variation in inflammatory markers and glycemic parameters after 12 months of exenatide plus metformin treatment compared with metformin alone: A randomized placebo-controlled trial.	Pharmacotherapy 2013; 33 (8):817-26
DeFronzo 2005	DeFronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2.	Diabetes Care 2005; 28 (5):1092-1100
Davies 2009	Davies MJ, Donnelly R, Barnett AH, Jones S, Nicolay C and Kilcoyne A. Exenatide compared with long-acting insulin to achieve glycaemic control with minimal weight gain in patients with type 2 diabetes: Results of the helping evaluate exenatide in patients with diabetes compared with long-acting insulin (HEELA) study.	Diabetes, Obesity and Metabolism 2009; 11 (12):1153-1162
Heine 2005	Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: A randomized trial.	Annals of Internal Medicine 2005; 143 (8):559-569+I30

Source: Table B11.7, p11-13 of Section Bii of the submission.

6.6 The key features of the randomised trials included in the indirect comparisons, along with the one head-to-head trial are summarised in the table below. Trials are presented according to the comparison they were applied to.

Table 3: Key features of the included evidence

Trial	N	Design/ duration of follow-up	Risk of bias	Patient population	Outcomes
<b>Main comparator - exenatide QW</b>					
<b>Triple therapy - dulaglutide vs. exenatide QW - indirect comparison (glargine as common reference)</b>					
AWARD-2	535	R, DB, OL, PG, MC/ 78 weeks trial duration	High	Adults with type 2 diabetes; HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ for patients on monotherapy and $\geq 7.0\%$ and $\leq 10.0\%$ for patients on combination oral therapy	Change from baseline in HbA1c at 26 weeks
GBDK	517	R, DB, OL PG, MC/ 52 weeks trial duration	High	Adults with type 2 diabetes; HbA1c 7.0% to 11.0%.	
DURATION-3	461	R, OL, PG /26 weeks trial duration; extension to 156 weeks	High	Adults with type 2 diabetes; HbA1c 7.1% to 11.0%.	
<b>Dual therapy - dulaglutide vs. exenatide QW - indirect comparison (sitagliptin as common reference)</b>					
AWARD-5	796	R, DB, PG, PC, MC with two stages /104 weeks trial duration	Low	Adults with type 2 diabetes; HbA1c 7.0% to 11.0%.	Change from baseline in HbA1c at 26 weeks
DURATION-2	331	R, DB, PG/26 weeks trial duration	Low		
<b>Supplementary comparator - exenatide BID</b>					
<b>Triple therapy - dulaglutide vs. exenatide BID - head-to-head comparison</b>					
AWARD-1	696	R, DB, OL, PC, PG/64 weeks trial duration	High	Adults with type 2 diabetes; HbA1c $\geq 7.0\%$ and $\leq 11.0\%$ for patients on monotherapy and $\geq 7.0\%$ and $\leq 10.0\%$ for patients on combination oral therapy	Change from baseline in HbA1c at 26 weeks
<b>Dual therapy - dulaglutide vs. exenatide BID - indirect comparison (placebo as common reference)</b>					
AWARD-5	As above				
DeFronzo 2005	336	R, TB, PC, MC/30 weeks trial duration	Low	Adults with type 2 diabetes; HbA1c 7.0% to 9.5%	Change from baseline in HbA1c at 26 weeks
Apovian 2010	194	R, DB, PC, PG, MC/24 weeks trial duration	Low	Adults with type 2 diabetes; HbA1c 6.6% to 10.0%	
Derosa 2013	171	R, DB, PC, MC/12 months trial duration	Low	Adults with type 2 diabetes; HbA1c $\geq 7.5\%$	
<b>Trials included in supplementary indirect comparison vs. exenatide BID in triple therapy</b>					
Davies 2009	235	R, OL, MC/26 weeks follow-up	High	Adults with type 2 diabetes; HbA1c 7.5% to 10.0%	Change from baseline in HbA1c at 26 weeks
Heine 2005	549	R, OL, MC/26 weeks follow-up	High	Adults with type 2 diabetes; HbA1c 7.0% to 10.0%	

DB=double-blind; MC=multicentre; OL=open label; R=randomised; TB=triple-blind

Source: Table 2(a).2-2, p46-47; Table 2(a).3-1, p49-50; Table 2(b).2-2, p120-21; Table 2(b).3-1, p122; Table 2(c).2-2, p160-61; Table 2(c).3-1, p163-64; Table 2(d).2-2, p216-17; Table 2(d).3-1, p215-16 of the submission and Table 2(e).2-2, p6-7; Table 2(e).3-1, p9-10 of 8.1 Section 2e\_Triple appendix provided with the submission.

6.7 The AWARD-2, GBDK and AWARD-1 trials were only blinded in regard to dose level of dulaglutide and exenatide that was provided open label. Given the open label nature of treatment, these trials were considered to be at high risk of bias.

6.8 All trials contained other glycaemic outcomes, i.e. change in fasting blood glucose, occurrence of hypoglycaemia, but as the focus of the efficacy comparisons in the submission was change from baseline in HbA1c at 26 weeks, that is the only outcome included in the table.

## Comparative effectiveness

6.9 The table below provides the results for the indirect comparison of dulaglutide and the main comparator exenatide QW in triple therapy.

**Table 4: Results of the indirect comparison in triple therapy versus the main comparator exenatide QW**

Trial	Change from baseline in HbA1c at 26 weeks LSM (SE)			LSM (95% CI)
	Dulaglutide	Common reference glargine	Exenatide QW	
AWARD-2	██████████	██████████	█	██████████
GBDK	██████████	██████████	█	██████████
			██████████	██████████
DURATION-3	█	██████████	██████████	██████████
				Indirect WMD (95% CI) ██████████

LSM=least square means; QW=once weekly; SE=standard error; WMD=weighted mean difference  
Source: Table 2(a).6-2, p88 of the submission.

6.10 While there was a statistically significantly greater decrease in HbA1c for dulaglutide compared to exenatide QW at week 26 in change from baseline in HbA1c, the difference was not significant at the later time point of 78/84 weeks, based on an indirect comparison of AWARD-2 and DURATION-3 (WMD=██████; 95% CI: ██████).

6.11 Results for proportion of patients achieving target HbA1c <7.0%, proportion achieving target HbA1c ≤6.5%, and change from baseline in fasting blood glucose all showed statistically significant advantages for dulaglutide. In contrast, change in body weight showed a statistically significantly greater decrease for exenatide QW (WMD=██████████) at both weeks 26 and week 78/84. The ESC noted that the PSCR (p3) claimed that HbA1c reduction is the outcome that PBAC has previously used to judge the clinical claim for exenatide, (Exenatide PSD July 2011 and November 2013) and that weight loss is not the primary aim of GLP-1 therapy (Exenatide PSD 2008).

6.12 The results of this comparison in relation to triple therapy should be interpreted with caution given that only 30% of patients in the exenatide trial (DURATION-3) were on triple therapy. The submission argued (p83) that this is a conservative approach as it is likely that the incremental response to treatment is likely to be reduced as more therapies are added. However, since the comparison was intended for triple therapy, it would appear appropriate for triple therapy trials to be required, arguments around impact on response when a third therapy is added therefore are not relevant. Instead of the comparison conducted in the submission being conservative, it was actually not a valid comparison for triple therapy as only a small proportion of patients in DURATION-3 were on triple therapy. Consequently, the results do not provide strong support regarding the difference between dulaglutide and exenatide QW in triple therapy.

6.13 The ESC noted that the PSCR (p2) provided a comparison between the whole population in the GBDK (dulaglutide) trial on the basis that this trial most closely matched the DURATION-3 (exenatide) trial in that █████% were on dual therapy. These results indicated a statistically significant greater reduction in HbA1c for dulaglutide

( [REDACTED] ) compared to exenatide once weekly.

6.14 The table below provides the results for the indirect comparison of dulaglutide and the main comparator exenatide QW in dual therapy.

**Table 5: Results of the indirect comparison in dual therapy versus the main comparator exenatide QW**

Trial	Change from baseline in HbA1c at 26 weeks LSM (SE)			LSM (95% CI)
	Dulaglutide	Common reference sitagliptin	Exenatide QW	
AWARD-5	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
DURATION-2	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
<b>Indirect comparison</b>				[REDACTED]

LSM=least square means; QW=once weekly; SE=standard error; WMD=weighted mean difference  
Source: Table 2(c).6-2, p196 of the submission.

6.15 The indirect comparison demonstrated no statistically significant difference in change from baseline in HbA1c at 26 weeks between dulaglutide and exenatide QW. Similarly, results for proportion of patients achieving target HbA1c <7.0%, proportion achieving target HbA1c ≤6.5%, change from baseline in fasting blood glucose and change in body weight all showed no statistically significant differences for dulaglutide and exenatide QW.

6.16 The table below provides the results for the comparison of dulaglutide and the supplementary comparator exenatide BID in triple therapy. This was a direct comparison in the head-to-head trial AWARD-1.

**Table 6: Results of the direct comparison of dulaglutide and exenatide BID (supplementary comparator) in triple therapy**

Analysis	Dulaglutide 1.5mg N=279	Exenatide BID N=276	LSM (95% CI)
Change from baseline in HbA1c at week 26 LSM (SE)	-1.51 (0.06)	-0.99 (0.06)	<b>-0.52 (-0.66, -0.39)</b>

LSM=least square means; QW=once weekly; SE=standard error; WMD=weighted mean difference  
Source: Table 2(b).5-1, p136 of the submission.

6.17 The analysis showed a statistically significant advantage for dulaglutide compared to exenatide BID. This advantage was maintained at the week 52 analysis. Results for proportion of patients achieving target HbA1c <7.0%, proportion achieving target HbA1c ≤6.5% and change from baseline in fasting blood glucose all showed statistically significant advantages for dulaglutide compared to exenatide BID. For change in body weight, there was no statistically significant difference between dulaglutide and exenatide BID.

6.18 The relevance of the AWARD-1 trial was limited given that the background therapy used was metformin plus pioglitazone, which does not correspond to the requested PBS restriction (metformin+sulfonylurea). The submission argued that metformin+pioglitazone and metformin+sulfonylurea have similar impacts on change in HbA1c, citing published papers. The submission also provided, in an attachment to the submission, another complete Section 2 containing a supportive indirect comparison of dulaglutide and exenatide BID. Results of that comparison are provided below.

**Table 7: Results of the supportive indirect comparison in triple therapy versus the supplementary comparator exenatide BID**

Trial	Change from baseline in HbA1c at 26 weeks LSM (SE)			LSM (95% CI)
	Dulaglutide	Common reference glargine	Exenatide BID	
AWARD-2				
GBDK				
				WMD=
Heine 2005				
Davies 2009				
<b>Indirect WMD (95% CI)</b>				<b>WMD=</b>

LSM=least square means; QW=once weekly; SE=standard error; WMD=weighted mean difference  
 Source: Table 2(e).6-2, p50 of Attachment 8, Section 2(e) of the submission

6.19 The indirect comparison demonstrated a statistically significant advantage for dulaglutide compared to exenatide BID in triple therapy. Additional indirect comparisons presented in the submission's attachment showed statistically significant advantages for dulaglutide compared to exenatide BID for proportion of patients achieving target HbA1c of 7.0%, and for reduction in fasting plasma glucose. The indirect comparison for change in body weight (including only AWARD-2 for dulaglutide) showed a statistically significantly greater loss of weight with exenatide BID than with dulaglutide (WMD=). This corresponded to the result in the indirect comparison of triple therapy with the main comparator exenatide QW. The results of this indirect comparison have more relevance to the requested restriction than the results from the head-to-head trial AWARD-1 which used a background therapy combination (metformin+pioglitazone) that was not relevant to the requested restriction.

6.20 The table below provides the results for the indirect comparison of dulaglutide and the supplementary comparator exenatide BID in dual therapy.

**Table 8: Results of the indirect comparison in dual therapy versus the supplementary comparator exenatide BID**

Trial	Change from baseline in HbA1c at 26 weeks LSM (SE)			LSM (95% CI)
	Dulaglutide	Common reference placebo	Exenatide BID	
AWARD-5				
DeFronzo 2005				
Apovian 2010				
Derosa 2013				
<b>Pooled exenatide I<sup>2</sup>=68%; p=0.04</b>				<b>WMD=-</b>
<b>Indirect WMD (95% CI)</b>				<b>WMD=</b>

LSM=least square means; QW=once weekly; SE=standard error; WMD=weighted mean difference  
 Source: Table 2(d).6-2, p268 of the submission.

- 6.21 The pooling of the exenatide BID trials demonstrated significant heterogeneity ( $I^2=68\%$ ;  $p=0.04$ ). While the submission acknowledged the heterogeneity (p259) and provided discussion of differences in change in the placebo group across the exenatide trials, differences in diet and exercise and differences in baseline HbA1c levels the submission did not directly account for the potential impact of the heterogeneity on the indirect comparison.
- 6.22 The ESC noted that the PSCR (p3) provided a further analysis comparing AWARD-5 to the DeFronzo trial to examine the issue of heterogeneity, on the basis that the DeFronzo trial with exenatide more closely matched the AWARD-5 trial with dulaglutide. The results supported a smaller statistically significant benefit for dulaglutide for change in HbA1c compared to exenatide BID ( [REDACTED] ). The ESC also noted that this analysis had not been independently evaluated.
- 6.23 For proportion of patients achieving target HbA1c <7.0% the indirect comparison demonstrated no statistically significant difference between dulaglutide and exenatide BID while for proportion achieving target HbA1c  $\leq 6.5\%$  there was a statistically significant advantage for dulaglutide based on relative risk, but no significant difference when risk difference of odds ratio were used. Similarly, for change from baseline in fasting blood glucose and change in body weight, the indirect comparison showed there was no statistically significant difference between dulaglutide and exenatide BID.
- 6.24 The submission provided an assessment of transitivity. As for earlier comparisons, the submission highlighted differences in baseline HbA1c as potentially affecting results of the indirect comparison. The submission also suggested that the shorter duration of type 2 diabetes in patients in Derosa (2013) may impact response to treatment. The submission stated (p263) that this was likely to favour exenatide BID in the indirect comparison as the duration of disease for patients in both Derosa (2013) and Apovian (2010) was much shorter than that for patients in AWARD-5. While there was a considerable difference in disease duration between the Derosa (2013) trial and AWARD-5, disease duration in the Apovian (2010) trial was around 4 years, while in AWARD-5 it is just less than 7 years. It cannot be ascertained how much, or if any, difference this may make to the results of the indirect comparison.
- 6.25 The submission also raised the point that patients in Apovian (2010) and Derosa (2013) were placed on diets and a moderate physical activity program. It was not clear how this may impact results, as patients in the placebo arms of those trials also received those lifestyle modifications. The submission acknowledged this (p264). Overall, while there was a statically significant advantage for dulaglutide in the indirect comparison for change in HbA1c at 26 weeks, there was significant heterogeneity in the pooled exenatide trials, and further, there were varied results for other efficacy outcomes.

### **Comparative harms**

- 6.26 The submission did not provide statistical comparisons of any of the safety outcomes (i.e. hypoglycaemia) in the indirect comparisons, on the basis that it was possible differences existed across the trials in terms of how adverse events were collected

and in the definition of ‘treatment emergent’. It was not clear how this latter point (definition of treatment emergent) applies to hypoglycaemia, which is associated with anti-hyperglycaemic medications.

- 6.27 Given the lack of statistical comparisons for safety outcomes, it is difficult to draw any firm conclusions regarding comparative harms. A summary of the results provided by the submission (frequency results for adverse events were supplied) follows, with a focus on the occurrence of hypoglycaemia, a relevant outcome for diabetes trials.
- 6.28 Safety - triple therapy versus exenatide QW: There was no significant difference in hypoglycaemic events between dulaglutide and glargine in the AWARD-2 trial (RD=-0.07, 0.06) while there were statistically significantly fewer hypoglycaemic events with exenatide QW than with glargine (RD=-0.18; 95% CI: -0.25, -0.11). Again, the comparison of AWARD-2 and DURATION-3 for triple therapy may not be appropriate given that 70% of patients in DURATION-3 were not using triple therapy, but the lack of a difference in hypoglycaemia with dulaglutide compared to glargine should be noted.
- 6.29 Safety - dual therapy versus exenatide QW: While there were no statistically significant differences between dulaglutide or exenatide BID and the common reference sitagliptin in the occurrence of hypoglycaemia, there was a slightly greater proportion of dulaglutide patients (2.3%) experiencing hypoglycaemia than exenatide-treated patients (1%). While not a statistically based comparison, this difference, along with the lack of a statistically significant difference in hypoglycaemic events between dulaglutide and glargine in the triple therapy comparison discussed above, suggests that it is possible there are differences in the occurrence of hypoglycaemia with dulaglutide and exenatide.
- 6.30 Safety - triple therapy versus exenatide BID: The submission did not provide any risk difference or relative risk-based results for adverse events in the AWARD-1 trial, although p values were provided for some events, including the occurrence of hypoglycaemia over 26 and 52 weeks. These results indicated significantly fewer dulaglutide-treated patients had experienced hypoglycaemia at week 26 ( $p < 0.007$ ) while at week 52 there was no statistically significant difference in occurrence of hypoglycaemic events between dulaglutide and exenatide BID ( $p = 0.053$ ). It is difficult to draw firm conclusions regarding overall safety outcomes with the lack of comparative analyses provided by the submission. The results for hypoglycaemia indicated an advantage for dulaglutide at week 26, but that appeared to have dissipated at week 52.
- 6.31 Safety - dual therapy versus exenatide BID: Visual comparison of the dulaglutide (2.3%) and exenatide BID (5.3%) arms of the two trials showed a greater proportion of patients in the exenatide trial experienced hypoglycaemia, but, as for all other safety outcomes in this comparison, given the lack of indirect comparisons, no conclusions can be drawn.
- 6.32 The ESC noted that the PSCR (p6-7) provided a new statistical analysis of some adverse events. For triple therapy compared to once weekly exenatide, the only adverse event reported as statistically significant was an increase in diarrhoea [REDACTED]. Similarly for dual therapy compared to once weekly exenatide the [REDACTED].

only statistically significant adverse event was greater incidence of diarrhoea (██████████). For triple therapy compared to exenatide BID there was a statistically significant lower incidence of nausea and vomiting (██████████ respectively). In dual therapy compared to exenatide BID there was a statistically significant lower incidence of discontinuations due to adverse effects (██████████). The ESC and PBAC noted that the details of these analyses were not independently verified.

## Benefits and harms

- 6.33 A summary of the comparative benefits for dulaglutide versus exenatide QW and exenatide BID is provided in the ‘Comparative effectiveness’ section above. As the submission provided no statistical comparisons for safety outcomes, a benefits and harms summary cannot be provided.

## Interpretation of clinical evidence

- 6.34 The submission’s initial claim was that dulaglutide was non-inferior to exenatide QW in both dual and triple therapy; non-inferior to exenatide BID in dual therapy and superior to exenatide BID in triple therapy.
- 6.35 The PSCR (p2) revised the therapeutic claims made in the submission to a claim of non-inferiority in terms of efficacy and safety for both dual and triple therapy between dulaglutide and both exenatide QW and BID, stating *“when dulaglutide 1.5 mg is compared with exenatide QW and exenatide BID in both dual and triple settings, taking into account the totality of this evidence, the conclusion is that dulaglutide is at least non-inferior to these comparators.”* The ESC advised that this claim may be reasonable based on the body of evidence for efficacy, and the new statistical analysis of safety outcomes, although it noted that the analysis of safety outcomes had not been independently verified.
- 6.36 The PBAC noted that the pre-PBAC response claimed that the PSCR had not revised the claim for comparison against exenatide BID in triple therapy and continued to claim superiority in this setting. The PBAC did not accept this claim.
- 6.37 The PBAC noted that acceptance of the claim superiority over exenatide BD in triple therapy rests on acceptance of 0.3% and not 0.4% as the minimum clinically important different (MCID) for change in HbA1c [██████████ (95% CI) ██████████]. The PBAC recalled it had previously considered both 0.3% and 0.4% as relevant MCID. The PBAC further noted that in the other three comparisons presented by the submission (vs exenatide QW in dual and triple therapy, and exenatide BID in dual therapy) the upper bound of the confidence interval did not exceed the MCID of 0.3%. Lastly, the PBAC recalled it had previously accepted that exenatide 2 mg once weekly was at least non-inferior to exenatide 10 mcg twice daily in terms of efficacy (based on mean change in HbA1c from baseline) and non-inferior in terms of safety. On balance, the PBAC considered the claim that dulaglutide was superior to exenatide BID in triple therapy was not adequately substantiated.

6.38 Overall, the PBAC considered that a claim of non-inferior comparative effectiveness for dulaglutide versus exenatide QW or BID in terms of reduction in HbA1c was reasonable.

6.39 The PBAC considered that a claim of non-inferior comparative safety was reasonable.

### Economic analysis

6.40 The submission presented two cost-minimisation analyses, one comparing dulaglutide and exenatide QW and the second comparing dulaglutide and exenatide BID. The table below summarises the key assumptions and components of both cost-minimisation analyses.

**Table 9: Key assumptions and components of the cost-minimisation approach**

Component	Claim or assumption
<b>Dulaglutide vs. exenatide QW</b>	
Therapeutic claim: effectiveness	<ul style="list-style-type: none"> <li>Based on evidence presented in Sections 2(a) and 2(c), dulaglutide 1.5mg is at least as favourable as exenatide QW.</li> </ul>
Therapeutic claim: safety	<ul style="list-style-type: none"> <li>Based on evidence presented in Sections 2(a) and 2(c), the safety profiles of dulaglutide and exenatide QW are similar.</li> </ul>
Evidence base	<ul style="list-style-type: none"> <li>Indirect comparisons of dulaglutide and exenatide QW in triple and dual therapy.</li> </ul>
Equi-effective doses	<ul style="list-style-type: none"> <li>Dulaglutide 1.5mg/wk = exenatide 2mg QW.</li> </ul>
Direct medicine costs	<ul style="list-style-type: none"> <li>The cost of dulaglutide 1.5mg and exenatide QW per patient per year are equivalent.</li> </ul>
Other costs or cost offsets	<ul style="list-style-type: none"> <li>None.</li> </ul>
<b>Dulaglutide vs. exenatide BID</b>	
Therapeutic claim: effectiveness	<ul style="list-style-type: none"> <li>Based on evidence presented in Sections 2(b), 2(d) and 2(e), dulaglutide 1.5mg is more favourable (triple therapy) or at least as favourable (dual therapy) as exenatide BID. <i>Note claim of superiority not accepted by the PBAC.</i></li> </ul>
Therapeutic claim: safety	<ul style="list-style-type: none"> <li>Based on evidence presented in Sections 2(b), 2(d) and 2(e), the safety profiles of dulaglutide 1.5mg and exenatide BID are similar.</li> </ul>
Evidence base	<ul style="list-style-type: none"> <li>Direct and indirect comparisons of randomised controlled trials.</li> </ul>
Equi-effective doses	<ul style="list-style-type: none"> <li>Dulaglutide 1.5mg/wk = exenatide 10µg BID/day</li> </ul>
Direct medicine costs	<ul style="list-style-type: none"> <li>The cost of dulaglutide 1.5mg is greater than exenatide BID per patient per year.</li> </ul>
Other costs or cost offsets	<ul style="list-style-type: none"> <li>Yes: Cost offsets associated with differences in prescribing and administration costs (ie reduced needle use and improved compliance).</li> </ul>

BID=twice daily; QW=once weekly; wk=week

Source: Table 3(a).1-1, p290; Table 3(a).1-2 p291; Table 3(b).1-1, p296 and Table 3(b).2-1, p296 of the submission.

6.41 For dulaglutide versus exenatide QW, the submission nomination the equi-effective doses as: in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy): dulaglutide 1.5mg = exenatide 2mg QW.

6.42 For the comparison of dulaglutide and exenatide BID, the submission described the equi-effective doses as follows: When used in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy): dulaglutide 1.5mg = exenatide 10µg BID.

6.43 The PBAC noted that for both comparisons, the equi-effective doses match the dosing in the exenatide PI and the draft dulaglutide PI and it considered that these equi-effective doses were reasonable.

6.44 The submission stated that the comparison of prescribing and administration profiles of dulaglutide 1.5mg and exenatide QW demonstrated that both medicines are the same in terms of frequency of administration (once weekly; see table above). The

submission added that exenatide QW was recommended for PBS listing on a cost minimisation basis with exenatide BID with a cost offset for reduced needle use and a further small price advantage based on potential health benefits from likely improved adherence by a small number of high clinical need populations (submission cited the exenatide July 2015 PSD). The PBAC’s statement in that PSD (paragraph 7.4) was that the simplified treatment regimen of reducing dosing frequency by 13 injections per week may translate into filling an unmet need for high clinical need populations such as Indigenous, aged and mental health patients. The evaluation noted that the submission did not provide any discussion of how dulaglutide may be used in high clinical need populations, the magnitude of its use in those populations, and whether its use may impact adherence.

6.45 The ESC noted that the PSCR (p1) claimed that for some patients who require a once weekly GLP-1 RA, exenatide QW may not be suitable. Dulaglutide has a finer needle that is hidden from the patient’s view, it does not require medicine preparation (exenatide QW requires shaking the pen to dissolve the components) and it has a different excretion (non renal) route than exenatide which may make it a more appropriate choice for some high clinical need populations such as the elderly and Australian indigenous populations. The size of the population with remaining unmet need was not quantified in the PSCR.

6.46 The PBAC noted that the pre-PBAC response maintained that dulaglutide would meet an unmet clinical need in patients suitable for a once weekly GLP-1 RA, as it provides an additional option that can cater to an individual patient’s requirements. The PBAC agreed with its ESC that any residual clinical need not currently met by exenatide QW would likely be small.

**Table 10: Results of the submission’s cost-minimisation analyses - dulaglutide 1.5mg versus exenatide QW**

Profile	Dulaglutide 1.5mg	Exenatide QW
<b>AEMP</b>		
AEMP per dose	\$ [REDACTED]	\$27.86 <sup>a</sup>
Dose duration (days)	7	7
Administrations per week	1	1
Total medicine cost per week	\$ [REDACTED]	\$27.86
Difference in cost per week	\$0.00	
<b>DPMQ<sup>b</sup></b>		
DPMQ per dose	\$ [REDACTED]	\$32.73
Dose duration (days)	7	7
Administrations per week	1	1
Total medicine cost per week	\$ [REDACTED]	\$32.73
Difference in cost per week	\$ [REDACTED]	

<sup>a</sup> Exenatide once weekly has a special pricing arrangement.

<sup>b</sup> All DPMQs have been updated with dispensing fee and AHI fee current as of 1 July 2017.

AEMP=approved ex-manufacturer price; BID=twice daily; DPMQ=dispensed price maximum quantity; QW=once weekly;  
Source: Table 3(a).4-2, p292 of the submission.

**Table 11: Results of the submission’s cost-minimisation analyses - dulaglutide 1.5mg versus exenatide BID**

Profile	Dulaglutide 1.5mg	Exenatide BID
<b>AEMP</b>		
AEMP per dose	\$ [REDACTED]	\$1.22 <sup>a</sup>
Administrations per week	1	14
Total medicine cost per week	\$ [REDACTED]	\$17.02
Difference in medicine cost per week		\$ [REDACTED]
Included cost offsets	-\$ [REDACTED]	\$0.00
Difference in weekly cost per treatment		\$ [REDACTED]
<b>DPMQ<sup>b</sup></b>		
DPMQ per dose	\$ [REDACTED]	\$1.49
Administrations per week	1	1
Total medicine cost per week	\$ [REDACTED]	\$20.89
Difference in medicine cost per week		\$ [REDACTED]
Included cost offsets	-\$ [REDACTED]	\$0.00
Difference in weekly cost per treatment		\$ [REDACTED]

<sup>a</sup> Exenatide BID does not have a special pricing arrangement.

<sup>b</sup> All DPMQs have been updated with dispensing fee and AHI fee current as of 1 July 2017.

AEMP=approved ex-manufacturer price; BID=twice daily; DPMQ=dispensed price maximum quantity; QW=once weekly;

Source: Table 3(b).4-4 p300 of the submission.

6.47 The submission’s cost offsets applied to dulaglutide versus exenatide BID were based on the estimated cost offsets for exenatide QW versus exenatide BID. The submission estimated these offsets based on the difference between the cost of treatment with exenatide QW and exenatide BID. The following table provides the submission’s estimated cost offsets for reduced needle use and improved compliance.

**Table 12: Cost offsets applied to exenatide QW**

Resource	Cost per pack	Cost per dose	Doses per pack	Doses per week	Cost per week	Cost offset
<b>AEMP</b>						
Exenatide QW	\$111.44	\$27.86	4	1	\$27.86	\$ [REDACTED]
Exenatide 10µg BID	\$72.96	\$1.22	60	14	\$17.02	
<b>DPMQ<sup>a</sup></b>						
Exenatide QW	\$130.91	\$32.73	4	1	\$32.73	\$ [REDACTED]
Exenatide 10µg BID	\$89.54	\$1.49	60	14	\$20.89	

<sup>a</sup> All DPMQs have been updated with dispensing fee and AHI fee current as of 1 July 2017.

AEMP=approved ex-manufacturer price; BID=twice daily; DPMQ=dispensed price maximum quantity; QW=once weekly

Source: Table 3(b).4-2, p299 of the submission.

6.48 The PBAC considered the more appropriate approach is for the cost-minimisation analysis to be conducted against exenatide QW and BID, [REDACTED]. The cost-minimisation conducted using this approach is presented in Table 13.

**Table 13: Results of the alternate cost-minimisation analyses - dulaglutide 1.5mg versus exenatide QW & BID**

	Dulaglutide 1.5mg	Exenatide QW	Exenatide 10 µg BID
AEMP	█	\$111.44*	\$72.96
AEMP per dose	█	\$27.86	\$1.22
Dose duration (days)	█	7	
Administrations per week	█	1	14
Total medicine cost per week	█	\$27.86	\$17.02
Proportion of Use (Table 14)	█	█	█

\* Exenatide QW has a special pricing arrangement. This calculation uses the published AEMP.

6.49 The PBAC considered an additional small cost-offset for reduced needle use compared to exenatide BID to be reasonable.

### Drug cost/patient/year

6.50 The estimated cost for a year of treatment with dulaglutide was \$█. This was based on one script providing 28 days of treatment and the requested price of \$█ per script (updated for current dispensing and AHI fees). Treatment is ongoing.

6.51 Exenatide BID is estimated to cost \$1,090.15 per patient per year (1 script at \$89.54 provides 30 days of treatment) while exenatide QW is estimated to cost \$1,707.67 per patient per year (1 script at \$130.91 provides 28 days of treatment).

### Estimated PBS usage & financial implications

6.52 This submission was not considered by DUSC. The submission applied a market share approach to estimate the use and financial implications of the requested listing on the PBS.

6.53 The expected number of exenatide scripts, in the absence of a PBS listing for dulaglutide, as estimated in the submission is provided in the table below.

**Table 14 Total number of exenatide scripts in absence of dulaglutide 1.5mg**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Exenatide 5µg BID	█	█	█	█	█	█
Exenatide 10µg BID	█	█	█	█	█	█
Exenatide QW	█	█	█	█	█	█
Total	█	█	█	█	█	█

BID=twice daily; QW=once weekly

Source: Table 4.2-1, p303 of the submission.

6.54 The PBAC noted that the pre-PBAC response presented updated information on the projected market share of exenatide BID and QW, but those data have not been evaluated. The PBAC considered that it was appropriate to rely on the submission's original estimates for its decision making.

6.55 The submission (Table 4.2-2, p304) estimated that the proportion of exenatide scripts that are expected to be substituted by dulaglutide would be █% in Year 1 and increasing to █% for Years 5 and 6. The submission estimated dulaglutide would substitute for exenatide QW and exenatide BID (both strengths) at the same rates.

6.56 The commentary and the PBAC considered these substitution rates may be underestimated, particularly in the earlier years, as the dulaglutide QW presentation

is easier to use than the exenatide QW presentation and it was likely that more patients would switch exenatide BID to dulaglutide QW.

6.57 The PBAC considered that the overall market for GLP1 inhibitors may grow as a result of this listing with the potential for some substitution for insulin glargine.

6.58 The table below provides the submission’s estimated number of dulaglutide scripts that will be dispensed over the first 6 years of listing, the net cost to the PBS/RPBS and the cost of substituted exenatide. These estimates use the published DPMQ of exenatide QW and the proposed published DPMQ of dulaglutide.

**Table 15: Estimated financial implications<sup>a</sup> to the PBS/RPBS for listing of dulaglutide**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Estimated extent of use</b>						
Number of scripts						
<b>Net financial implications</b>						
Net cost to PBS/RPBS						
Net exenatide PBS/RPBS cost – substituted						
<b>Overall net cost to PBS/RPBS</b>						

<sup>a</sup> All DPMQs used in the cost calculations have been updated with dispensing fee and AHL fee current as of 1 July 2017.

Source: Table 4.4-1, p312 and Excel workbook ‘Trulicity (dulaglutide) Section 4.xlsx’ of the submission.

The redacted table shows that at year 5, the estimated number of scripts was over 200,000 per year and the net cost to the PBS would be less than \$10 million per year.

6.59 The submission estimated the net cost to the PBS/RPBS as \$20 - \$30 million over the first 6 years of listing. The cost associated with this cost-minimisation listing was largely due to three things:

- Increase in dulaglutide scripts was required to equal one month of treatment with exenatide BID, i.e. 1.07 dulaglutide scripts are required. The cost associated with this was reasonable.
- Assumption that the cost offsets and price advantage accorded to exenatide QW should be provided to dulaglutide.
- The use of published prices for dulaglutide and exenatide QW and effective prices for exenatide BID.

6.60 The PBAC noted the submission’s financial estimates would need to be revised to take into account the outcomes of the PBAC’s deliberations and be based on the effective prices of both exenatide QW and dulaglutide.

6.61 The PBAC noted that as dulaglutide is not TGA-registered for use in dual therapy with a sulfonylurea while exenatide is. This may result in a small risk for use outside of the restriction.

### Quality use of medicines

6.62 The submission stated that the sponsor planned to implement a range of activities supporting the quality use of medicines in the treatment of type 2 diabetes and the appropriate use of dulaglutide. The submission did not indicate whether any post-market surveillance would be carried out.

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

## 7 PBAC Outcome

- 7.1 The PBAC recommended the listing of dulaglutide for the treatment of type 2 diabetes mellitus in dual therapy in combination with metformin and in triple therapy in combination with metformin and a sulfonylurea.
- 7.2 The PBAC considered, amongst other matters, that dulaglutide would be acceptably cost-effective if it were cost minimised against [REDACTED] the QW and BID forms of exenatide (5 mcg + 10 mcg) [REDACTED].
- 7.3 The PBAC did not accept the sponsor's approach to making exenatide QW and exenatide BID different alternative therapies, rather considering that they were different dosing regimens of the same therapy. The PBAC recalled that, in July 2015, it had recommended exenatide 2 mg once weekly for dual combination therapy with metformin or a sulfonylurea and triple combination therapy with metformin and a sulfonylurea in patients with T2DM. The recommendation was on a cost-minimisation basis with exenatide 10 mcg BID with a cost offset for reduced needle use and a further small price advantage based on potential health benefits from likely improved adherence by a small number of high clinical need populations. At that time, the PBAC considered that the data available for exenatide, supported exenatide 2 mg QW being at least non-inferior to exenatide 10 mcg BID in terms of efficacy (based on mean change in HbA1c from baseline) and non-inferior in terms of safety.
- 7.4 Moreover, the PBAC noted that:
- exenatide, is available in both QW and BID presentations, whereas dulaglutide is only available in a QW presentation;
  - dulaglutide QW will take market share from both the QW and BID presentations of exenatide; and
  - dulaglutide QW has not demonstrated superior effectiveness or safety over exenatide in either dosing regimen (QW or BID) in either dual or triple therapy.
- 7.5 Thus overall, the PBAC considered it appropriate that dulaglutide be afforded the same price premium as exenatide QW has over exenatide BID, but [REDACTED].
- 7.6 The equi-effective doses are:
- When used in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy): dulaglutide 1.5mg = exenatide 2mg QW.

- When used in combination with metformin (dual therapy) and in combination with metformin plus a sulfonylurea (triple therapy): dulaglutide 1.5mg = exenatide 10µg BID.
- 7.7 The PBAC noted the pre-PBAC response continued to maintain that the listing of dulaglutide would address an unmet clinical need. However, it considered that only a small subset of patients with renal impairment would be considered to have an unmet clinical need, and that that unmet clinical need did not warrant the price premium over exenatide sought by the submission.
- 7.8 The PBAC noted that the requested listing, in line with the TGA registration, does not include use as a dual therapy with sulfonylurea, which is different to the exenatide listing, and may lead to use outside of the restriction.
- 7.9 The PBAC advised that dulaglutide is suitable for prescribing by nurse practitioners.
- 7.10 The PBAC recommended that the Early Supply Rule should apply.
- 7.11 The PBAC advised that, under subsection 101(3BA) of the *National Health Act, 1953* dulaglutide should be treated as interchangeable on an individual patient basis with exenatide.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

**Outcome:**

Recommended

## 8 Recommended listing

### 8.1 Add new item:

Name, restriction, manner of administration, form	Maximum quantity (packs)	Maximum quantity (units)	No. of repeats	Proprietary name and manufacturer
DULAGLUTIDE Solution for injection 1.5 mg in 0.5mL	1	4 single use pen (auto-injector)	5	Trulicity®, Eli Lilly Australia Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule(Code GE)
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS indication:</b>	Diabetes mellitus type 2
<b>Restriction:</b>	<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"/> Authority Required - Streamlined
<b>Clinical criteria:</b>	The treatment must be in combination with metformin AND Patient must have a contraindication to a combination of metformin and a sulfonylurea; OR Patient must not have tolerated a combination of metformin and a sulfonylurea, 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 (SGLT2) inhibitor despite treatment with either metformin or a sulfonylurea
<b>Prescribing Instructions</b>	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.  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.  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 SGLT2 inhibitor, must be documented in the patient's medical records.
<b>Administration Advice</b>	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin, an SGLT2 inhibitor or a sulfonylurea.

<b>Category / Program</b>	GENERAL – General Schedule(Code GE)
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS indication:</b>	Diabetes mellitus type 2
<b>Restriction:</b>	<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"/> Authority Required – Streamlined
<b>Clinical criteria:</b>	<p>The treatment must be in combination with metformin            AND            The treatment must be in combination with a sulfonylurea            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 (SGLT2) inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea            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 SGLT2 inhibitor despite treatment with maximally tolerated doses of metformin and a sulphonylurea.</p>
<b>Prescribing Instructions</b>	<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:            (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.</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>
<b>Administration Advice</b>	This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), an insulin, an SGLT2 inhibitor or a sulfonylurea alone.

## 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.