

**7.05 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 Authority Required (Streamlined) listing for linagliptin and linagliptin/metformin fixed dose combination (FDC) tablets as part of triple oral therapy for treatment of type 2 diabetes.

**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	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Manufacturer	Name and
LINAGLIPTIN linagliptin 5 mg tablet	30	5	\$61.50	Trajenta®	Boehringer Ingelheim Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS Indication:</b>	Diabetes mellitus type 2
<b>Restriction Level / Method:</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

<p><b>Clinical criteria:</b></p>	<p>The treatment must be in combination with metformin,</p> <p>AND</p> <p>The treatment must be in combination with a sulfonylurea,</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 (SGLT-2) inhibitor despite treatment with <del>either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug</del> <i>optimal doses of dual oral therapy</i>; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor despite treatment with <del>either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug</del> <i>optimal doses of dual oral therapy</i>.</p> <p><del>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor is initiated.</del></p> <p><del>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor was initiated.</del></p> <p><del>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</del></p> <p><del>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</del></p> <p><del>(b) Had red cell transfusion within the previous 3 months.</del></p> <p><del>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor, must be documented in the patient's medical records.</del></p>
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<p><b>Prescriber Instructions</b></p>	<p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:                  (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 SGLT-2 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</p>
<p><b>Administrative Advice</b></p>	<p><u>Note: Continuing Therapy Only:</u>                  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.</p> <p><u>Note:</u>                  This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a <del>sodium glucose co-transporter 2 (SGLT-2) inhibitor</del> or a glucagon-like peptide-1, or an SGLT2 inhibitor.</p> <p><u>Note</u>                  PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>

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

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
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<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS Indication:</b>	Diabetes mellitus type 2
<b>Restriction Level / Method:</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>Clinical criteria:</b>	<p>The treatment must be in combination with a sulfonylurea,</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 <del>either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug</del> <i>optimal doses of dual oral therapy</i>; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with <del>either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug</del> <i>optimal doses of dual oral therapy</i>.</p>
<b>Prescriber 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:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The 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.</p> <p><i>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.</i></p>

<b>Administrative Advice</b>	<p><u>Note: Continuing Therapy Only:</u> 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.</p> <p><u>Note:</u> The fixed dose combination is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a SGLT-2 inhibitor or a glucagon-like peptide-1 or an SGLT2 inhibitor.</p> <p><u>Note:</u> PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>
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- 2.2 Listing of linagliptin 5mg tablets was requested on a cost-minimisation basis compared to sitagliptin. Listing of the linagliptin/metformin FDC tablets was requested on a cost minimisation basis to the individual components taken concomitantly.

*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 by the TGA in November 2011 for the treatment of type 2 diabetes (as an adjunct to diet and exercise) as monotherapy when metformin or a sulfonylurea are not tolerated or contraindicated; dual oral therapy with metformin or a sulfonylurea; triple oral therapy with metformin and a sulfonylurea; combination therapy with insulin (with or without metformin).
- 3.2 Linagliptin/metformin FDC was registered by the TGA in May 2013. It was approved for use as monotherapy when metformin treatment alone is inadequate; triple oral therapy with a sulfonylurea; and combination therapy with insulin.
- 3.3 Linagliptin was considered by the PBAC in July 2012 for use in triple oral therapy on a cost minimisation basis versus pioglitazone. The submission was rejected on the basis of inadequate clinical evidence to support a claim of non-inferior effectiveness compared to pioglitazone.
- 3.4 At its March 2016 meeting, the PBAC also considered:
- A submission for linagliptin and linagliptin/metformin FDC for use in combination with insulin [item 6.05 refers].
  - A submission for vildagliptin and vildagliptin/metformin FDC for use in triple oral therapy with a metformin and a sulfonylurea [item 7.10 refers].

### 4 Clinical place for the proposed therapy

- 4.1 Treatment of type 2 diabetes as triple oral therapy in combination with metformin and a sulfonylurea, when dual therapy with metformin and a sulfonylurea does not

provide adequate glycaemic control. Alternative agents for triple therapy in combination with metformin and a sulfonylurea include other DPP-4 inhibitors, SGLT2 inhibitors, thiazolidinediones, acarbose, GLP-1 receptor agonists, and insulin.

## **5 Comparator**

- 5.1 The submission nominated sitagliptin 100mg as the main comparator, with dapagliflozin and saxagliptin included as supplementary comparators. Sitagliptin, a pharmacological analogue of linagliptin, was PBS listed for triple oral therapy on December 1, 2015. The choice of main comparator was appropriate.
- 5.2 Dapagliflozin may also be an appropriate main comparator, given that it has been PBS listed for use in triple oral therapy since July 2015, and sitagliptin was recommended by the PBAC for use in triple oral therapy on a cost minimisation basis versus dapagliflozin.

*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***

- 6.6 The submission was based on a series of indirect comparisons using placebo + metformin + sulfonylurea as common comparator:
- Linagliptin (Trial 1218.18) vs sitagliptin (Studies 229, 053, 253)
  - Linagliptin (Trial 1218.18) vs dapagliflozin (Matthaei 2015)
  - Linagliptin (Trial 1218.18) vs saxagliptin (Moses 2014).
- 6.7 Details of the trials presented in the submission are provided in Table 1.

**Table 1: Trials (and associated reports) presented in the submission**

<b>Trial</b>	<b>Protocol title/Publication title</b>	<b>Publication citation</b>
<i>Linagliptin</i>		
Trial 1218.18	A 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 with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea. NCT00602472; 2007-002450-28	Clinical Study Report, December 2009 Addendum to Clinical Study Report, August 2010 Addendum to Clinical Study Report, July 2011
	Owens DR, Swallow R, Dugi KA, Woerle HJ. Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: A 24-week randomized study.	Diabetic Medicine 2011; 28(11), 1352-1361.
	Zeng Z, Yang JK, Tong N, Yan S, Zhang, X, Gon Y, Woerle HJ. Efficacy and safety of linagliptin added to metformin and sulphonylurea in Chinese patients with type 2 diabetes: a sub-analysis of data from a randomised clinical trial.	Current Medical Research & Opinion 2013; 29(8), 921-929.
<i>Sitagliptin</i>		
Study 229	Round E, Shentu Y, Golm GT, O'Neill EA, Gantz I, Engel SS, Kaufman KD, Goldstein BJ. Safety and efficacy of sitagliptin added to the combination of sulfonylurea and metformin in patients with type 2 diabetes mellitus and inadequate glycemic control. NCT01076075	Diabetes 2013; 62(S1): A299.
Study 035	Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P, Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. NCT00106704	Diabetes, Obesity and Metabolism 2007; 9 (5): 733-745.
Study 253	A study in China evaluating the safety and efficacy of adding sitagliptin to stable therapy with sulfonylurea with or without metformin in participants with type 2 diabetes mellitus. MK-0431-253	NCT01590771
<i>Dapagliflozin</i>		
Matthaei 2015	Matthaei S, Bowering K, Rohwedder K, Grohl A, Parikh S, Study 05 Group. Dapagliflozin Improves Glycemic Control and Reduces Body Weight as Add-on Therapy to Metformin Plus Sulfonylurea: A 24-Week Randomized, Double-Blind Clinical Trial. NCT01392677	Diabetes Care 2015; 38(3):365-72.
	Matthaei S, Bowering K, Rohwedder K, Sugg J, Parikh S, Johnsson E, Study 05 Group. Durability and tolerability of dapagliflozin over 52 weeks as add-on to metformin and sulphonylurea in type 2 diabetes.	Diabetes Obes Metab. Nov 2015; 17(11):1075-84.
<i>Saxagliptin</i>		
Moses 2014	Moses, RG, Kalra S, Brook D, Sockler J, Monyak J, Visvanathan J, Montanaro M, Fisher SA. A randomized controlled trial of the efficacy and safety of saxagliptin as add-on therapy in patients with type 2 diabetes and inadequate glycaemic control on metformin plus a sulphonylurea. NCT01128153	Diabetes, Obesity and Metabolism 2014; 16 (5): 443-450.

Source: Table B-2, pp39-40 of the submission; Table B-3, p7 of Appendix 1; Table B-3, pp6-8 of Appendix 2.

6.8 The key features of the randomised trials are summarised in Table 2.

**Table 2: Key features of the included evidence**

Trial	N	Design/ duration	Risk of bias	Patient population	Outcomes
<b>Linagliptin 5mg vs placebo, in combination with metformin and a sulfonylurea</b>					
Trial 1218.18	1058	R, DB, MC, PG, PC, 24 weeks	Low	Aged 18-80 years with T2DM; HbA1c 7.0%-10.0%	ΔHbA1c; HbA1c responders <7%, <6.5%; FPG
<b>Sitagliptin 100mg vs placebo, in combination with metformin and a sulfonylurea</b>					
Study 229	427	R, DB, MC, PG, PC, 24 weeks	Low	Aged 18-78 years with T2DM; HbA1c 7.5%-10.5%	ΔHbA1c; FPG; 2hr PMG
Study 035 (subgroup)	229 <sup>a</sup>	R, DB, MC, PG, PC, 24 weeks	Low	Aged 18-75 years with T2DM; HbA1c 7.5%-10.5%	ΔHbA1c; HbA1c responders <7%; FPG; 2hr PMG
Study 253 (subgroup)	223 <sup>b</sup>	R, DB, MC, PG, PC, 24 weeks	Low	Aged 18-79 years with T2DM; HbA1c 7.5%-11.0%	ΔHbA1c; FPG; 2hr PMG
<b>Dapagliflozin 10mg vs placebo, in combination with metformin and a sulfonylurea</b>					
Matthaei 2015	218	R, DB, MC, PG, PC, 24 weeks (with 28 week extension)	Low	Aged ≥18 with T2DM; HbA1c 7.0%-10.5%	ΔHbA1c; HbA1c responders <7%; FPG; Δweight; SBP
<b>Saxagliptin 5mg vs placebo, in combination with metformin and a sulfonylurea</b>					
Moses 2014	257	R, DB, MC, PG, PC, 24 weeks	Low	Aged ≥18 with T2DM; HbA1c 7.0%-10.0%	ΔHbA1c; HbA1c responders <7%; FPG; 2hr PMG

<sup>a</sup> Number of patients in the triple therapy subgroup (stratum 2). <sup>b</sup> Full analysis set for the triple therapy subgroup (number of patients randomised to the triple therapy subgroup not reported).

Abbreviations: R, randomised; DB, double blind; MC, multi-centre; PG, parallel group; PC, placebo controlled; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated haemoglobin; ΔHbA1c, change from baseline in HbA1c; FPG, fasting plasma glucose; PMG, post meal glucose; Δweight, change in total body weight; SBP, systolic blood pressure.

Source: compiled during the evaluation.

### Comparative effectiveness

- 6.9 The results of the indirect comparison for the key outcome, mean change from baseline in HbA1c at 24 weeks are presented in Table 3.

**Table 3: Mean change in HbA1c (SE) from baseline to week 24**

Trial	LINA 5mg + MET + SU	PBO + MET + SU	Comparator + MET + SU	Mean difference (95% CI)
<b>Linagliptin trial</b>				
Trial 1218.18	-0.72 (0.03) (n=778)	-0.10 (0.05) (n=262)	-	-0.62 (-0.73, -0.50)
<b>Sitagliptin trials</b>				
Study 229	-	-0.16 (0.06) (n=202)	-0.84 (0.07) (n=203)	-0.68 (-0.86, -0.50)
Study 035	-	0.30 (0.08) (n=109)	-0.59 (0.08) (n=115)	-0.89 (-1.10, -0.68)
Study 253	-	-0.45 (0.08) (n=112)	-0.86 (0.08) (n=111)	-0.41 (-0.60, -0.20)
Meta-analysis of sitagliptin 100mg (+MET+SU) vs placebo (+MET+SU) Heterogeneity: I <sup>2</sup> =80%				██████████
Indirect comparison: linagliptin 5mg (+MET+SU) vs sitagliptin 100mg (+MET+SU) Result <0 favours linagliptin				██████████
<b>Dapagliflozin trial</b>				
Matthaei 2015	-	-0.17 (0.07) (n=108)	-0.86 (0.07) (n=108)	-0.69 (-0.89, -0.49)
Indirect comparison: linagliptin 5mg (+MET+SU) vs dapagliflozin 10mg (+MET+SU) Result <0 favours linagliptin				██████████
<b>Saxagliptin trial</b>				
Moses 2014	-	-0.08 (0.08) (n=127)	-0.74 (0.08) (n=127)	-0.66 (-0.86, -0.47)
Indirect comparison: linagliptin 5mg (+MET+SU) vs saxagliptin 5mg (+MET+SU) Result <0 favours linagliptin				██████████

Abbreviations: HbA1c, glycosylated haemoglobin; SE, standard error; LINA, linagliptin; MET, metformin; SU, sulfonylurea; PBO, placebo; SITA, sitagliptin; CI, confidence interval, DAPA, dapagliflozin; SAXA, saxagliptin

Source: Table B-24, pp89-90 of the submission; Table B-16, p30, Appendix 2 of the submission; Table B-14, p26, Appendix 1 of the submission.

- 6.10 The indirect comparison of linagliptin with the pooled sitagliptin estimate resulted in an upper limit of the 95% confidence interval below the pre-specified non-inferiority margin of 0.4%. There was statistical heterogeneity between sitagliptin trials (I<sup>2</sup>=80%), with differences in HbA1c reduction in placebo arms between trials suggesting that pooling of the data may not be appropriate. Sensitivity analyses presented in the submission excluding various sitagliptin trials were suggestive of non-inferiority.
- 6.11 Indirect comparisons of linagliptin to the supplementary comparators dapagliflozin and saxagliptin were consistent with non-inferiority.
- 6.12 No studies were presented that examined the linagliptin/metformin FDC in triple oral therapy. The submission noted that equivalence between the linagliptin/metformin FDC and its individual components had previously been accepted by the PBAC (April 2013 linagliptin/metformin FDC PSD). This was reasonable.

**Comparative harms**

- 6.13 A summary of the key adverse events reported in the trials is provided in Table 4.

**Table 4: Summary of reported adverse events in the linagliptin, sitagliptin, dapagliflozin, and saxagliptin trials included in the indirect analyses**

Trial - treatment arm	N	Any AE n (%)	Treatment-related AE n (%)	AE leading to discontinuation n (%)	Serious AE n (%)	Hypoglycaemia n (%)
<b>Trial 1218.18 (24 weeks)</b>						
- LINA 5mg	792	525 (66.3)	142 (17.9)	23 (2.9)	25 (3.2)	188 (23.7)
- PBO	263	157 (59.7)	30 (11.4)	5 (1.9)	10 (3.8)	42 (16.0)
<b>Study 229 (24 weeks)</b>						
- SITA 100mg	210	NR	13 (6.2)	NR	NR	31 (14.8) <sup>a</sup>
- PBO	212	NR	5 (2.4)	NR	NR	10 (4.7) <sup>a</sup>
<b>Study 035 subgroup (24 weeks)</b>						
- SITA 100mg	116	73 (62.9)	13 (6.2)	2 (1.7)	7 (6.0)	19 (16.4)
- PBO	113	60 (53.1)	5 (2.4)	2 (1.8)	2 (1.8)	1 (0.9)
<b>Study 253 (24 weeks)<sup>b</sup></b>						
- SITA 100mg	248	106 (42.7)	21 (18.1)	3 (1.2)	7 (2.8)	35 (14.1)
- PBO	249	98 (39.4)	8 (7.1)	7 (2.8)	7 (2.8)	17 (6.8)
<b>Matthaei 2015 (24 weeks)</b>						
- DAPA 10mg	109	53 (48.6)	18 (16.5)	2 (1.8)	1 (0.9)	14 (12.8)
- PBO	109	56 (51.4)	8 (7.3)	3 (2.8)	6 (5.5)	4 (3.7)
<b>Moses 2014 (24 weeks)</b>						
- SAXA 5mg	129	81 (62.8)	21 (16.3)	1 (0.8)	3 (2.3)	13 (10.1)
- PBO	127	91 (71.7)	13 (10.2)	3 (2.3)	7 (5.5)	8 (6.3)

<sup>a</sup> Results reported in sitagliptin product information. Results reported in Round et al (2013) conference abstract: sitagliptin 12 (5.7%); placebo 4 (1.9%). <sup>b</sup> Data for triple oral therapy subgroup not available, presented data include patients treated with dual therapy and triple therapy.

Abbreviations: AE, adverse event; DAPA, dapagliflozin; LINA, linagliptin; PBO, placebo; SAXA, saxagliptin; SITA, sitagliptin. Source: Tables B-27, p101; B-28, p104; B-29, p107; B-30, p110; B-31, p113 of the submission. Tables B-20, p32; B-21, p33; B-22, p33; B-23, p34; B-24, p35 of Appendix 2 of the submission. Tables B-17, p29; B-18, p29; B-19, p30; B-20, p31; B-21, p32 of Appendix 1 of the submission.

- 6.14 Apart from a statistically significant difference for 'any adverse event' when linagliptin was indirectly compared to saxagliptin (in favour of saxagliptin), there were no other statistically significant differences observed. However, the results of the indirect safety analysis should be interpreted with caution due to differences in adverse event definitions between trials, and wide confidence intervals for some of the examined variables.

### **Clinical claim**

- 6.15 The submission described linagliptin as non-inferior in terms of comparative efficacy and safety to sitagliptin, dapagliflozin and saxagliptin, when used in triple oral therapy with metformin and a sulfonylurea. This claim was adequately supported.
- 6.16 The submission reiterated the claim that linagliptin/metformin FDC is equivalent to the individual components taken concomitantly. This claim was previously accepted by the PBAC (April 2013 linagliptin/metformin FDC PSD).
- 6.3 The PBAC considered that the claim of non-inferior comparative effectiveness was reasonable.
- 6.4 The PBAC considered that the claim of non-inferior comparative safety was reasonable.

**Economic analysis**

- 6.17 The submission presented a cost-minimisation analysis for linagliptin versus sitagliptin. This was consistent with the claim of non-inferiority between linagliptin and sitagliptin.
- 6.18 The submission included a cost-minimisation analysis of linagliptin/metformin FDCs against their individual components. This was reasonable.
- 6.19 The equi-effective doses for linagliptin and sitagliptin proposed in the submission were based on the dose regimens of the included randomised trials (linagliptin 5mg and sitagliptin 100mg). These doses were previously accepted by the PBAC in its recommendation of linagliptin for dual oral therapy with metformin or a sulfonylurea on the basis of cost-minimisation with sitagliptin (November 2011 linagliptin PSD).
- 6.20 Table 5 summarises the proposed equi-effective doses of the linagliptin/metformin FDCs and their individual components, which were based on the results of the bioequivalence trials previously considered by the PBAC (April 2013 linagliptin/metformin FDC PSD). The equi-effective doses used in the submission were appropriate.

**Table 5: Equi-effective doses for the linagliptin/metformin FDC**

Linagliptin/metformin FDC	Equi-effective doses
2.5mg/500mg twice daily	Linagliptin 5mg daily/metformin 500mg twice daily
2.5mg/850mg twice daily	Linagliptin 5mg daily/metformin 850mg twice daily
2.5mg/1000mg twice daily	Linagliptin 5mg daily/metformin 1000mg twice daily

Abbreviations: FDC, fixed dose combination.  
Source: Table D.1.1 of the submission.

- 6.21 The prices requested for linagliptin and linagliptin/metformin FDCs are equivalent to the prices for dual oral therapy in type 2 diabetes.
- 6.22 Sitagliptin is scheduled to have a 5% statutory price reduction on 1 April 2016. At the proposed ex-manufacturer price for linagliptin 5mg, the daily cost of treatment is \$0.08 more than for sitagliptin (reduced to account for the April 2016 price reduction). Linagliptin is scheduled to have a 5% statutory price reduction in April 2017.

**Drug cost/patient/year:**

- \$748.25 for linagliptin 5mg;
  - \$770.15 for linagliptin 2.5mg/metformin 500mg FDC;
  - \$784.75 for linagliptin 2.5mg/metformin 850mg FDC; and
  - \$790.71 for linagliptin 2.5mg/metformin 1000mg FDC.
- 6.23 At the requested DPMQ of \$61.50 for a 30 pack of linagliptin 5mg, 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).
  - 6.24 The DPMQ for sitagliptin 100mg 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).

**Estimated PBS usage & financial implications**

- 6.25 The submission was not considered by DUSC. The analysis was based on a market share approach where a proportion of the patients taking a PBS listed DPP-4 inhibitor (sitagliptin or saxagliptin) in triple oral therapy with metformin and a sulfonylurea switch to linagliptin triple oral therapy.
- 6.26 The total DPP-4 inhibitor triple oral therapy market for the first two years of PBS listing was estimated by linear extrapolation of the historical DPP-4 inhibitor triple oral therapy utilisation for the period July 2008 to November 2014, derived from a 10% Medicare sample. The sponsor assumed growth rates for the remaining three years of the analysis. Prior to December 2015, no DPP-4 inhibitors were PBS listed for use in triple oral therapy, and therefore the projections are based on DPP-4 inhibitor use outside of PBS restrictions. Utilisation rates based solely on a cohort using DPP-4 inhibitors outside of PBS restrictions are likely to underestimate the size of the DPP-4 inhibitor triple oral therapy market.
- 6.27 The DPP-4 inhibitor triple oral therapy market estimates did not identify PBS compliant patients with private scripts for the metformin, sulfonylurea, or DPP-4 inhibitor component of triple oral therapy, as they were not included in the 10% Medicare sample data. The impact of substitution for other listed triple oral therapy agents (such as dapagliflozin, pioglitazone, exenatide, and insulin) was not explored.
- 6.28 The sponsor argued that the listing of linagliptin was unlikely to affect growth of the DPP-4 inhibitor triple oral therapy market, given that sitagliptin and saxagliptin had both received positive PBAC recommendations at the time of the submission, and were expected to be PBS listed prior to linagliptin. This was reasonable.
- 6.29 Dapagliflozin was PBS listed for triple oral therapy in July 2015. As the 10% Medicare sample preceded this date, the impact of dapagliflozin PBS listing on the triple therapy market, and the dynamics between DPP-4 inhibitor and SGLT2 inhibitor utilisation for triple oral therapy are unclear.
- 6.30 The sponsor proposed a market share for linagliptin of █% rising to █% by the end of year 1, and █% from the end of year 2 onwards. The submission suggested that the market share assumptions were justified given that, unlike sitagliptin and saxagliptin, linagliptin does not require dose reduction in renal impairment. The linagliptin/metformin FDC share of the linagliptin market was estimated at █% in year 1, increasing to █% by year 5. Market share projections for linagliptin and the linagliptin/metformin FDCs are inherently uncertain, especially given differences in the timing of PBS listings, historical usage outside of PBS restrictions, listing of SGLT2 inhibitors for use in triple oral therapy, and the availability of FDCs with immediate and extended release metformin.
- 6.31 The financial analysis provided in the submission did not incorporate the 5% statutory price reduction for sitagliptin which will occur on April 1, 2016; prior to the proposed date of PBS listing for linagliptin (August 1, 2016). The submission's estimates were updated during the evaluation to reflect the change in price for sitagliptin. Price reductions for linagliptin and saxagliptin are scheduled for April 1, 2017. The estimates were updated to reflect the 2016 co-payment rates. The Pre-Sub-

Committee Response (p. 2) included the scheduled price reductions for linagliptin and saxagliptin in 2017 into a revised table of estimated financial implications.

- 6.32 Table 6 summarises the estimated use and net financial implications of listing linagliptin and linagliptin/metformin FDC tablets for triple oral therapy.

**Table 6: Estimated use and net financial implications of listing linagliptin and linagliptin/metformin FDC tablets for triple oral therapy**

	Year 1	Year 2	Year 3	Year 4	Year 5
<b>Patients (linagliptin not PBS listed)</b>					
Sitagliptin (80%)					
Saxagliptin (20%)					
<b>Patients (linagliptin PBS listed)</b>					
Sitagliptin			( %)	( %)	( %)
Saxagliptin			( %)	( %)	( %)
Linagliptin	<sup>1</sup>	<sup>2</sup>	( %)	( %)	( %)
<b>Scripts (linagliptin PBS listed)</b>					
Linagliptin 5mg					
Linagliptin 2.5mg/met 500mg					
Linagliptin 2.5mg/met 850mg					
Linagliptin 2.5mg/met 1000mg					
<b>Cost to PBS (linagliptin not PBS listed)</b>					
DPP-4 market (DPMQ)	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Net cost to PBS	\$	\$	\$	\$	\$
<b>Cost to PBS (linagliptin PBS listed)</b>					
DPP-4 market (DPMQ)	\$	\$	\$	\$	\$
Patient co-payments	\$	\$	\$	\$	\$
Net cost to PBS	\$	\$	\$	\$	\$
<b>Difference in costs to PBS (linagliptin PBS listed – linagliptin not PBS listed)</b>					
Costs at DPMQ	-\$	-\$	-\$	-\$	-\$
Patient co-payments	\$	\$	\$	\$	\$
Net costs to the PBS	\$	\$	-\$	-\$	-\$

Abbreviations: met, metformin; DPP-4, dipeptidyl peptidase-4; DPMQ, dispensed price for maximum quantity.

<sup>1</sup> Market share increases linearly from % to % in first year; <sup>2</sup> Market share increases linearly from % to % in second year.

Numbers in italics updated during the evaluation to incorporate 5% statutory price reduction for sitagliptin (from 1 April 2016) and 2016 patient co-payments

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

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.

- 6.33 The updated estimates represented a net cost to the PBS in Year 1 (less than \$10 million) and Year 2 (less than \$10 million), progressing to net savings in Year 3 (less than \$10 million), Year 4 (less than \$10 million) and Year 5 (less than \$10 million), with a cumulative saving of less than \$10 million over the 5 year period examined. This differed from the estimates in the submission, which suggested a saving of less than \$10 million in Year 1, increasing to less than \$10 million in Year 5, with a cumulative saving of less than \$10 million over the first 5 years. The difference in estimates was due to the inclusion of the 5% statutory price reduction for sitagliptin, and incorporation of the 2016 co-payment rates.

- 6.34 The estimates for comparators sitagliptin and saxagliptin were based on use as individual components only, and potential cost savings from substitution for their respective FDCs were not included in the analysis.
- 6.35 Overall, limitations in the methodology used to forecast DPP-4 inhibitor triple oral therapy utilisation (which was based solely on use outside of PBS restrictions); coupled with inherent uncertainty in the market share assumptions, suggest that the financial estimates may not be reliable.

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

## **7 PBAC Outcome**

- 7.1 The PBAC recommended the Authority Required (Streamlined) listing of linagliptin in triple oral combination with metformin and a sulfonylurea on a cost minimisation basis with sitagliptin. The equi-effective doses were linagliptin 5mg and sitagliptin 100mg.
- 7.2 The PBAC recommended the Authority Required (Streamlined) listing of linagliptin with metformin (FDC) in combination with a sulfonylurea on a cost minimisation basis to the individual components taken concomitantly. The PBAC noted that the equi-effective doses were based on the results of the bioequivalence trials previously considered by the Committee (April 2013 linagliptin/metformin FDC PSD).
- 7.3 The PBAC accepted that sitagliptin and saxagliptin were appropriate comparators. The PBAC considered that dapagliflozin was also an appropriate comparator, given that sitagliptin was recommended by the PBAC for use in triple oral therapy on a cost-minimisation basis versus dapagliflozin.
- 7.4 The PBAC considered the clinical claim of non-inferior comparative effectiveness and safety for linagliptin compared with sitagliptin, dapagliflozin and saxagliptin when used in triple oral therapy with metformin and a sulfonylurea, was reasonable.
- 7.5 The PBAC recalled that it previously accepted the claim that linagliptin with metformin FDC is equivalent to the individual components taken concomitantly (April 2013 linagliptin/metformin FDC PSD).
- 7.6 The PBAC recommended that the restriction permit a patient who had previously demonstrated that their diabetes was unable to be controlled with metformin or a sulfonylurea to access PBS subsidised linagliptin and linagliptin with metformin FDC without the need to requalify. The PBAC noted that this was consistent with the restrictions for sitagliptin, dapagliflozin and saxagliptin.
- 7.7 The PBAC recommended that the restriction wording for these listings be consistent with the restrictions for triple oral therapy listings for sitagliptin and its FDC, which are in turn consistent with the SGLT2 inhibitor restrictions.
- 7.8 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 of linagliptin and linagliptin with metformin for triple oral therapy.

- 7.9 The PBAC advised that linagliptin and linagliptin with metformin FDC are suitable for prescribing by Nurse Practitioners for Continuing Therapy Only
- 7.10 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that linagliptin should be treated as interchangeable on an individual patient basis with sitagliptin and saxagliptin for triple oral therapy. The PBAC also advised under Section 101(3BA) that linagliptin with metformin should be treated as interchangeable on an individual patient basis with sitagliptin with metformin and saxagliptin with metformin for triple oral therapy.
- 7.11 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	No. of Rpts	Proprietary Name and Manufacturer	
LINAGLITPIN linagliptin 5 mg tablet	30	5	Trajenta®	Boehringer Ingelheim Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS Indication:</b>	Diabetes mellitus type 2
<b>Restriction Level / Method:</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

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<p><b>Clinical criteria:</b></p>	<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 (SGLT-2) inhibitor despite treatment with optimal doses of dual oral therapy; 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 gliptazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor despite treatment with optimal doses of dual oral therapy.</p>
<p><b>Prescriber Instructions</b></p>	<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 gliptazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a gliptazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (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 gliptazone, a glucagon-like peptide-1 or an SGLT-2 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this drug.</p>

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<b>Administrative Advice</b>	<p><u>Note: Continuing Therapy Only:</u> 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.</p> <p><u>Note:</u> This drug is not PBS subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1, or an SGLT2 inhibitor.</p> <p><u>Note</u> PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>
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Name, Restriction, Manner of administration and form	Max. Qty	No. 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 Ingelhiem Pty Ltd

<b>Category / Program</b>	GENERAL – General Schedule (Code GE)
<b>Prescriber type:</b>	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
<b>Condition:</b>	Diabetes mellitus type 2
<b>PBS Indication:</b>	Diabetes mellitus type 2
<b>Restriction Level / Method:</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>Clinical criteria:</b>	<p>The treatment must be in combination with a sulfonylurea,</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 optimal doses of dual oral therapy; OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor despite treatment with optimal doses of dual oral therapy.</p>

<p><b>Prescriber Instructions</b></p>	<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 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.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin or a sulfonylurea does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.</p>
<p><b>Administrative Advice</b></p>	<p><u>Note: Continuing Therapy Only:</u>  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.</p> <p><u>Note:</u>  The 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.</p> <p><u>Note:</u>  PBS subsidised dual oral therapy does not include concomitant use of a combination of: a gliptin, a glitazone or an SGLT2 inhibitor.</p>

**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.

