

**6.12 VILDAGLIPTIN,
Tablet 50mg, Galvus®
VILDAGLIPTIN WITH METFORMIN,
Tablet containing 50 mg vildagliptin with 500 mg
metformin hydrochloride, Galvumet® 50/500
Tablet containing 50 mg vildagliptin with 850 mg
metformin hydrochloride, Galvumet® 50/850
Tablet containing 50 mg vildagliptin with 1000 mg
metformin hydrochloride, Galvumet® 50/1000
Novartis Pharmaceuticals Australia Pty Ltd**

1 Purpose of application

- 1.1 The major submission requested an Authority Required (STREAMLINED) listing for vildagliptin and vildagliptin with metformin fixed dose combination (FDC) for the treatment of type 2 diabetes mellitus (T2DM) in combination with insulin.
- 1.2 Listing was requested on a cost-minimisation basis compared to sitagliptin, linagliptin, dapagliflozin and empagliflozin.

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

Component	Description
Population	Patients with type 2 diabetes using insulin therapy
Intervention	Vildagliptin, 50mg, tablet qd (once daily) or 100 mg (50 mg bid (twice daily)) Vildagliptin 50mg + metformin hydrochloride 500mg FDC tablet bid Vildagliptin 50mg + metformin hydrochloride 850mg FDC tablet bid Vildagliptin 50mg + metformin hydrochloride 1000mg FDC tablet bid
Comparator	Main comparators: linagliptin 5mg/day and sitagliptin 100mg/day Secondary comparators: dapagliflozin 10mg/day and empagliflozin 25mg/day
Outcomes	Mean change in HbA1c from baseline and overall safety outcomes
Clinical claim	In adult patients with type 2 diabetes mellitus, vildagliptin is non-inferior in terms of comparative effectiveness and safety to linagliptin, sitagliptin, dapagliflozin and empagliflozin, in combination with insulin therapy, at improving blood glucose levels.

Abbreviation: bid- twice daily; qd- once per day, HbA1c – haemoglobin A1c. Source: Table 1.1, p2 of the submission, Section 1.1.3, p4 of the submission

2 Requested listing

- 2.1 The submission sought Authority Required (STREAMLINED) listing for vildagliptin and vildagliptin with metformin FDC with restrictions similar to those of its main comparators, sitagliptin and linagliptin, when used in combination with insulin.
- 2.2 The requested restriction is consistent with the TGA indications and PBS restrictions for vildagliptin, vildagliptin with metformin FDC and its comparators.

- 2.3 In the Pre-Subcommittee Response (PSCR, p1) the sponsor acknowledged and accepted the listing should be consistent with other PBS-listed dipeptidyl peptidase 4 (DPP4) inhibitors when used in combination with insulin and to clarify prescriber instructions.

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

3 Background

Registration status

- 3.1 TGA status at time of PBAC consideration: Vildagliptin was approved, on 19 November 2013, for use in the treatment of T2DM in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control: in combination with insulin (with or without metformin) when diet, exercise and a stable dose of insulin alone do not result in adequate glycaemic control. Vildagliptin with metformin FDC was approved on 19 November 2013, for patients with T2DM, as an add-on to insulin as an adjunct to diet and exercise to improve glycaemic control in patients when stable dose of insulin and metformin alone do not provide adequate glycaemic control.
- 3.2 Vildagliptin and vildagliptin with metformin FDC have not previously been considered by the PBAC for treatment of T2DM in combination with insulin with or without metformin.
- 3.3 Vildagliptin and vildagliptin with metformin FDC are currently PBS listed for use in dual oral combination therapy (vildagliptin with metformin or a sulfonylurea) and triple oral combination therapy (vildagliptin with metformin and a sulfonylurea).

4 Population and disease

- 4.1 Adult patients whose T2DM is not adequately controlled on insulin therapy with or without metformin.
- 4.2 The clinical management algorithm for T2DM patients on third line therapy in combination with insulin includes diabetes medicines, both listed and not listed on the PBS:
- FDCs of oral diabetes medicines with metformin; and
 - Other diabetes medicines including sulfonylureas, other dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose co-transporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, thiazolidinediones and acarbose.
- 4.3 The submission proposed the PBS listing of vildagliptin will become an alternative treatment to other PBS listed DPP-4 inhibitors in the third line treatment of T2DM patients not adequately controlled on insulin with or without metformin (p10 of the submission).

5 Comparator

- 5.1 The submission nominated both sitagliptin and linagliptin as the main comparators. The main arguments provided in support of this nomination were that both linagliptin and sitagliptin are DPP-4 inhibitors, pharmacological analogues of vildagliptin, and currently listed on the PBS for use in combination with insulin therapy in T2DM (p4 of the submission).
- 5.2 The submission nominated dapagliflozin and empagliflozin (both SGLT2 inhibitors) as secondary comparators (p4 of the submission). The main argument provided in support of this nomination was that dapagliflozin, along with sitagliptin, was previously accepted by PBAC as a comparator for linagliptin (Linagliptin PSD, March 2016 PBAC meeting). PBS therapeutic relativity sheets show sitagliptin, linagliptin and empagliflozin are recommended on a cost-minimisation basis with dapagliflozin in combination with insulin. Based on the PBS therapeutic relativity sheets, the submission concluded that linagliptin, sitagliptin, dapagliflozin and empagliflozin are equivalent (p25 of the submission).
- 5.3 The PBAC agreed that the comparators were appropriate.

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 three head-to-head randomised controlled trials (RCTs) comparing vildagliptin to sitagliptin and linagliptin, in combination with insulin:
 - Study 23138: vildagliptin (n=83) vs. sitagliptin (n=65) in T2DM patients with severe renal impairment
 - Tang 2015: vildagliptin (n=166) vs. sitagliptin (n=165) vs. linagliptin (n=164) in T2DM patients
 - Study ADE07: vildagliptin (n=25) vs. sitagliptin (n=26) in T2DM patients with a pre-existing cardiovascular disease.
- 6.4 The submission also presented additional three placebo-controlled vildagliptin studies, plus insulin, to support the clinical claim of non-inferiority (Study 23135, Study 2311 and Study 23137). These studies were used for the vildagliptin TGA label (indication) application.
- 6.5 No trials were identified for vildagliptin with metformin FDC used in combination with insulin. Three bioequivalence trials were presented comparing free combination of vildagliptin and metformin to vildagliptin with metformin FDC (Study LMF2302,

Study LMF 2307 and Study LMF 2301). The three trials were presented in previous PBAC submissions for vildagliptin (PBAC November 2010 meeting and March 2016 meeting).

- 6.6 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
Direct randomised trial(s)		
Study 23138 (CLAF237A23138)	Naik R, Wilkinson C, Lyathakula S, Lukashevich V. A multi-center, randomized, double-blind, active-controlled clinical trial to evaluate the safety and tolerability of 24 weeks treatment with vildagliptin (50 mg qd) versus sitagliptin (25 mg qd) in patients with type 2 diabetes and severe renal insufficiency	2011 Novartis Clinical Study Report
	Kothny, W., Lukashevich, V., Foley, J. E., Rendell, M. S., & Schweizer, A. Comparison of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment: a randomised clinical trial.	2015 Diabetologia, 58(9), 2020–2026.
	Kothny, W., V., Foley, Schweizer, A., Rendell, M. S., & Lukashevich, J. E. Efficacy of vildagliptin and sitagliptin in patients with type 2 diabetes and severe renal impairment	2014 Diabetologia 57(1): S357-S358 (extension study, record no. 81, ABSTRACT)
	Safety and Tolerability of Vildagliptin Versus Sitagliptin in Patients With Type 2 Diabetes and Severe Renal Insufficiency (Study 2, NCT00616811)	
	Safety and Tolerability of Vildagliptin Versus Sitagliptin in Patients With Type 2 Diabetes and Severe Renal Insufficiency (28-week Extension Study 4, NCT00770081)	
Tang	Tang, Y.-Z., Wang, G., Jiang, Z.-H., Yan, T.-T., Chen, Y.-J., et al. Efficacy and safety of vildagliptin, sitagliptin, and linagliptin as add-on therapy in Chinese patients with T2DM inadequately controlled with dual combination of insulin and traditional oral hypoglycemic agent.	2015 Diabetology & Metabolic Syndrome, 7, 91.
Study ADE07 (CLAF237ADE07)	Multicentric cross-over trial to assess the glycemic profiles on 8 weeks of vildagliptin and sitagliptin treatment, each, in type 2 diabetic patients with a pre-existing cardiovascular disease pre-treated with insulin, using a PROBE design. Vildagliptin vs. Sitagliptin add-on to insulin - impact on glycaemic profile and correlation of hypoglycaemic episodes and heart function (Study 7, NCT01686932)	2015 Novartis Clinical Study Report
Supplementary placebo-controlled trials		
Study 23135 (CLAF237A23135)	Wraith L, Paramal R, Kozlovski P, Lukashevich V A 24-week, multi-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of vildagliptin 50mg bid as an add-on therapy to insulin, with or without metformin, in patients with type 2 diabetes mellitus	2012 Novartis Clinical Study Report
Study 2311 (CLAF237A2311)	Albrecht, D., Shirt L., Dejager S., Schweizer A. A multi-center, double-blind, randomized, parallel-group study to compare the effect of 24 weeks treatment with LAF237 50 mg bid to placebo as add-on therapy in patients with type 2 diabetes treated with insulin	2005 Novartis Clinical Study Report
Study 23137 (CLAF237A23137)	Naik R, Wilkinson C, Paramal R, Lukashevich V A multi-center, randomized, double-blind, clinical trial to evaluate the safety and tolerability of 24 weeks treatment with vildagliptin (50 mg qd) versus placebo in patients with type 2 diabetes and moderate or severe renal insufficiency	2011 Novartis Clinical Study Report

Trial ID	Protocol title/ Publication title	Publication citation
Re-presented bioequivalence Trials		
LMF2303 (LMF237A2303)	He YL, Paladini S, Leon S, Ligueros M An open-label, randomized, single-dose, crossover, study to establish the bioequivalence between the fixed combination of 50/500 mg LAF237/Metformin tablet and the free combination of LAF237 50 mg and Metformin (Glucophage®) 500 mg tablets	2006 Novartis Clinical Study Report
LMF2307 (LMF237A2307)	He YL, Sabia H, Ligueros M, Leon S An open-label, randomized, single-dose, crossover, study to establish the bioequivalence between the fixed combination of 50/850 mg LAF237/metformin FMI tablet and the free combination of LAF237 50 mg tablet and metformin (Glucophage®) 850 mg tablet	2006 Novartis Clinical Study Report
LMF2301 (CLMF237A2301)	He YL, Paladini S, Leon S, Ligueros M An open-label, randomized, single-dose, crossover, study to establish the bioequivalence between the fixed combination of 50/1000 mg LAF237/metformin tablet and the free combination of LAF237 50 mg and metformin (Glucophage®) 1000 mg (2 x 500 mg) tablets	2006 Novartis Clinical Study Report

Abbreviation: bid – twice per day; qd- once per day; Source: Table 2.3, p22-24 and Table 2.4, p24 of the submission, Attachments 9-11 of the submission, UMIN-CTR Clinical Trial website

6.7 Key features of the three direct randomised trials are summarised in Table 3.

Table 3: Key features of the three randomised trials of vildagliptin compared to sitagliptin and linagliptin

Trial	N	Design/ duration/ follow-up	Risk of bias	Patient population	Outcome(s)
Study 23138	N=148	DB, R, MC 24 weeks (28 weeks follow-up)	Low	T2DM + severe renal insufficiency; 18-85 years; HbA1c 6.5-10.0%; BMI 18-42 kg/m ² ; GFR<30mL/min/1.73m ² Treatment: Untreated or treated ^A with AD therapy (SU, TZD, meglitinide or insulin) on a stable dose (stable insulin±20%) for 4 weeks prior to 1st visit	Primary: AEs and serious AEs at week 24 Secondary: Δ HbA1c or Δ FPG at week 24
Tang 2015	N=495	R, OL 12 weeks	High	T2DM; >18 years; HbA1c >7.0%; BMI 22-45 kg/m ² ; Treatment: Insulin at a stable dose of 20-80U/d Metformin or acarbose for at least 12 weeks prior to screening	Primary: Endpoint of the mean Δ HbA1c, % of patients <7% HbA1c at week 12 Secondary: Δ FPG, Δ PPG and Δ insulin dose at week 12
Study ADE07	N=51	R, OL,MC, CO 8 weeks	Uncertain	T2DM + cardiovascular risk factors; 40-80 years; HbA1c 7.0-9.0%; Cardiovascular risk factors Treatment: Insulin (±10%) for at least 12 weeks prior to 1st visit Optional treatment with stable dose of metformin (≥1500mg/d) for at least 12 weeks prior to screening	Primary: CGM (3 measures, for 5 days each) ¹ Secondary: CGM, ECG, Inflammatory biomarkers, β-cell biomarkers ²
Meta-analysis	N=694	Included Study 23138, Tang 2015 and Study ADE07; assessed Δ HbA1c comparing vildagliptin and sitagliptin in combination with insulin.			

Note: ^A-about 60.8% patients were on insulin only and 12.22% patients on SU+insulin therapy, and the remainder not reported; 1 defined as the area under the glucose/time curve and cumulatively obtained by a 5-day CGM; 2 CGM and ECG (3 measures, for 5 days each), inflammatory biomarkers (IL6, hsCRP), β-cell biomarkers (insulin, pro-insulin, C-peptide)

Abbreviations: Δ- change in; AD, anti-diabetic; AE- adverse events; BMI, body mass index; CGM, Continuous glucose monitoring; CO, cross over; DB, double blind; HbA1c, haemoglobin A1c; FPG, fasting plasma glucose; GFR, glomerular filtration rate; MC, multi-centre; OL, open label; PPG, postprandial plasma glucose; R, randomised; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, Thiazolidinediones.

Source: Compiled during the evaluation; Table 2.20, p.42-43 of the submission; CSR 23138 pp6-70; Tang et al. 2015; CSR ADE07 pp35-45; all publications in Attachment 9.

- 6.8 Tang 2015 has a high risk of bias due to the trial not reporting the method of randomisation, whether the outcome assessors were blinded and the method used to address missing data.
- 6.9 Study ADE07 has a risk of bias that was uncertain as blinding of outcome assessors was not reported.
- 6.10 The risk of bias in the three placebo-controlled trials is low.
- 6.11 In the Pre-PBAC Response (p1) the sponsor noted the heterogeneity, adding that “the evidence from the direct comparison is still considered to represent the best evidence in the hierarchy preferred by the PBAC” (p1).

Comparative effectiveness

6.12 Table 4 summarises the trials and pooled results of change in haemoglobin A1c (HbA1c) from baseline in the vildagliptin, sitagliptin and linagliptin head-to-head RCTs, in combination with insulin, and the vildagliptin-placebo trials, in combination with insulin, between the treatments for the duration of the trial.

Table 4: Results of mean change in HbA1c across the head-to-head randomised trials and placebo trials

Study ID/ treatment arm	Weeks	Baseline HbA1c Mean \pm SD	Adj Δ from baseline Mean \pm SD	Difference to control Mean \pm SD	Mean (95% CI)	p-value
HbA1c OUTCOME						
HEAD-TO-HEAD TRIALS						
Study 23138 (Secondary outcome)						
Vildagliptin 50 mg qd (n=79)	24	7.50 \pm 0.10	-0.39 \pm 0.14	0.10 (0.18)	0.10 (-0.32, 0.52)	0.591
Sitagliptin 25mg qd (n=62)		7.80 \pm 0.14	-0.49 \pm 0.16			
Study 23138 extension study^{1,2} (Secondary outcome)						
Vildagliptin 50 mg qd (n=41)	28	7.52 \pm 0.13	-0.49 \pm 0.16	0.10 (0.18)	0.04 (-0.46, 0.54) ²	0.88 ²
Sitagliptin 25mg qd (n=33)		7.82 \pm 0.21	-0.53 \pm 0.20			
Tang 2015 (Primary outcome)						
Vildagliptin 50 mg bid (n=166)	12	9.59 \pm 1.84	-1.33 \pm 0.11	NR	-0.49 (-0.51, -0.47) ²	0.000
Sitagliptin 100mg qd (n=165)		9.22 \pm 1.60	-0.84 \pm 0.08			
Linagliptin 5mg qd (n=164)		9.58 \pm 1.80	-0.81 \pm 0.08			
Study ADE07 (Secondary outcome)						
Vildagliptin 50 mg bid (n=49)	8	7.83 \pm 0.52	-0.62 \pm 0.57	NR	-0.12 (-0.34, 0.10)	0.29 ²
Sitagliptin 100mg qd (n=49)		7.83 \pm 0.52	-0.50 \pm 0.55			
Meta-analysis³ of Study 23138, Tang 2015 and Study ADE07 [$X^2=18.22$, $df=2$ ($p=0.0001$);$I^2 = 89\%$]					-0.21 (-0.56, 0.14)	0.24
PLACEBO-CONTROLLED TRIALS						
Study 23137 moderate renal impairment⁴						
Vildagliptin 50 mg qd (n=157)	24	7.86 \pm 0.08	-0.74 \pm 0.10	-0.53 (0.11)	-0.53 (-0.75, -0.31)	<0.0001
Placebo (n=128)		7.79 \pm 0.08	-0.21 \pm 0.11			
Study 23137 severe renal impairment⁴						
Vildagliptin 50 mg qd (n=122)	24	7.69 \pm 0.09	-0.88 \pm 0.16	-0.56 (0.13)	-0.56 (-0.83, -0.30)	<0.0001
Sitagliptin (n=95)		7.65 \pm 0.10	-0.32 \pm 0.16			
Study 23135						
Vildagliptin 50 mg bid (n=221)	24	8.80 \pm 0.07	-0.77 \pm 0.08	-0.72 (0.10)	-0.72 (-0.92, -0.52)	<0.001
Placebo (n=215)		8.84 \pm 0.07	-0.05 \pm 0.08			
Study 2311						
Vildagliptin 50 mg bid (n=125)	24	8.52 \pm 0.09	-0.51 \pm 0.09	-0.27 (0.12)	-0.27 (-0.51, -0.04) ²	0.022
Placebo (n=131)		8.54 \pm 0.09	-0.05 \pm 0.08			
Meta-analysis³ of Study 23137, Study 23135 and Study 2311 [$X^2=7.00$, $df=3$ ($p=0.07$);$I^2 = 57\%$]					-0.52 (-0.74, -0.30)	<0.0001

Note: 1 values are expressed as mean \pm standard error; 2 estimated in Review Manager 5.1, Attachment 16 of the submission; when p value is not reported in the study, it is estimated in the Review Manager 5.1; 3 pooled results using random effects model, from Review Manager 5.1, Attachment 16 and 17 of the submission; 4 measured as change in HbA1c from baseline to rescue-censored endpoint; Abbreviations: bid, twice per day; qd, once per day; SD, standard deviation; CI, confidence interval; n, number of participants; NR, not reported.

Source: CSR 23138 p82; CSR 23138e p59; Tang et al. 2015; CSR ADE07 p85; all publications in Attachment 9; CSR 23135 p76; CSR2311 p55; CSR 23137 p85; CSR 23137e p78; all publications in Attachment 10.

6.13 Using the non-inferiority margin of 0.4%, Tang 2015 found a statistically significant difference in HbA1c reduction which provided the foundation to claim superiority of vildagliptin over sitagliptin or linagliptin. The submission claimed that Study ADE07 and Study 23138 demonstrated non-inferiority to both vildagliptin and sitagliptin with the 95% confidence intervals crossing zero (the difference was not statistically

significant) (p48 of the submission). Study ADE07 and Study 23138 were not powered to demonstrate non-inferiority in HbA1c reduction. The guidelines¹ on the clinical investigation of medicinal products in the treatment of diabetes recommend a non-inferiority margin of 0.3% for reductions in HbA1C. Furthermore the upper limit of the confidence interval in Study 23138 was greater than 0.3%, and Study ADE07 only descriptively compared the change in HbA1c levels.

- 6.14 Based on a pooled analysis of the head-to-head trials, no statistically significant difference in the change in HbA1C levels between the treatments was observed (p=0.24), however the results (-0.21, (95% CI:-0.56, 0.14)) numerically favour vildagliptin.
- 6.15 Tang 2015 did not report whether it was powered to identify changes in HbA1C levels, while Study 23138 and Study ADE07 were only powered for the primary outcomes, and not the secondary outcomes of change in HbA1c. This increases the likelihood of not finding a statistically significant difference between the drugs. Significant heterogeneity ($X^2=18.22$, $df=2$ (p=0.0001); $I^2=89%$) existed across the trials. The upper limit of confidence interval was below the non-inferiority margin of 0.3%, indicating the pooled difference between vildagliptin and sitagliptin in combination with insulin is not statistically significant. The PSCR (p1) acknowledged the heterogeneity across the three head-to-head trials and the issues created when the trials were pooled. The PSCR (p1) also noted the commentary's conclusion (p22) that the "diabetic population represented in the trials are generally similar to the Australian diabetic population".
- 6.16 Based on a pooled analysis of the placebo-controlled trials, the mean change in HbA1c was statistically significant with vildagliptin compared to placebo (mean between group difference of -0.52 [95%CI: -0.74,-0.30]).
- 6.17 The trials were limited in generalisability to the target PBS Australian population with type 2 diabetes mellitus (T2DM). In particular Study 23138 had T2DM patients with moderate and severe renal insufficiency, who were not all on insulin therapy to manage their diabetes, and had a much longer duration of diabetes compared to the target population. Tang 2015 was conducted in Chinese participants only, who had a higher mean HbA1c level compared to the target population. Study ADE07 had T2DM patients with a pre-existing cardiovascular disease, with a higher percentage of male participants, and the duration of diabetes was not reported.

Comparative harms

- 6.18 A summary of key adverse events (AEs) and pooled results reported in the three head-to-head RCTs and three placebo trials is provided in Table 5. The submission entered the incorrect values for the relative risk (RR) and risk difference (RD) for study ADE07.

¹ Committee for Medicinal Products for Human Use (CHMP) (2011). Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus (p9).

Table 5: Summary of adverse events reported in the head-to-head randomised trials and placebo trials

Safety outcome	Vildagliptin n/N (%)	Sitagliptin n/N (%)	Relative risk ¹ (RR) vild-sita 95%CI	Risk difference ¹ (RD) vild-sita (95%CI)
HEAD-TO-HEAD TRIALS				
Any AE (at least one)				
Study 23138	██████████	██████████	██████████	██████████
Study ADE07	██████████	██████████	██████████ ██████████	██████████ ██████████
Pooled analysis²			1.03 (0.78, 1.36)	0.01 (-0.13, 0.15)
Any SAE				
Study 23138	██████████	██████████	██████████	██████████
Study ADE07	██████████	██████████	██████████	██████████
Pooled analysis²			1.08 (0.61, 1.91)	0.02 (-0.04, 0.08)
Any AE resulting discontinuation				
Study 23138	██████████	██████████	██████████	██████████
Study ADE07	██████████	██████████	██████████	██████████
Pooled analysis²			0.81 (0.30, 2.22)	-0.01 (-0.05, 0.04)
Death				
Study 23138	██████████	██████████	██████████	██████████
Study ADE07	██████████	██████████	█	██████████
Pooled analysis² [X²=0.27, df=1 (p=0.60);I² = 0%			1.13 (5.87)	0.01 (-0.03, 0.04)
PLACEBO-CONTROLLED TRIALS				
Safety outcome	Vildagliptin n/N (%)	Placebo n/N (%)	Relative risk ¹ vild-placebo (95%CI)	Risk difference ¹ vild-placebo (95%CI)
Any AE (at least one)				
Study 23135	██████████	██████████	██████████	██████████
Study 2311	██████████	██████████	██████████	██████████
Study 23137 (moderate renal impairment)	██████████	██████████	██████████	██████████
Study 23137 (severe renal impairment)	██████████	██████████	██████████	██████████
Pooled analysis²			1.01 (-0.91, 1.12)	0.01 (-0.06, 0.08)
Any SAE				
Study 23135	██████████	██████████	██████████	██████████
Study 2311	██████████	██████████	██████████	██████████
Study 23137 (moderate renal impairment)	██████████	██████████	██████████	██████████
Study 23137 (severe renal impairment)	██████████	██████████	██████████	██████████
Pooled analysis²			0.95 (0.67, 1.34)	-0.00 (-0.03, 0.03)
AEs resulting in discontinuation				
Study 23135	██████████	██████████	██████████	██████████
Study 2311	██████████	██████████	██████████	██████████
Study 23137 moderate renal impairment	██████████	██████████	██████████	██████████

Safety outcome	Vildagliptin n/N (%)	Sitagliptin n/N (%)	Relative risk ¹ (RR) vild-sita 95%CI	Risk difference ¹ (RD) vild-sita (95%CI)
Study 23137 severe renal impairment	██████████	██████████	██████████	██████████
Pooled analysis²	34/658 (5.2%)	20/599 (3.3%)	1.47 (0.62, 3.48)	0.02 (-0.02, 0.05)
Deaths				
Study 23135	██████████	██████████	██████████	██████████
Study 2311	██████████	██████████	██████████	██████████
Study 23137 moderate renal impairment	██████████	██████████	██████████	██████████
Study 23137 severe renal impairment	██████████	██████████	██████████	██████████
Pooled analysis²	5/658 (0.8%)	7/599 (1.2%)	0.63 (0.21, 1.90)	-0.00 (-0.01, 0.01)

Note: 1 relative risk and risk difference for each trial are estimated in Review Manager 5.1; 2 pooled results using random effects model, from Review Manager 5.1, in Attachment 16.

Abbreviations: n, number of participants, N=total participants in group; AE, adverse event; CI, confidence interval; RR, relative risk; RD, risk difference; SAE, serious adverse event; NA, not applicable.

Source: Table 2.28, p55 of the submission, Table 2.29 p57 of the submission; CSR 23138 p93, 96; CSR 23138e p59; Tang et al. 2015; CSR ADE07 p75; all publications in Attachment 9; all publications in Attachment 9; CSR 23135 p92, 95; CSR 2311 p68, 71; CSR 23137 pp96-98,100; all publications in Attachment 10. Compiled during evaluation.

- 6.19 No severe AEs were reported in Tang 2015. All the AEs reported during the study were mild.
- 6.20 No statistically significant difference in the proportion of patients who had more AE or serious AE when treated with vildagliptin compared with sitagliptin in combination with insulin was observed in the pooled results of the three head-to-head trials.
- 6.21 No statistically significant differences in adverse events were observed between vildagliptin and placebo in combination with insulin in the pooled results. There was slightly higher incidence of AEs in Study 23135 with vildagliptin compared to placebo group but not in Study 2311 and Study 23137.

Interpretation of clinical evidence

- 6.22 The submission described vildagliptin 100mg/day [50mg bid] in combination with insulin as:
- non-inferior to sitagliptin 100 mg/day, with insulin, with respect to efficacy and safety in the treatment of T2DM patients; and
 - non-inferior to linagliptin 5mg/day with insulin, with respect to efficacy and safety in the treatment of T2DM patients
- 6.23 The submission described vildagliptin with metformin FDC to be bio-equivalent to vildagliptin and metformin taken separately as:
- Vildagliptin with metformin 50/500mg, 50/850mg and 50/1000mg FDC bid is equivalent to the concomitant administration of vildagliptin 50mg bid and metformin hydrochloride 500/850/1000mg bid.
- 6.24 The PBAC considered that, on balance the claim of non-inferior comparative effectiveness was reasonable. Although there were some uncertainties arising from

the data in terms of heterogeneity and power of the studies, the PBAC accepted that the data support a claim of non-inferiority to the comparators in populations generally similar to the Australian diabetic population.

- 6.25 The PBAC considered that the claim of non-inferior comparative safety was reasonable

Economic analysis

- 6.26 The equi-effective doses are estimated as:

- Vildagliptin 100mg/day = sitagliptin 100mg/day
- Vildagliptin 100mg/day = linagliptin 5mg/day
- Vildagliptin with metformin 50/500 mg; 50/850 mg; 50/1000mg FDC bid = the concomitant administration of vildagliptin 50 mg bid and metformin hydrochloride 500mg; 850mg; 1000mg bid.

- 6.27 These estimates were based on the doses used in the three head-to-head trials and three bio-equivalence trials.

- 6.28 The vildagliptin product information (PI) recommends monitoring of liver enzymes prior to initiation of vildagliptin, every 3 months in the first year of therapy and periodically thereafter. The vildagliptin PI also notes that patients who develop increased transaminase levels should be monitored with a second liver function test (LFT) to confirm the finding and be followed thereafter with frequent LFTs until the abnormalities return to normal. The price of the vildagliptin with metformin FDCs includes an offset to account for the cost of LFTs, however no such offset is included in the single agent vildagliptin price (LFTs). The submission includes an analysis of current prescription data to demonstrate that the average ex-man price of vildagliptin is lower than that of sitagliptin and linagliptin.

- 6.29 The PBAC recalled that when it considered vildagliptin with metformin in 2010 it noted that any applications to subsidise new vildagliptin monotherapy or combination products may need to be priced differently to take into account additional costs association with LFTs for vildagliptin compared to sitagliptin.

- 6.30 The PBAC noted that the ESC considered that the current offset in the price of the vildagliptin with metformin FDC products to account for the cost of additional LFTs, recommended in the TGA Product Information (PI) of vildagliptin and vildagliptin with metformin FDC, may not be appropriate as it is unlikely that additional costs for LFTs would be incurred in practice. Most patients on a DPP4 inhibitor would be having blood tests 6 monthly to monitor HbA1c, and the MBS claiming rules mean that even if LFTs are only included for vildagliptin patients and not for patients on other DPP4 inhibitors, the actual added cost to government of these tests would be nil.

Drug cost/patient/year:

- 6.31 The drug cost was calculated as:

- \$725.45 for vildagliptin 50mg;
- \$711.09 for vildagliptin 50mg/metformin 500 mg FDC;

- \$724.24 for vildagliptin 50mg/metformin 850 mg FDC; and
\$729.59 for vildagliptin 50mg/metformin 1000 mg FDC.

Estimated PBS usage & financial implications

- 6.32 This submission was not considered by DUSC. The submission presented a market share approach, with estimates based on extrapolated trends of sitagliptin and linagliptin use with insulin derived from an analysis of the 10% PBS sample and 2016 Medicare data.
- 6.33 Table 6 summarises the estimated extent of use and financial implications associated with listing vildagliptin and vildagliptin with metformin FDC in combination with insulin.

Table 6: Estimated use and financial implications of listing Vildagliptin

	2018	2019	2020	2021	2022	2023
Estimated extent of use						
Patients						
Vildagliptin patients (Without PBS listing)	████	████	████	████	████	████
Vildagliptin patients (With PBS listing)	████	████	████	████	████	████
Incremental vildagliptin patients	████	████	████	████	████	████
Scripts						
Scripts (Without PBS listing)	████	████	████	████	████	████
Scripts (With PBS listing)	████	████	████	████	████	████
Incremental vildagliptin scripts dispensed	████	████	████	████	████	████
Reduction in sitagliptin and linagliptin scripts	████	████	████	████	████	████
Overall change in scripts	████	████	████	████	████	████
Cost to PBS/RPBS of vildagliptin						
Packs/scripts ¹	████	████	████	████	████	████
Cost at average DPMQ ²	████████	████████	████████	████████	████████	████████
Cost net of co-payment ²	████████	████████	████████	████████	████████	████████
Cost to MBS of vildagliptin						
Cost for LFT testing	████████	████████	████████	████████	████████	████████
Cost of LFT testing with 5 consultations	████████	████████	████████	████████	████████	████████
Overall cost to government health budget						
PBS/RPBS – MBS²	████████	████████	████████	████████	████████	████████
PBS/RPBS – MBS cost with cost of LFT testing with 5 consultations	████████	████████	████████	████████	████████	████████

Note: 1- Submission noted that slight discrepancies in net script numbers occur vs. patient model due to rounding during allocation to PBS/RPBS categories.

2- The costs have been updated using the DPMQ price using current pharmacy mark-up as of June 2017, which increased by 40 cents
 Abbreviation: DPMQ: Dispensed Price for Maximum Quantity; LFT: liver function tests; MBS: Medicare benefits schedule; PBS: pharmaceutical benefits scheme; RPBS: Repatriation schedule of the PBS

Source: Table 4.12 p95, Table 4.14, p96-97 of the submission; Calculations provided in the Attachment 15, spreadsheet “Cost&NetCost to PBS&RPBS”, and “Summary PBS&RPBS&MBS” in the submission, and compiled during the evaluation.

The redacted table shows that at year 5, the estimated number of patients was less than 10,000 per year and the net savings to the Government would be less than \$10 million per year.

6.34 The evaluation considered the financial implications may be underestimated due to the following reasons:

- There is uncertainty regarding the estimates of new patients as the relatively new DPP-4 in combination with insulin market is not stable. Furthermore, the approach used to estimate the number of patients treated from the number of

scripts for sitagliptin and linagliptin assumed 100% adherence, and thus may underestimate the number of patients treated.

- The submission did not apply the latest DPMQ (as of June 2017).
 - There is the potential for leakage beyond the requested PBS population for the vildagliptin with metformin FDC, from third line use, to earlier in the treatment algorithm in patients unable to tolerate or contraindicated to sulfonylurea therapy. This potential currently exists with all DPP-4 inhibitors.
- 6.35 The ESC considered that the requested listing is unlikely to impact on the frequency of consultations or the number of LFTs.
- 6.36 At year 5, the estimated number of patients was less than 10,000 per year. The net save to the PBS over the first 5 years of listing was estimated to be less than \$10 million per year.

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 vildagliptin and vildagliptin with metformin fixed dose combination (FDC) for use in combination with insulin.
- 7.2 The PBAC's recommendation for listing was based on, among other matters, its assessment, as described above, that the cost-effectiveness of vildagliptin would be acceptable if it were cost-minimised against sitagliptin and linagliptin. Similarly, the cost effectiveness of vildagliptin with metformin in this setting would be acceptable if cost-minimised against the component drugs.
- 7.3 The PBAC recommend the restriction wording, maximum quantities and repeats should be consistent with that for the other dipeptidyl peptidase 4 (DPP4) inhibitors.
- 7.4 The estimated equi-effective doses for vildagliptin were:
- Vildagliptin 100mg daily is equivalent sitagliptin 100mg daily or linagliptin 5mg daily.
 - Vildagliptin with metformin 50/500mg, 50/850mg and 50/1000mg FDC bid is equivalent to the concomitant administration of vildagliptin 50mg bid and metformin hydrochloride 500/850/1000mg bid.
- 7.5 The PBAC accepted that the clinical place for the proposed therapy was appropriate.
- 7.6 The PBAC considered the nominated comparators were appropriate as the primary comparators are both DPP-4 inhibitors, pharmacological analogues of vildagliptin, and currently listed on the PBS for use in combination with insulin therapy in T2DM. The secondary comparators were also considered appropriate based on the rationale provided by the sponsor.
- 7.7 The PBAC considered that, on balance the claim of non-inferior comparative effectiveness was reasonable. Although there were some uncertainties arising from the data in terms of heterogeneity and power of the studies, the PBAC accepted that

the data support a claim of non-inferiority to the comparators in populations generally similar to the Australian diabetic population.

- 7.8 The PBAC accepted that the safety of vildagliptin and vildagliptin with metformin was non-inferior to the comparators.
- 7.9 The PBAC agreed with the sponsor provided estimates and proposed costs, noting the advice of the ESC that the financial implications may have been underestimated and noting that this may increase longer term savings compared to the use of the comparator. The PBAC noted that the cost of treatment with vildagliptin and vildagliptin with metformin will lead to a save of less than \$10 million per year, over five years.
- 7.10 The PBAC advised that vildagliptin and vildagliptin with metformin are suitable for prescribing by nurse practitioners as continuing therapy only.
- 7.11 The PBAC recommended that the Early Supply Rule should apply.
- 7.12 The PBAC noted that this submission is not eligible for an Independent Review because the PBAC has made a positive recommendation.

Outcome:

Recommended.

8 Recommended listing

Add new item:

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Name, Restriction, Manner of administration and form	Max. Qty (tablets)	No. of Rpts	Proprietary Manufacturer	Name and
VILDAGLIPTIN Tablet, 50mg	60	5	Galvus®	Novartis Pharmaceuticals Australia Pty Limited

* the DPMQ have been updated from those included in the submission to reflect the 1 July 2017 increase of 40 cents in the dispensing fee

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

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Name, Restriction, Manner of administration and form	Max. Qty (tablets)	No. of Rpts	Proprietary Manufacturer	Name and
VILDAGLIPTIN + METFORMIN FIXED DOSE COMBINATION	60	5	Galvumet®	Novartis Pharmaceuticals
Tablet, 50mg/500mg	60	5	Galvumet®	Australia Pty Limited
Tablet, 50mg/850mg	60	5	Galvumet®	

* the DPMQ have been updated from those included in the submission to reflect the 1 July 2017 increase of 40 cents in the dispensing fee

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