

An addendum to this Public Summary Document (PSD) has been included at the end of the document.

5.08 DULAGLUTIDE,

**Injection 3 mg in 0.5 mL single dose pre-filled pen,
Injection 4.5 mg in 0.5 mL single dose pre-filled pen,
Trulicity[®],
Eli Lilly Australia Pty Ltd.**

1 Purpose of submission

- 1.1 The Category 2 submission requested Section 85 (General Schedule) Authority Required (STREAMLINED) listing for dulaglutide 3.0 mg and 4.5 mg for the treatment of patients with type 2 diabetes mellitus (T2DM) who require treatment intensification to achieve glycaemic targets, as dual therapy in combination with metformin.
- 1.2 Listing was requested on the basis of a cost-minimisation analysis versus dulaglutide 1.5 mg.

Table 1: Key components of the clinical issue addressed by the submission (as stated in the submission)

Component	Description
Population	Adults with T2DM who are not achieving adequate glycaemic control with dulaglutide 1.5 mg with metformin.
Intervention	Dulaglutide (Trulicity [®]) 3.0 mg or 4.5 mg injection in a single use pre-filled pen (autoinjector), administered once weekly in combination with metformin
Comparator	Dulaglutide (Trulicity [®]) 1.5 mg injection in a single use pre-filled pen (autoinjector), administered once weekly in combination with metformin
Outcomes	<p>Primary efficacy outcome Change in HbA1c% baseline to week 36</p> <p>Secondary efficacy outcomes Patients achieving target HbA1c <7% at week 36 Change in fasting blood glucose baseline to week 36 Change in bodyweight from baseline to week 36</p> <p>Safety objectives Safety parameters through 36 weeks and 52 weeks</p>
Clinical claim*	For patients with T2DM who require treatment intensification to obtain glycaemic targets, dulaglutide 3.0 mg and dulaglutide 4.5 mg provide at least non-inferior efficacy with respect to glycaemic control (HbA1c), and non-inferior safety with respect to adverse events, compared to dulaglutide 1.5 mg once weekly, when all medicines are used in combination with metformin.

Source: Table ES 1.1, p i of the submission.

2 Background

Registration status

- 2.1 **TGA status at time of PBAC consideration:** The submission was made under the TGA/PBAC Parallel Process. The second round TGA Clinical Evaluation Report was

available. The Delegate’s Overview is expected 31 March 2022. The submission provided the EMA assessment report.

Previous PBAC consideration

2.2 The PBAC initially recommended dulaglutide 1.5 mg for listing in November 2017 as dual therapy in combination with metformin and as triple therapy in combination with metformin and a sulfonylurea. The PBAC recommended extending the listing of dulaglutide to include the treatment of T2DM in combination with insulin and metformin in July 2020. The PBAC has not previously considered the higher strengths.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
DULAGLUTIDE injection 3.0 mg/0.5 mL, 4.5 mg/0.5 mL, 4 single use pens	1 pack containing 4 pens	5	\$ 132.89 [Published] \$ [SPA Effective ex-man]	Trulicity® Eli Lilly Pty Ltd
Category/Program:	General Schedule			
PBS indication:	Diabetes mellitus type 2			
Restriction:	Authority Required (Streamlined)			
Clinical criteria:	<p>The treatment must be in combination with metformin</p> <p>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 metformin 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 of a gliptin, a glitazone, a glucagon-like peptide-1 receptor agonist or an SGLT2 inhibitor despite treatment metformin</p>			
Prescriber criteria:	Medical Practitioners, Nurse Practitioners			
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 receptor agonist 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 clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or 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	This drug is not PBS-subsidised for use as monotherapy or in combination with a sulphonylurea, a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone), or an SGLT2 inhibitor.
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- 3.1 The submission requested that the existing SPA for dulaglutide be applied to the requested listing, and that the current public price of dulaglutide (ex-manufacturer price of \$111.44) be maintained.
- 3.2 The pricing structure proposed is therefore flat pricing across all three strengths of dulaglutide.

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

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 (T2DM), 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. The main goals of treatment for T2DM are to prevent or delay complications and maintain quality of life in current practice.
- 4.2 The submission proposed that dulaglutide 3.0 mg and 4.5 mg will be used in the same place in therapy as dulaglutide 1.5 mg (or other GLP-1 RAs). The proposed place in the treatment algorithm for dulaglutide 3.0 mg and 4.5 mg in combination with metformin, is for people with T2DM treated with dulaglutide 1.5 mg who require treatment intensification to achieve glycaemic targets. The submission did not propose listing for use in combination with insulin.
- 4.3 Dulaglutide is a once-weekly glucagon-like peptide-1 (GLP-1) receptor agonist (RA).

5 Comparator

- 5.1 The submission nominated dulaglutide 1.5 mg as the main comparator as it is the medicine most likely to be displaced by a listing for dulaglutide 3.0 mg and 4.5 mg. The submission nominated semaglutide as a supplementary comparator as it is also a GLP-1 RA but represents a smaller proportion of the GLP-1 RA T2DM market. These comparators are appropriate.

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (1) and organisations (1) via the Consumer Comments facility on the PBS website. The comment from the individual described their experience using Ozempic® (semaglutide) for weight loss and was therefore not directly relevant to the submission.
- 6.3 Diabetes Australia supported listing dulaglutide 3 mg and 4.5 mg on the PBS. Diabetes Australia highlighted the importance of ensuring access to medicines for T2DM noting that the number of people developing the condition is likely to continue increasing. Diabetes Australia noted the results of the AWARD-11 trial and considered that including dulaglutide 3 mg and 4.5 mg on the PBS would provide options to ensure people can access the treatment needed to manage their T2DM successfully.

Clinical studies and trials

6.4 The submission was based on one head-to-head trial comparing dulaglutide 1.5 mg to dulaglutide 3.0 mg and dulaglutide 4.5 mg (AWARD-11), and a ‘supplementary’ indirect comparison using this trial and a trial comparing semaglutide 0.5 mg and semaglutide 1.0 mg vs dulaglutide 0.75 mg and 1.5 mg (SUSTAIN 7).

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-11	A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Investigational Dulaglutide Doses When Added to Metformin in Patients with Type 2 Diabetes Mellitus. Approval date: 9 October 2020 (Week 36 data) Approval date: 15 October 2020 (Week 52 data)	NCT03495102
	Frias, Bonora et al. Efficacy and Safety of Dulaglutide 3.0 mg and 4.5 mg Versus Dulaglutide 1.5 mg in Metformin-Treated Patients With Type 2 Diabetes in a Randomized Controlled Trial (AWARD-11).	<i>Diabetes Care</i> 2021; 44: 765-773.
	Frias, Bonora et al. Efficacy and safety of dulaglutide 3.0 mg and 4.5 mg in patients aged younger than 65 and 65 years or older: Post hoc analysis of the AWARD-11 trial.	<i>Diabetes Obes Metab</i> 2021; 23 (10): 2279-2288.
	Bonora, Frias et al. Effect of dulaglutide 3.0 mg and 4.5 mg on weight in patients with type 2 diabetes: Exploratory analyses of AWARD-11.	<i>Diabetes Obes Metab</i> 2021; 23 (10): 2242-2250.
	Van, Frias et al. Gastrointestinal Tolerability of Once-Weekly Dulaglutide 3.0 mg and 4.5 mg: A Post Hoc Analysis of the Incidence and Prevalence of Nausea, Vomiting, and Diarrhea in AWARD-11.	<i>Diabetes Ther</i> 2021; 12: 2783-2794.
SUSTAIN 7	Efficacy and Safety of Semaglutide Versus Dulaglutide as add-on to Metformin in Subjects With Type 2 Diabetes. (SUSTAIN 7)	NCT02648204
	Pratley, Aroda et al. Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial. Pratley, Aroda et al. Impact of patient characteristics on efficacy and safety of once-weekly semaglutide versus dulaglutide: SUSTAIN 7 post hoc analyses.	<i>Lancet Diabetes Endocrinol</i> 2018; 6: 275-86 <i>BMJ Open</i> 2020;10:e037883. doi:10.1136/bmjopen-2020-037883
AWARD-11 and SUSTAIN 7	Pratley, Catarig et al. (2021) An indirect treatment comparison of the efficacy of semaglutide 1.0 mg versus dulaglutide 3.0 mg and 4.5 mg	<i>Diabetes Obes Metab</i> 2021; 23 (11): 2513-2520

Source: Table 2.2.1, p38 of the submission and Table 2.2.1, p8 Appendix 1 of the submission.

6.6 The key features of the randomised trials are summarised in the table below. The PBAC previously assessed SUSTAIN 7 as having a high risk of bias at its November 2019 meeting.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
AWARD 11	1842	R, DB 52 weeks	Low	Age ≥ 18 years T2DM diagnosis ≥ 6 months	Change in HbA1c at 36 weeks
SUSTAIN 7	1201	R,OL, 40 weeks	High	Age ≥ 18 years T2DM diagnosis ≥ 6 months	Change in HbA1c at 40 weeks

Source: Table 2.3.1, p 40 and Table 2.3.1, p11, Appendix 1 of the submission.

Abbreviations: DB = double blind; OL = open label; R = randomised, T2DM=Type 2 diabetes mellitus.

Comparative effectiveness

6.7 The results for the AWARD 11 trial are presented in the Table below. Treatment with both dulaglutide 3.0 mg and 4.5 mg resulted in greater HbA1c reductions from baseline to Week 36 compared with dulaglutide 1.5 mg. Significantly greater proportions of patients on dulaglutide 3.0 mg and 4.5 mg achieved the HbA1c target of < 7.0% and the more stringent target of ≤ 6.5% compared with those on dulaglutide 1.5 mg, and significantly greater proportions of patients on dulaglutide 3.0 mg and 4.5 mg compared with 1.5 mg achieved both weight loss targets of ≥ 5% and ≥ 10% weight loss from baseline.

Table 4: Results - AWARD 11.

Outcome at week 36	Dulaglutide 1.5mg n/N (%)	Dulaglutide 3mg n/N (%)	Dulaglutide 4.5mg n/N (%)	Dulaglutide 3mg vs 1.5mg OR (95% CI)	Dulaglutide 4.5mg vs 3mg OR (95% CI)
HbA1C < 7%	298/523 (57%)	337/521 (64.7%)	376/526 (71.5%)	1.49 (1.12, 1.98) P = 0.06	1.49 (1.10, 2.03) P = 0.011
HbA1C ≤ 6.5%	199/523 (38.0%)	252/521 (48.4%)	272/526 (51.7%)	1.62 (1.24, 2.13) P<0.001	1.20 (0.91, 1.58) P=0.194
Body Weight Loss ≥ 5%	162/522 (31.0%)	209/520 (40.2%)	260/526 (49.4%)	1.49 (1.16, 1.93) P = 0.002	1.46 (1.14, 1.86) P = 0.002
Body Weight Loss ≥ 10%	32/522 (6.1%)	62/520 (11.9%)	71/526 (13.5%)	2.11 (1.35, 3.29) P = 0.001	1.12 (0.78, 1.62) P = 0.527
HbA1C < 7% and Body Weight Loss ≥ 5% and no documented symptomatic or severe hypoglycaemia	112/591 (19%)	169/595 (29.4%)	219/594 (36.9%)	1.71 (1.30, 2.27) P<0.001	1.51 (1.17, 1.95) P = 0.001

Source: CSR p462, p468, p548, p554, p557.

Abbreviations: CI=confidence interval; n = number of participants with event; N = total participants in group; OR=odds ratio.

Bold indicates statistically significant results

6.8 At 36 weeks the decrease in mean HbA1c was significantly greater with dulaglutide 3.0 mg (least square mean difference: 0.17; 95% CI: 0.29, 0.06; p = 0.003) and 4.5 mg

(least square mean difference: 0.34; 95% CI: 0.45, 0.22; $p < 0.001$) compared with dulaglutide 1.5 mg.

Comparative harms

- 6.9 Adverse events as reported in the AWARD-11 trial are summarised in the table below. There was no relationship between the proportion of patients who reported events and the different dulaglutide doses except for diarrhoea and vomiting (which occurred in a higher proportion of patients on the high dulaglutide doses than dulaglutide 1.5 mg.
- 6.10 Dulaglutide 1.5 mg was initially chosen by the manufacturer as the optimal dose because of concern arising in early studies that higher doses might be associated with adverse cardiovascular effects and with elevated pancreatic enzymes.

Table 5: Summary of key adverse events in AWARD-11

	Dulaglutide 1.5mg N = 612 n (%)	Dulaglutide 3mg N = 616 n (%)	Dulaglutide 4.5 mg N = 614 n (%)
All TEAE	346 (55.6%)	351 (57%)	378 (62%)
Treatment-related TEAE*	145 (23.7%)	184 (29.9%)	190 (30.9%)
All SAE#	39 (6.4%)	30 (4.9%)	26 (4.2%)
Withdrawal due to AE#	6 (1.0%)	8 (1.3%)	11 (1.8%)
Discontinuation of study treatment due to AE#	28 (4.6%)	36 (5.8%)	32 (5.2%)
Deaths	2 (0.3%)	2 (0.3%)	2 (0.3%)
Nausea	82 (13.4%)	96 (15.6%)	101 (16.4%)
Diarrhoea	43 (7.0%)	70 (11.4%)	66 (10.7%)
Vomiting	34 (5.6%)	51 (8.3%)	57 (9.3%)
Discontinuations due to N,V and/or D	1 (0.2%)	11 (1.7%)	13 (2.1%)
Any non-fatal Cardiovascular Event	0	5 (0.8%)	2 (0.3%)
Abnormal Pancreatic Enzymes	10 (1.6%)	9 (1.5%)	11 (1.8%)
Injection Site Reactions	1 (0.2%)	2 (0.3%)	7 (1.1%)

Source: Table 12.2, CSR p177, Table 12.3, CSR p179, CSR p180.

Abbreviations: D=diarrhoea; N=nausea; V=vomiting.

* As judged by investigator

Deaths are included

Benefits/harms

- 6.11 As the claim was non-inferiority, information for benefits and harms is not presented.

Clinical claim

- 6.12 The submission described dulaglutide 3.0 mg and 4.5 mg as non-inferior in terms of effectiveness compared to dulaglutide 1.5 mg. The PBAC considered this claim was adequately supported.

- 6.13 The submission described dulaglutide 3.0 mg and 4.5 mg as non-inferior in terms of safety compared to dulaglutide 1.5 mg. The PBAC considered this claim was adequately supported, as there were no significant differences in the adverse events.

Economic analysis

- 6.14 The submission presented a cost-minimisation analysis.
- 6.15 Although the clinical data from the AWARD-11 trial indicated a dose response relationship to efficacy (based on reduction in HbA1c) for dulaglutide 1.5 mg vs dulaglutide 3.0 mg vs dulaglutide 4.5 mg, the submission proposed that for pricing purposes, these doses be considered equi-effective.
- 6.16 The submission appropriately did not include additional cost or cost-offsets for adverse events.
- 6.17 The prices proposed were therefore flat-priced, i.e., the same as for the currently listed 1.5 mg form.
- 6.18 The results of the cost-minimisation analysis are shown below.

Table 6: Results of the cost-minimisation analysis

Medicine	Cost per dose (\$)	Administrations per week	Total medicine cost per week (\$)	Difference in medicine cost per week vs dulaglutide 1.5 mg
Cost-minimisation analysis: AEMP (effective)				
Dulaglutide 4.5 mg	\$ [REDACTED]	1	\$ [REDACTED]	\$0.00
Dulaglutide 3.0 mg	\$ [REDACTED]	1	\$ [REDACTED]	\$0.00
Dulaglutide 1.5 mg	\$ [REDACTED]	1	\$ [REDACTED]	-
Cost minimisation analysis: DPMQ				
Dulaglutide 4.5 mg	\$33.22	1	\$33.22	\$0.00
Dulaglutide 3.0 mg	\$33.22	1	\$33.22	\$0.00
Dulaglutide 1.5 mg	\$33.22	1	\$33.22	-

Source: Table 3.4.2, , p84 of the submission.

Drug cost/patient/year

- 6.19 The cost per patient per year using the effective DPMQ of \$ [REDACTED], assuming 2 scripts per patient per year, is \$ [REDACTED]

Estimated PBS usage & financial implications

- 6.20 This submission was not considered by DUSC. The submission presented a market share approach to estimating likely use of dulaglutide 3.0 mg and 4.5 mg injections, based on an extrapolation of the use of the 1.5 mg strength for the period from June 2018 to February 2021. This is the period when dulaglutide was not listed for use in combination with insulin, which commenced in March 2021.

Table 7: Key inputs for financial estimates

	Value	Source	comments
Number of dulaglutide 1.5 mg prescriptions			
Dulaglutide 1.5 mg	Refer to worksheet '13. Actual dula services' in spreadsheet 'A7.1_Dulaglutide Section 4 Model.xlsx'	Services Australia Pharmaceutical Benefits Schedule Item Reports	
Extrapolation of dulaglutide 1.5 mg prescriptions			
Projected dulaglutide 1.5 mg prescriptions	Refer to worksheet '14.Forecasted dula services' in spreadsheet 'A7.1_Dulaglutide Section 4 Model.xlsx'	Triple exponential smoothing analysis using MS excel built-it function	May be an underestimate – observed growth since initial listing for dual therapy only may not reflect current market
Changes in utilisation			
Market share of dulaglutide 3.0 mg and 4.5 mg (combined)	Year 1 (2022): 7% Year 2 (2023): 12% Year 3 (2024): 18% Year 4 (2025): 19% Year 5 (2026): 20% Year 6 (2027): 20%	Eli Lilly	May be an underestimate – does not include use with insulin
Substitution rate	Across all years of analysis: Dulaglutide 3.0 mg: 50% Dulaglutide 4.5 mg: 50%	Eli Lilly	May be an underestimate – may be preference for higher dose particularly with respect to weight management
Cost of medicines (Published DPMQ)			
Dulaglutide 1.5 mg	\$132.89	PBS item 11364D	
Dulaglutide 3.0 mg	\$132.89	Eli Lilly proposed	
Dulaglutide 4.5 mg	\$132.89	Eli Lilly proposed	
Cost of medicines (Effective AEMP)			
Dulaglutide 1.5 mg	\$ [REDACTED]	Confidential effective AEMP	
Dulaglutide 3.0 mg	\$ [REDACTED]	Eli Lilly proposed	
Dulaglutide 4.5 mg	\$ [REDACTED]	Eli Lilly proposed	

Source: Table 4.1.1, p87 of the submission. Abbreviations: AEMP = Approved ex-manufacturer price; DPMQ = Dispensed Price Maximum Quantity; PBS= Pharmaceutical Benefits Scheme.

6.21 The estimated use and financial implications are shown below.

Table 8: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of scripts dispensed ^a	■ ¹	■ ³	■ ⁴	■ ⁴	■ ⁴	■ ⁴
Estimated financial implications of dulaglutide 3.0 mg and 4.5 mg						
Cost to PBS/RPBS less copayments (\$)	■ ²	■ ²	■ ⁵	■ ⁵	■ ⁵	■ ⁵
Estimated financial implications for dulaglutide 1.5 mg						
Cost to PBS/RPBS less copayments (\$)	■ ²	■ ²	■ ⁵	■ ⁵	■ ⁵	■ ⁵
Net financial implications						
Net cost to PBS/RPBS	\$0	\$0	\$0	\$0	\$0	\$0
Net cost to MBS/ Services Australia/other	\$0	\$0	\$0	\$0	\$0	\$0
Net cost to PBS/RPBS	\$0	\$0	\$0	\$0	\$0	\$0

Source: Tables 4.2.5, 2.4.7 pp100 – 102 of the submission.

^a Assuming 2 scripts per patient year as estimated by the submission.

The redacted values correspond to the following ranges:

¹ 40,000 to < 50,000

² \$0 to <\$10 million

³ 80,000 to < 90,000

⁴ 100,000 to < 200,000

⁵ \$10 million to <\$20 million

6.22 The total cost to the PBS/RPBS of listing dulaglutide 3.0 mg and 4.5 mg was estimated to be \$10 million to < \$20 million per year in Year 6, and a total of \$60 million to < \$70 million in the first 6 years of listing. The net cost to the PBS was proposed to be zero.

6.23 The submission assumed that there will be no changes to the overall market for GLP-1 RAs from listing dulaglutide 3.0 mg and 4.5 mg. The evaluation considered there are three main factors that suggest that this is unlikely to be the case and that these estimates are likely to be underestimates: (1) The proposed TGA indication for dulaglutide 3.0 mg and 4.5 mg includes use with insulin, so these higher strengths could potentially be used outside of the proposed PBS-listing in patients requiring triple therapy; (2) The submission included no substitution from GLP-1 RAs other than dulaglutide 1.5 mg, which may not be the case if high strength injections of dulaglutide are seen to offer the possibility of dose intensification; (3) There is a beneficial effect of increasing the dose of dulaglutide on short-term weight loss in AWARD-11 and semaglutide is under TGA evaluation for weight management (Semaglutide Stakeholder Meeting Outcome Statement, 26 August 2021). While dulaglutide is currently not specifically approved for use in weight management, the GLP-1 RA market may expand overall. The pre-PBAC Response indicated that listing dulaglutide 3.0 mg and 4.5 mg would likely have a financial impact close to nil irrespective of uncertainty regarding GLP-1 RA market dynamics, noting that the proposed price is equal to dulaglutide 1.5 mg and that semaglutide had also been cost-minimised to dulaglutide 1.5 mg. The pre-PBAC Response stated there is currently no data available or in development which would meet requirements for TGA registration of any

formulation of dulaglutide as an obesity/weight loss medication. The pre-PBAC Response noted that the weight loss benefit observed in AWARD-11 with treatment intensification from dulaglutide 1.5 mg to higher doses was moderate. The pre-PBAC Response considered that treatment intensification from dulaglutide 1.5 mg to higher doses of dulaglutide is likely to be driven primarily by a need for additional glycaemic control rather than potential weight loss benefits.

Quality Use of Medicines

6.24 No specific quality use of medicines activities were proposed.

Financial Management – Risk Sharing Arrangements

6.25 No risk sharing arrangement was proposed.

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

7 PBAC Outcome

- 7.1 The PBAC deferred making its decision on whether to recommend the listing of dulaglutide 3.0 mg and 4.5 mg for the treatment of Type II Diabetes Mellitus (T2DM) in combination with metformin as a TGA Delegate's Overview was not available at the time of PBAC consideration. The PBAC was of a mind to recommend dulaglutide 3.0 mg and 4.5 mg on a cost-minimisation basis compared to dulaglutide 1.5 mg pending receipt of a positive TGA Delegate's Overview.
- 7.2 The PBAC accepted that dulaglutide 1.5 mg was the appropriate main comparator
- 7.3 The PBAC noted that the submission was based on AWARD-11, a head-to-head randomised trial comparing dulaglutide 1.5 mg to dulaglutide 3.0 mg and dulaglutide 4.5 mg in patients treated with metformin. The PBAC noted that at 52 weeks, the majority (96.5%) of patients remained on a stable dose of metformin and did not require metformin discontinuation or dose adjustment. The PBAC also noted that the proportion of patients requiring additional rescue therapy was small and similar across the arms of the trial.
- 7.4 The PBAC noted that at 36 weeks, both dulaglutide 3.0 mg and 4.5 mg treatment arms had a statistically significantly greater reduction from baseline in HbA1c compared to the dulaglutide 1.5 mg treatment arm. The PBAC also noted that a statistically significantly greater proportion of patients in the dulaglutide 3.0 mg and 4.5 mg treatment arms achieved HbA1C < 7% and HbA1C < 6.5% at 36 weeks, compared to the dulaglutide 1.5 mg treatment arm. The PBAC considered that the claim of non-inferior effectiveness compared to dulaglutide 1.5 mg was reasonable noting that a non-inferiority margin was not nominated as AWARD-11 was designed as a superiority trial.
- 7.5 The PBAC noted the proportion of adverse events was similar between treatment arms in AWARD-11 with the exception of a higher rate of diarrhoea and vomiting in patients treated with dulaglutide 3.0 mg and 4.5 mg compared to patients treated

with dulaglutide 1.5 mg. The PBAC noted that the proportion of patients in AWARD-11 who discontinued due to diarrhoea, vomiting or nausea was low. Overall, the PBAC considered that the claim of non-inferior safety compared to dulaglutide 1.5 mg was reasonable.

- 7.6 The PBAC considered that PBS listing of dulaglutide 3.0 mg and 4.5 mg was unlikely to substantially expand the GLP-1 RA market. The PBAC considered that combination use of dulaglutide 3.0 mg and 4.5 mg with insulin outside the proposed restriction was unlikely given semaglutide is PBS-listed for use in combination with insulin. The PBAC considered that most patients currently treated with semaglutide would not be switched to dulaglutide 3.0 mg or 4.5 mg given that higher doses of dulaglutide have not been established as superior to semaglutide. The PBAC also considered there would unlikely be substantial expansion of the GLP-1 RA market due to use of dulaglutide 3.0 mg and 4.5 mg for weight loss, as the currently listed semaglutide is also perceived to have weight loss benefits.
- 7.7 The PBAC noted that irrespective of GLP-1 RA market dynamics, listing of dulaglutide 3.0 mg and 4.5 mg would result in minimal financial impact if cost-minimised to dulaglutide 1.5 mg.
- 7.8 The PBAC considered that the restriction should allow treatment in patients who are contraindicated to or intolerant to metformin.
- 7.9 Although the PBAC noted the proposed restriction would allow use of dulaglutide 3.0 mg and 4.5 mg without prior use of dulaglutide 1.5 mg, it considered this would not be a frequent occurrence in clinical practice due to the gastrointestinal adverse events associated with starting treatment at a dose higher than 1.5 mg.
- 7.10 The PBAC noted that its foreshadowed recommendation was on a cost-minimisation basis, and advised that, because dulaglutide 3.0 mg and 4.5 mg doses are not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity, over dulaglutide 1.5 mg, or not expected to address a high and urgent unmet clinical need given the presence of an alternative therapy, the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met.

Outcome:

Deferred

Addendum to the March 2022 PBAC PSD:

**4.04 DULAGLUTIDE,
Injection 3 mg in 0.5 mL single dose pre-filled pen,
Injection 4.5 mg in 0.5 mL single dose pre-filled pen,
Trulicity[®],
Eli Lilly Australia Pty Ltd.**

8 Background

- 8.1 At the March 2022 meeting, the PBAC deferred making its decision on whether to recommend the listing of dulaglutide 3.0 mg and 4.5 mg for the treatment of Type II Diabetes Mellitus as a TGA Delegate's Overview was not available at the time of PBAC consideration. The PBAC was of a mind to recommend dulaglutide 3.0 mg and 4.5 mg on a cost-minimisation basis compared to dulaglutide 1.5 mg pending receipt of a positive TGA Delegate's Overview.
- 8.2 **TGA status at time of PBAC consideration:** The submission was made under TGA/PBAC Parallel Process. At the time of PBAC consideration on 6 May 2022, the TGA Delegate's Overview was available.
- 8.3 The TGA Delegate considered that dulaglutide 3.0 mg and 4.5 mg may be approvable with enhanced post market surveillance including Phase 4 efficacy/safety study.

9 PBAC Outcome

- 9.1 The PBAC recommended the listing of dulaglutide 3.0 mg and 4.5 mg for the treatment of Type II Diabetes Mellitus in combination with metformin in patients who are contraindicated or intolerant to a combination of metformin and a sulfonylurea. The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness of dulaglutide 3.0 mg and 4.5 mg would be acceptable if it were cost-minimised against dulaglutide 1.5 mg.
- 9.2 PBAC maintained its previous consideration that the claim of non-inferior effectiveness and safety compared to dulaglutide 1.5 mg was reasonable. The PBAC advised that the equi-effective doses are dulaglutide 3.0 mg once weekly (QW), dulaglutide 4.5 mg QW and dulaglutide 1.5 mg QW.
- 9.3 The PBAC recalled its previous consideration that the restriction should allow treatment in patients who are contraindicated to or intolerant to metformin. The PBAC clarified its position that the restriction should be consistent with the current restriction for dulaglutide 1.5 mg, noting the recommendation is on a cost-minimisation basis. The current restriction for dulaglutide 1.5 mg requires patients to have a contraindication to, or not have tolerated a combination of metformin and a

sulfonylurea, and does not allow use in monotherapy for patients contraindicated or intolerant to metformin.

- 9.4 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

10 Recommended listing

10.1 Add new item(s):

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DULAGLUTIDE					
dulaglutide 3.0 mg/0.5 mL injection, 4 x 0.5 mL pen devices	NEW	1	4	5	Trulicity
dulaglutide 4.5 mg/0.5 mL injection, 4 x 0.5 mL pen devices	NEW	1	4	5	Trulicity
<p>Category / Program: GENERAL – General Schedule (Code GE)</p> <p>Prescriber type: <input checked="" type="checkbox"/>Medical Practitioners <input checked="" type="checkbox"/>Nurse practitioners</p> <p>Restriction type: <input checked="" type="checkbox"/>Authority Required (Streamlined) [new code]</p>					
	<p>Administrative Advice: This drug is not PBS-subsidised for use as monotherapy or in combination with a dipeptidyl peptidase 4 inhibitor (gliptin), insulin, a thiazolidinedione (glitazone), an SGLT2 inhibitor or a sulfonylurea.</p>				
	<p>Administrative Advice: Special pricing arrangements apply.</p>				
	<p>Indication: Diabetes mellitus type 2</p>				
	<p>Clinical criteria:</p>				
	<p>The treatment must be in combination with metformin</p>				
	<p>AND</p>				
	<p>Clinical criteria:</p>				
	<p>Patient must have a contraindication to a combination of metformin and a sulfonylurea; or</p>				
	<p>Patient must not have tolerated a combination of metformin and a sulfonylurea</p>				
	<p>AND</p>				
	<p>Clinical criteria:</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 metformin; or</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 metformin.
	Prescribing Instructions: 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.
	Prescribing Instructions: 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>Prescribing Instructions: 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>
	Prescribing Instructions: 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.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

11 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.

12 Sponsor's Comment

The sponsor had no comment.