6.05 LINAGLIPTIN, 5mg tablet, LINAGLIPTIN AND METFORMIN, 2.5mg/500mg, 2.5mg/850mg, 2.5mg/1000mg, Trajenta®, Trajentamet®, Boehringer Ingelheim.

1 Purpose of Application

1.1 The submission sought to extend the current listing for linagliptin and linagliptin/metformin fixed dose combinations to include an Authority Required (Streamlined) listing for the treatment of type 2 diabetes in combination with insulin.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LINAGLITPIN linagliptin 5 mg tablet	30	5	$61.50	Trajenta®	Boehringer Ingelheim Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined
Clinical criteria:	The treatment must be in combination with insulin, 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.

	~~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.~~
Prescriber 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.* *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.*
Administrative Advice	Note: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor, a glucagon-like peptide-1 or a thiazolidinedione (glitazone).

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
LINAGLITPIN + METFORMIN					
linagliptin 2.5 mg + metformin hydrochloride 500 mg tablet, 60	60	5	$63.30	Trajentamet®	Boehringer Ingelhiem Pty Ltd
linagliptin 2.5 mg + metformin hydrochloride 850 mg tablet, 60			$64.50		
linagliptin 2.5 mg + metformin hydrochloride 1 g tablet, 60			$64.99		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined

Clinical criteria:	The treatment must be in combination with insulin, 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated. ~~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 result 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.~~
Prescriber 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.* *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 result 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.*

Administrative Advice	Note: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. Note: This fixed dose combination ~~tablet~~ is not PBS-subsidised for use ~~in combination with a sulfonylurea (triple oral therapy),~~[a] as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor. ~~Note:~~ ~~PBS subsidised dual oral therapy does not include concomitant use of two of either: a gliptin, a glitazone or an SGLT2 inhibitor~~

[a] To be removed as linagliptin was also recommended by the PBAC for use as triple therapy at the March 2016 meeting [item 7.05 refers].

2.2 Listing was requested on a cost-minimisation basis compared to both sitagliptin and dapagliflozin.

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

3 Background

3.1 TGA status at time of PBAC consideration: Linagliptin was registered in November 2011 for use in type 2 diabetes: as an adjunct to diet and exercise in monotherapy and dual oral combination therapy with metformin, or a sulfonylurea, or a thiazolidinedione; in triple oral combination therapy with metformin and a sulfonylurea; and in combination with insulin. Linagliptin/metformin fixed dose combinations were registered in May 2013 for use as initial or continuing dual oral therapy in combination with metformin or a sulfonylurea, and in combination with insulin.

3.2 Linagliptin was listed on the PBS for dual oral therapy with metformin or a sulfonylurea on 1 March 2012, and linagliptin/metformin fixed dose combinations were listed on 1 March 2014 for Type 2 diabetes (excluding triple oral therapy, and initial therapy).

3.3 Linagliptin has not previously been considered by the PBAC for type 2 diabetes in combination with insulin.

3.4 The sponsor requested listing for linagliptin for triple oral therapy in type 2 diabetes in a concurrent submission to the March 2016 PBAC meeting [item 7.05 refers].

4 Clinical place for the proposed therapy

4.1 Type 2 diabetes in combination with insulin, with or without metformin when therapy with insulin (± metformin) does not provide adequate glycaemic control.

4.2 Alternative agents for the treatment of type 2 diabetes in combination with insulin include diabetes medicines, both listed and not listed on the PBS:

- Up-titration of basal insulin
- Pre-mixed and rapid acting insulins
- Other diabetes medicines including sulfonylureas, other DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, pioglitazone and acarbose; and
- Fixed dose combinations of oral diabetes medicines with metformin (where available).

5 Comparator

5.1 The submission nominated both sitagliptin and dapagliflozin as main comparators. Dapagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, was PBS listed for use in combination with insulin on 1 April 2015. Sitagliptin is a pharmacological analogue of linagliptin which is not currently PBS listed for use in combination with insulin. As dapagliflozin is an oral diabetes medicine already PBS listed for an identical indication, this may be the most appropriate main comparator.

5.2 An informal stepped comparison with insulin intensification via exenatide plus insulin was presented in an attachment to the submission as a supplementary comparator.

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

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on two indirect comparisons:

- An indirect analysis comparing linagliptin 5 mg plus insulin (Trials 1218.36, 1218.43, and 1218.63) with dapagliflozin plus insulin (Trial CT-006), using placebo plus insulin as the common comparator.
- An indirect analysis comparing linagliptin 5 mg plus insulin (Trials 1218.36, 1218.43 and 1218.63) with sitagliptin plus insulin (Vilsboll 2010, Mathieu 2015, NCT01590797), using placebo plus insulin as the common comparator.

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

Table 1: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Linagliptin + insulin vs placebo + insulin		
Trial 1218.36 (NCT00954447)	A Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of Linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy Sheu WH, Park SW, Gong Y, Pinnetti S, Bhattacharya S, Patel S, Seck T, Woerle HJ. Linagliptin improves glycaemic control after 1 year as add-on therapy to basal insulin in Asian patients with type 2 diabetes mellitus. Yki-Järvinen H, Rosenstock J, Durán-Garcia S, Pinnetti S, Bhattacharya S, Thiemann S, Patel S, Woerle HJ. Effects of adding linagliptin to basal insulin regimen for inadequately controlled type 2 diabetes: a ≥52-week randomized, double-blind study.	11 May 2012 *Current Medical Research and Opinion.* 2015 Mar;31(3):503-12. *Diabetes Care*. 2013 Dec;36(12):3875-81.
Trial 1218.43 (NCT00800683)	A phase III, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of BI 1356 (5 mg), compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulphonylurea or glinides as monotherapy; pioglitazone or any other antidiabetics, excluding only DPP-4 inhibitors other than BI 1356) over 52 weeks in type 2 diabetic patients with severe chronic renal impairment. McGill JB, Sloan L, Newman J, Patel S, Sauce C, Von EM et al. Long-term efficacy and safety of linagliptin in patients with type 2 diabetes and severe renal impairment: A 1-year, randomized, double-blind, placebo-controlled study. McGill JB, Barnett AH, Lewin AJ, Patel S, Neubacher D, von Eynatten M, Woerle HJ. Linagliptin added to sulphonylurea in uncontrolled type 2 diabetes patients with moderate-to-severe renal impairment.	5 May 2011 *Diabetes Care* 2013; 36(2):237-244. *Diabetes and Vascular Disease Research* 2014 Jan; 11(1):34-40.
Trial 1218.63 (NCT01084005)	A Phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5 mg), administered orally once daily over 24 weeks in type 2 diabetic patients (age >70 years) with insufficient glycaemic control (HbA1c ≥7.0%) despite metformin and/or sulphonylurea and/or insulin therapy Barnett AH, Huisman H, Jones R, Von EM, Patel S, Woerle H-J. Linagliptin for patients aged 70 years or older with type 2 diabetes inadequately controlled with common antidiabetes treatments: A randomised, double-blind, placebo-controlled trial. Lajara R, Aguilar R, Hehnke U, Woerle HJ, von Eynatten M. Efficacy and safety of linagliptin in subjects with long-standing type 2 diabetes mellitus (>10 years): evidence from pooled data of randomized, double-blind, placebo-controlled, phase III trials.	2 December 2011 *Lancet* 2013;382(9902):1413-1423. *Clinical Therapeutics.* 2014; 36(11):1595-605.
Sitagliptin + insulin vs placebo + insulin		
Vilsboll 2010 (NCT00395343)	Vilsbøll T, Rosenstock J, Yki-Järvinen H, Cefalu WT, Chen Y, Luo E, Musser B, Andryuk PJ, Ling Y, Kaufman KD, Amatruda JM, Engel SS, Katz L. Efficacy and safety of sitagliptin when added to insulin therapy in patients with type 2 diabetes.	*Diabetes Obesity and Metabolism*. 2010;12(2):167-77.
Mathieu 2015	Mathieu C, Shankar RR, Lorber D, Umpierrez G, Wu F, Xu L, Golm	*Diabetes Therapy*.

Trial ID	Protocol title/ Publication title	Publication citation
(NCT01462266)	GT, Latham M, Kaufman KD, Engel SS. A Randomized Clinical Trial to Evaluate the Efficacy and Safety of Co-Administration of Sitagliptin with Intensively Titrated Insulin Glargine.	2015;6(2):127-42.
NCT01590797	A Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Clinical Trial in China to Study the Safety and Efficacy of the Addition of Sitagliptin in Patients With Type 2 Diabetes Mellitus Who Have Inadequate Glycemic Control on Insulin Therapy, Alone or in Combination With Metformin	Results first received 16 January 2015
Dapagliflozin + insulin vs. placebo + insulin		
CT-006 (NCT00673231) (Wilding 2012)	Wilding JP, Woo V, Rohwedder K, Sugg J, Parikh S; Dapagliflozin 006 Study Group. Dapagliflozin in patients with type 2 diabetes receiving high doses of insulin: efficacy and safety over 2 years. Wilding JP, Woo V, Soler NG, Pahor A, Sugg J, Rohwedder K, Parikh S; Dapagliflozin 006 Study Group. Long-term efficacy of dapagliflozin in patients with type 2 diabetes mellitus receiving high doses of insulin: a randomized trial.	*Diabetes Obesity and Metabolism*. 2014;16(2):124-36 *Annals of Internal Medicine*. 2012;156(6):405-15

Source: Table B.3, pp.47-48, Table B.5, pp.52-53, Table B.57, pp.178-179, Table B.59, pp. 182-183 of the submission

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

Table 2: Key features of the included evidence (indirect comparison)

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)
Linagliptin + insulin vs placebo + insulin					
1218.36	N=1263	R, DB, MC, PG, PC 24 weeks	Low	T2DM; ≥18 years; HbA1c 7.0-10.0%; BMI ≤45 kg/m^2.	Δ HbA1c, HbA1c responders <7%, Δ FPG; Δ insulin dose.
1218.43 subgroup	N=133 Subgroup N=107	R, DB, MC, PG, PC 24 weeks	Low	T2DM; ≥18 years HbA1c 7.0-10.0%; BMI ≤45 kg/m^2; eGFR < 30 mL/min	Δ HbA1c, HbA1c responders <7%, Δ FPG; Δ insulin dose.
1218.63 subgroup	N=241 Subgroup N=50	R, DB, MC, PG, PC 24 weeks	Low	T2DM; ≥70 years; HbA1c ≥7.0%	Δ HbA1c
Sitagliptin + insulin vs placebo + insulin					
Vilsboll 2010	N=641	R, DB, MC, PG, PC 24 weeks	Low	T2DM ≥21 years; HbA1c 7.5-11%; BMI 20-43kg/m^2.	Δ HbA1c, HbA1c responders <7%, Δ FPG; Δ insulin dose.
Mathieu 2015	N=660	R, DB, MC, PG, PC 24 weeks	Low	T2DM; 18-80 years; HbA1c 7.5-11%.	Δ insulin dose, Δ HbA1c, HbA1c responders <7%, Δ FPG
NCT01590797	N=467	R, DB, MC, PG, PC 24 weeks	Low	T2DM; 18-79 years; HbA1c 7.5-11%.	Δ HbA1c
Dapagliflozin plus insulin versus placebo plus insulin					
CT-006	N= 808	R, DB, MC, PG, PC 24 weeks	Low	T2DM; 18-80 years; HbA1c 7.5-10.5%; BMI ≤45 kg/m^2	Δ HbA1c, Δ FPG; Δ insulin dose.

Source: compiled during the evaluation

Abbreviations: BMI, body mass index; DB, double blind; FPG, fasting plasma glucose; HbA1c, glycosylated haemoglobin; MC, multi-centre; PC, placebo controlled; PG, parallel group; R, randomised; T2DM, type 2 diabetes

Comparative effectiveness

6.6 Table 3 summarises the results of change in HbA1c from baseline in the linagliptin, sitagliptin and dapagliflozin trials in combination with insulin, and the indirect comparison between these treatments after 24 weeks.

Table 3. Results of mean change in HbA1c from baseline across randomised trials (indirect comparisons)

Treatment group	Baseline HbA1c Mean (SD)	Week 24 HbA1c Mean (SD)	LS mean change from baseline (SD)	Difference in LS mean change in HbA1c (95% CI)
LINAGLIPTIN TRIALS				
1218.36 (Primary outcome)				
Linagliptin 5 mg (n=618)	8.31 (0.75)	7.69 (0.99)	-0.58 (1.99)	-0.65 (-0.87, -0.43)
Placebo (n=617)	8.29 (0.75)	8.32 (0.99)	0.07 (1.99)	
1218.43 (Primary outcome)				
Linagliptin 5 mg (n=52)	8.26 (0.95)	NR	-0.48 (0.85)	-0.64 (-0.95, -0.33)
Placebo (n=52)	8.32 (0.88)	NR	0.16 (0.78)	
1218.63 (Primary outcome)				
Linagliptin 5 mg (n=35)	NR	NR	-0.53 (0.59)	-0.67 (-1.04, -0.30)
Placebo (n=15)	NR	NR	0.14 (0.62)	
Meta-analysis of linagliptin trials [WMD (95% CI)] I^2 = 0%				[redacted]
DAPAGLIFLOZIN TRIAL				
CT-006 (Primary outcome)				
Dapagliflozin 10 mg (n=194)	8.57 (0.82)	NR	-0.97 (0.67)	-0.58 (-0.73, -0.43)
Placebo (n=193)	8.47 (0.77)	NR	-0.39 (0.72)	
Linagliptin vs dapagliflozin: Indirect estimate of effect [WMD (95% CI)] *Results <0 favour linagliptin*				[redacted]
SITAGLIPTIN TRIALS				
Vilsboll 2010 (Primary outcome)				
Sitagliptin 100 mg (n=305)	8.7 (0.9)	8.1 (1.0)	-0.6 (0.89)	-0.60 (-0.74, -0.46)
Placebo (n=312)	8.6 (0.9)	8.6 (1.2)	0.0 (0.9)	
Mathieu 2015 (Secondary outcome)				
Sitagliptin 100 mg (n=329)	8.7 (1.0)	7.3 (1.1)	-1.3 (0.93)	-0.40 (-0.54, -0.26)
Placebo (n=312)	8.8 (1.0)	7.9 (1.2)	-0.9 (0.93)	
NCT01590797 (Primary outcome)				
Sitagliptin 100 mg (n=223)	NR	NR	-0.67 (0.91)	-0.35 (-0.52, -0.18)
Placebo (n=219)	NR	NR	-0.32 (0.91)	
Meta-analysis of sitagliptin trials [WMD (95% CI)] I^2 = 67%				[redacted]
Linagliptin vs sitagliptin*: Indirect estimate of effect [WMD (95% CI)] *Results <0 favour linagliptin*				[redacted]

** The indirect estimate presented in the submission was based on a different meta-estimate of sitagliptin trials to that provided in Figure B.7 of the submission, which could not be verified [-0.42 (-0.56, -0.27)]. During the evaluation the indirect estimate was recalculated based on the meta-estimate of sitagliptin trials provided in Figure B.7. The indirect estimate presented in the submission was -0.23 (-0.45, -0.01).*

Source: Figures B.6, B.7 and B.31, and Tables B.32 and B.91 of the submission, relevant CSRs and publications.

Abbreviations: WMD, weighted mean difference, SD, standard deviation, CI, confidence interval.

6.7 The addition of linagliptin, dapagliflozin, or sitagliptin to background insulin therapy (± other oral diabetes therapies) produced significant reductions in HbA1c compared to placebo with insulin over 24 weeks.

6.8 In the indirect comparisons linagliptin demonstrated non-inferiority to both dapagliflozin and sitagliptin over 24 weeks. The upper limit of the 95% confidence interval was less than the pre-specified non-inferiority margin of 0.4%.

6.9 Table 4 summarises the results for change in mean daily insulin dose from baseline at 24 weeks for the linagliptin, sitagliptin and dapagliflozin trials in combination with insulin, and the indirect comparison between these treatments.

Table 4: Results of mean change from baseline in daily insulin dose (IU) at 24 weeks across randomised trials (indirect comparison).

Treatment group	Baseline insulin dose mean IU (SD)	Mean change from baseline insulin dose (SD)	Difference in LS mean change from baseline (95% CI)
LINAGLIPTIN TRIALS			
1218.36 (Secondary outcome)			
Linagliptin 5 mg (n=618)	41.5 (31.9)	0.1 (4.7)	-0.30 (-0.81, 0.21)
Placebo (n=617)	40.1 (27.3)	0.4 (4.5)	
1218.43 (Secondary outcome)			
Linagliptin 5 mg (n=52)	65.7 (49.2)	-2.75 (19.04)	-1.25 (-8.66, 6.16)
Placebo (n=52)	63.9 (59.1)	-1.50 (19.51)	
Meta-analysis of linagliptin trials [WMD (95% CI)] I^2 = 0%			[redacted]
DAPAGLIFLOZIN TRIAL			
CT-006 (Secondary outcome)			
Dapagliflozin 10 mg (n=194)	78.0 (45.0)	-1.15 (13.26)	-6.76 (-9.52, -4.00)
Placebo (n=193)	73.7 (42.4)	5.61 (12.92)	
Linagliptin vs dapagliflozin: Indirect estimate of effect [WMD (95% CI)] *Results <0 favour linagliptin*			[redacted]
SITAGLIPTIN TRIALS			
Vilsboll 2010 (Secondary outcome)			
Sitagliptin 100 mg (n=305)	Mix: 67.4 (35.4) LA: 44.2 (29.9)	0 (5.8)	-1.60 (-2.60, -0.60)
Placebo (n=312)	Mix: 74.5 (36.9) LA: 44.5 (25.7)	1.6 (7.0)	
Mathieu 2015 (Primary outcome)			
Sitagliptin 100 mg (n=329)	37.3 (20.8)	19 (23.14)	-4.80 (-8.34, -1.26)
Placebo (n=312)	36.6 (21.3)	23.8 (23.14)	
Meta-analysis of sitagliptin trials [WMD (95% CI)] I^2 = 66%			[redacted]
Linagliptin vs sitagliptin: Indirect estimate of effect [WMD (95% CI)] *Results <0 favour linagliptin*			[redacted]
Linagliptin vs sitagliptin: Indirect estimate of effect excl. Mathieu 2015 (sensitivity analysis) [WMD (95% CI)] *Results <0 favour linagliptin*			[redacted]

Source: Figures B.15, B.16, B.38, and B.39 and Tables B.35 and B.94 of the submission, relevant CSRs and publications.
Abbreviations: WMD, weighted mean difference, SD, standard deviation, CI, confidence interval.

6.10 The indirect comparison between linagliptin and dapagliflozin for mean change from baseline in insulin dose was statistically significantly in favour of dapagliflozin. However, there were a number of factors limiting the exchangeability of the included trials: there are notable differences in effect size in the common comparator arms; the dapagliflozin trial CT-006 had a higher mean daily insulin dose at baseline; and both CT-006 and 1218.43 allowed any insulin type, whereas 1218.36 was restricted to basal insulin only.

6.11 The indirect comparison between linagliptin and sitagliptin showed no statistically significant difference between treatments in mean change from baseline in insulin dose, although results favoured sitagliptin. Insulin titration protocols varied substantially across the included randomised trials. In particular, intensive insulin titration in Mathieu 2015 resulted in considerable increases in the daily dose of insulin in both arms over the treatment period. There was substantial heterogeneity between the two sitagliptin trials. In a sensitivity analysis excluding Mathieu 2015 from the sitagliptin meta-analysis, the difference in mean change in daily insulin dose from baseline was statistically significantly in favour of sitagliptin.

6.12 Although change in insulin dose may be considered an important clinical outcome, as it was held relatively constant during the first 12- 24 weeks in the linagliptin trials (and the sitagliptin trial Vilsboll 2010), this outcome is unlikely to reflect any real change in insulin dose associated with the use of these agents. Differences in mean daily insulin dose at baseline, and insulin type used also affect the results of this outcome. Lower initial doses and restriction to basal or long acting insulin types only tend to result in increases to insulin dose throughout the trial period. The ESC agreed that the interpretation of the change in insulin dose between trials was uncertain.

Comparative harms

6.13 Linagliptin was not statistically significantly different from placebo in terms of safety outcomes measured in the trials.

6.14 A series of formal indirect comparisons showed that there were no statistically significant differences between treatments in terms of safety outcomes overall, however linagliptin had statistically significantly lower rates of drug-related adverse events and discontinuations due to an adverse event compared to dapagliflozin. However, potential differences in definitions of adverse events, particularly hypoglycaemia and wide confidence intervals suggest the results based on indirect comparisons should be interpreted with caution.

6.15 A cardiovascular outcomes trial conducted with saxagliptin, another DPP-4 inhibitor, suggested there may be an increased risk of hospitalisation for cardiac failure (SAVOR-TIMI 53). It is currently unknown whether this is a class effect. Two cardiovascular outcome trials (CAROLINA and CARMELINA) with linagliptin are currently ongoing. Once they are finalised, the results of these trials will provide more information regarding this topic.

Clinical claim

6.16 The submission described linagliptin 5 mg once daily in combination with insulin as:

- non-inferior to sitagliptin 100 mg with insulin with respect to efficacy and safety in the treatment of patients with type 2 diabetes; and
- non-inferior to dapagliflozin 10 mg with insulin with respect to efficacy with a different but tolerable safety profile in the treatment of patients with type 2 diabetes.

6.17 These claims were adequately supported in terms of comparative efficacy (in terms of HbA1c) and safety; however results for mean change in daily insulin dose favoured sitagliptin and dapagliflozin (with smaller increases or larger decreases in

mean daily insulin dose). Differences in insulin titration protocols, mean daily insulin dose at baseline, and insulin type limit the exchangeability of the trials for this outcome. The results are likely to be attributable to a number of factors and are thus difficult to interpret. The ESC viewed these claims as reasonable, and considered that the change in HbA1c was the most appropriate measure for demonstrating comparative efficacy.

6.18 The PBAC has previously accepted non-inferiority between linagliptin and sitagliptin in terms of comparative safety in dual oral therapy (July 2011; November 2011 linagliptin Public Summary Document (PSD)).

6.19 The PBAC considered that the clinical claim of non-inferior comparative effectiveness between linagliptin and dapagliflozin, in terms of mean change in HbA1C at 24 weeks, was reasonable. The PBAC considered that the clinical claim of non-inferior safety between linagliptin and dapagliflozin was reasonable.

6.20 The PBAC agreed that change in insulin dose may be considered an important clinical outcome. The PBAC noted the ESC advice that the interpretation of changes in insulin dose (a secondary outcome) via the indirect comparisons was uncertain due to: type of insulin, baseline dose and titration protocol. The PBAC considered that it was not possible to confidently exclude the possibility that linagliptin used in combination with insulin would not result in a down-titration of insulin.

Economic analysis

6.21 The equi-effective doses in the submission were:
- Linagliptin 5 mg = dapagliflozin 10 mg;
- Linagliptin 5 mg = sitagliptin 100 mg.

6.22 These estimates were based on the doses used in the trials included in the indirect analyses. The PBAC has previously considered that linagliptin 5 mg is equi-effective to sitagliptin 100 mg (July 2011 and November 2011 linagliptin (dual therapy) PSD). The equi-effective doses of linagliptin 5 mg and dapagliflozin 10 mg have not previously been considered by the PBAC.

6.23 The proposed equi-effective doses of the linagliptin/metformin FDCs and their individual components are presented in Table 5.

Table 5: Equi-effective daily doses of linagliptin component and metformin versus linagliptin fixed dose combination

Linagliptin fixed dose combination	Equi-effective doses
Linagliptin 2.5 mg + metformin 500 mg FDC twice daily	Linagliptin 5 mg once daily + metformin 500 mg twice daily
Linagliptin 2.5 mg + metformin 850 mg FDC twice daily	Linagliptin 5 mg once daily + metformin 850 mg twice daily
Linagliptin 2.5 mg + metformin 1000 mg FDC twice daily	Linagliptin 5 mg once daily + metformin 1000 mg twice daily

Source; Table D.1-2, p.122 of the submission.
Abbreviations: FDC, fixed dose combination.

6.24 The equi-effective doses based on the clinical trials data were reasonable. The equi-effective doses for the fixed dose combinations of linagliptin/metformin assumed

similar efficacy between concomitant regimens and fixed dose combinations of linagliptin and metformin. This has been previously accepted by PBAC (Linagliptin with metformin, March 2013 and April 2013 PSD).

6.25 The prices requested for linagliptin and linagliptin/metformin fixed dose combinations are equivalent to the prices for dual oral therapy in type 2 diabetes.

6.26 Sitagliptin is scheduled to have a 5% statutory price reduction on 1 April 2016. At the proposed ex-manufacturer price for linagliptin 5 mg, the daily cost of treatment is $0.08 more than for sitagliptin (reduced to account for the April 2016 price reduction); but $0.02 less than for dapagliflozin. Linagliptin is scheduled to have a 5% statutory price reduction in April 2017. The Pre-Sub-Committee Response (PSCR, pp.2-3) presented revised daily costs of treatment accounting for the scheduled price reduction of linagliptin in 2017.

Drug cost/patient/year:

- $748.25 for linagliptin 5 mg;
- $770.15 for linagliptin 2.5 mg/metformin 500 mg FDC;
- $784.75 for linagliptin 2.5 mg/metformin 850 mg FDC; and
- $790.71 for linagliptin 2.5 mg/metformin 1000 mg FDC.

6.27 At the requested DPMQ of $61.50 for a 30 pack of linagliptin 5 mg, the drug cost per patient per year for linagliptin was estimated to be $748.25 (assuming 12.17 packs per year). The annual cost per patient of the fixed dose combinations of linagliptin and metformin will be up to $790.71 (assuming 12.17 packs per year).

6.28 The DPMQ for sitagliptin 100 mg will be $55.71 for a 28 pack from 1 April 2016, with a drug cost per patient per year of $726.46 (assuming 13.04 packs per year).

6.29 The DPMQ for dapagliflozin 10 mg is $57.60 for a 28 pack, with a drug cost per patient per year of $750.86 (assuming 13.04 packs per year).

Estimated PBS usage & financial implications

6.30 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of use of any therapy with insulin derived from an analysis of the 10% Medicare sample.

6.31 The submission estimated the utilisation of linagliptin and linagliptin with metformin fixed dose combination for 'linagliptin listed' and 'linagliptin not listed' scenarios.

6.32 The submission assumed that both sitagliptin and saxagliptin in combination with insulin would be listed on the PBS following their submissions for this indication to PBAC in November 2015, and the estimated linagliptin market is based on substitution from these treatments. However the sitagliptin submission was rejected and the saxagliptin submission was withdrawn. As such linagliptin would be the first DPP-4 inhibitor listed in combination with insulin and the estimated usage and financial implications would differ from what is presented in the submission.

6.33 Table 6 summarises the estimated extent of use and financial implications associated

with listing linagliptin in combination with insulin. The costs in this table account for the 5% statutory price reduction for sitagliptin (from 1 April 2016). The PSCR (p.4) presented revised figures incorporating the expected 5% statutory price reduction for linagliptin and saxagliptin (from 1 April 2017).

Table 6: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5
No. patients* insulin+DPP-4					
Patients* (linagliptin not PBS listed)					
- sitagliptin (80%)					
- saxagliptin (20%)					
Patients* (linagliptin PBS listed)					
- linagliptin	[1]	[2]	(%)	(%)	(%)
- sitagliptin			%)	(%)	(%)
- saxagliptin			(%)	(%)	(%)
Scripts (linagliptin not PBS listed)					
- sitagliptin (25, 50, 100 mg)					
- saxagliptin (2.5, 5 mg)					
Scripts (linagliptin PBS listed)					
- linagliptin 5 mg					
- linagliptin 2.5 mg/met 500 mg					
- linagliptin 2.5 mg/met 850 mg					
- linagliptin 2.5 mg/met 1000 mg					
- sitagliptin (25, 50, 100 mg)					
- saxagliptin (2.5, 5 mg)					
Cost to PBS (linagliptin not PBS listed)					
- sitagliptin, saxagliptin (DPMQ)	$	$	$	$	$
- patient copayments	$	$	$	$	$
- net cost to PBS	$	$	$	$	$
Cost to PBS (linagliptin PBS listed)					
- linagliptin, sitagliptin, saxagliptin (DPMQ)	$	$	$	$	$
- patient copayments	$	$	$	$	$
- net cost to PBS	$	$	$	$	$
Difference in costs to PBS (linagliptin PBS listed – linagliptin not PBS listed)					
- costs at DPMQ	-$	-$	-$	-$	-$
- patient copayments	-$	-$	-$	-$	-$
- net costs to the PBS	$	$	-$	-$	-$

Source: compiled during the evaluation using 'Linagliptin Insulin Section E Financial Implications' spreadsheet provided with the submission

Abbreviations: met, metformin

* Based on an average of monthly patient numbers

[1] Market share increases monthly from % to %

[2] Market share increases monthly from % to %

Numbers in italics updated during the evaluation to incorporate 5% statutory price reduction for sitagliptin (from 1 April 2016) and to update patient copayments which increased on 1 January 2016.

The redacted table shows that if linagliptin is PBS listed for this indication, the

estimated number of patients at year 5 was 10,000 – 50,000, and there would be an estimated cumulative saving for the PBS of less than $10 million over the 5 year period.

6.34 The impact and substitution of other diabetes medicines used in combination with insulin (e.g. SGLT2 inhibitors, exenatide) was not considered.

6.35 The submission assumed that extending the listing of linagliptin to include combination with insulin would not increase the market size. However, as the first DPP-4 inhibitor to be listed, with a different mode of action and safety profile compared to oral diabetes medicines already listed on the PBS, this assumption was not supported.

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

7 PBAC Outcome

7.1 The PBAC recommended an Authority Required (Streamlined) listing of linagliptin for treatment of type 2 diabetes mellitus in combination with insulin, on a cost-minimisation basis with dapagliflozin in combination with insulin. The equi-effective doses were linagliptin 5mg and dapagliflozin 10 mg.

7.2 The PBAC recommended an Authority Required (Streamlined) listing of linagliptin with metformin (FDC) for the treatment of type 2 diabetes mellitus in combination with insulin, on a cost-minimisation basis to the individual components taken concomitantly in combination with insulin. The PBAC noted that the equi-effective doses were based on bioequivalence trial previously considered by the PBAC (April 2013 linagliptin/metformin FDC PSD).

7.3 The PBAC recalled from previous consideration of treatments for diabetes that the PBS market for these drugs is not yet stable. The PBAC considered that it was not possible to exclude the possibility that the market would not grow further upon the PBS listing linagliptin and linagliptin with metformin for use in combination with insulin.

7.4 The PBAC recommended that the restriction wording for these listings be consistent with the restrictions for dapagliflozin and its FDC used in combination with insulin.

7.5 The PBAC advised that linagliptin and linagliptin with metformin FDC are suitable for prescribing by Nurse Practitioners for Continuing Therapy Only.

7.6 Under Section 101(3BA) of the National Health Act 1953, the PBAC advised that linagliptin in combination with insulin should be treated as interchangeable on an individual patient basis with sitagliptin in combination with insulin. The PBAC advised that linagliptin with metformin in combination with insulin should be treated as interchangeable on an individual patient basis with: sitagliptin with metformin in combination with insulin.

7.7 The PBAC considered that there was no reason to exempt linagliptin and linagliptin with metformin FDC from the Early Supply Rule.

Outcome:
Recommended

8 Recommended listing

8.1 Amend existing/recommended listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty Units	№.of Rpts	Proprietary Name and Manufacturer
LINAGLITPIN linagliptin 5 mg tablet, 30	30	5	Trajenta® Boehringer Ingelhiem Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐ Dental ☒ Medical Practitioners ☒ Nurse practitioners ☐ Optometrists ☐ Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐ Restricted benefit ☐ Authority Required - In Writing ☐ Authority Required - Telephone ☐ Authority Required - Emergency ☐ Authority Required - Electronic ☒ Streamlined
Clinical criteria:	The treatment must be in combination with insulin, 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
Prescriber 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. 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.
Administrative Advice	Note: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. Note: This drug is not PBS-subsidised for use as monotherapy or in combination with a sodium-glucose co-transporter 2 (SGLT2) inhibitor, a glucagon-like peptide-1 or a thiazolidinedione (glitazone).

Name, Restriction, Manner of administration and form	Max. Qty Units	№.of Rpts	Proprietary Name and Manufacturer	
LINAGLITPIN + METFORMIN				
linagliptin 2.5 mg + metformin hydrochloride 500 mg tablet, 60 linagliptin 2.5 mg + metformin hydrochloride 850 mg tablet, 60 linagliptin 2.5 mg + metformin hydrochloride 1 g tablet, 60	60	5	Trajentamet®	Boehringer Ingelheim Pty Ltd

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	☐Dental ☒Medical Practitioners ☒Nurse practitioners ☐Optometrists ☐Midwives
Condition:	Diabetes mellitus type 2
PBS Indication:	Diabetes mellitus type 2
Restriction Level / Method:	☐Restricted benefit ☐Authority Required - In Writing ☐Authority Required - Telephone ☐Authority Required - Emergency ☐Authority Required - Electronic ☒Streamlined

Clinical criteria:	The treatment must be in combination with insulin, 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 insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated; OR Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with insulin and oral antidiabetic agents, or insulin alone where metformin is contraindicated.
Prescriber 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. 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 result 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.
Administrative Advice	Note: Continuing Therapy Only: For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners. Note: This fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.

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.