Public Summary Document

Product: Vildagliptin, tablet, 50 mg, Galvus®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested an Authority required (Streamlined) listing for treatment of patients with type 2 diabetes as triple oral combination therapy with metformin and a sulfonylurea.

2. Background

The PBAC had not previously considered vildagliptin for triple oral combination therapy in type 2 diabetes mellitus (T2DM).

In March 2010, the PBAC recommended listing vildagliptin as an Authority required (Streamlined) benefit for treatment of T2DM in combination with metformin or a sulfonylurea in a patient whose HbA_{1c} is greater than 7% despite treatment with either metformin or a sulfonylurea and where combination of metformin and a sulfonylurea is contraindicated or not tolerated.

3. Registration Status

Vildagliptin was TGA registered on 2 March 2010 for treatment of diabetes mellitus type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes: in dual combination with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

Vildagliptin was TGA registered on 27 August 2013 for the extended indication: in triple combination with a sulfonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.

4. Listing Requested and PBAC's View

Authority required (Streamlined)
Triple oral combination therapy with metformin and a sulfonylurea

Type 2 diabetes, in combination with metformin and a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with maximally tolerated doses of metformin and a sulfonylurea.

The date and level of the qualifying HbA1c must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:
(a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or
(b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records.

Note
Vildagliptin is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1.

Listing was requested on a cost-minimisation with pioglitazone on the basis of a claim of comparative effectiveness and safety.

5. Clinical Place for the Proposed Therapy

T2DM is a chronic, progressive disease characterised by hyperglycaemia resulting from the inability of insulin secretion to compensate for insulin resistance and hyperglucagonaemia. T2DM is associated with significant long term micro and macrovascular complications.

Vildagliptin is an incretin mimetic drug and acts to extend the action of GLP-1 by inhibiting dipeptidyl peptidase-4 (DPP-4). Pioglitazone is a selective agonist for the peroxisome proliferator activated receptor gamma.

Vildagliptin was proposed as an alternative to pioglitazone in triple oral therapy (i.e. combination treatment with both metformin and a sufonylurea) when diet and exercise and dual therapy becomes inadequate to achieve glycaemic control.

6. Comparator

The submission nominated pioglitazone as the comparator as it is the only oral triple therapy currently listed on the PBS. The submission nominated exenatide and linagliptin as secondary comparators.

The PBAC did not accept pioglitazone as the appropriate comparator in view of concerns about adverse cardiovascular events and its diminishing use in the clinical treatment algorithm for type 2 diabetes.

The PBAC considered insulin may be an appropriate comparator. The PBAC recalled that it rejected a submission in July 2012 for combination with metformin and a sulfonylurea (triple oral therapy). The PBAC considered that although there is evidence of utilisation of gliptins in triple oral therapy, the cost effectiveness of this combination is not supported by evidence. The PBAC therefore considered that linagliptin is not a comparator.

The PBAC considered that although exenatide is PBS listed for triple therapy with metformin and a sulfonylurea and may therefore be viewed as a comparator, the rapid evolution of treatment algorithms for diabetes meant that it was not possible to be certain that vildagliptin would replace exenatide in practice. It would therefore not be appropriate as the sole comparator.

Given the rapidly changing treatment patterns, the PBAC considered that overall an appropriate comparator for third line treatment with an oral product would need to be a mixed comparator of sulfonylurea, acarbose, insulin and exenatide. The PBAC also noted the advice from the professional societies suggested that this approach was likely to be more consistent with the current and evolving management strategies for type 2 diabetes mellitus.

7. Clinical Trials

The submission did not identify direct head to head trials comparing vildagliptin with pioglitazone, linagliptin or exenatide. The submission presented indirect comparisons of vildagliptin versus pioglitazone, linagliptin and exenatide, using placebo as the common comparator.

The published trials presented in the submission are shown in the following table:

Trial ID/ First author	Protocol title/ Publication title	Publication citation
Study 23152		
Lukashevich VW et al.	Vildagliptin efficacy and safety in patients with type 2 diabetes inadequately controlled on dual metformin plus sulfonylurea therapy.	Diabetologia, Conference, October.
Scheen AJ et al.	Long-term glycaemic control with metformin-sulphonylurea-pioglitazone triple therapy in PROactive (PROactive 17).	Diabetic Medicine, 26, 1033-1039.
Charbonnel B et al.	The prospective pioglitazone clinical trial in macrovascular events (PROactive): Can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5,238 patients.	Diabetes Care, 27, 1647-1653.
Dormandy JA et al.	Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial in macroVascular Events): A randomised controlled trial.	Lancet, 366, 1279-1289.
Charpentier et al.	Earlier triple therapy with pioglitazone in patients with type 2 diabetes.	Diabetes, Obesity and Metabolism, 11, 844-854.
Pan et al.	The efficacy and safety of pioglitazone hydrochloride in combination with sulphonylureas and metfomin in the treatment of type 2 diabetes mellitus a 12-week randomized multi-centres placebo-controlled parallel study.	Zhonghua nei ke za zhi [Chinese journal of internal medicine], 41, 388-392.
Owens DR et al.	Efficacy and safety of linagliptin in persons with Type2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: A 24-week randomized study.	Diabetic Medicine, 28, 1352-1361.

Kendall et al	Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea.	Diabetes Care, 28, 1083-1091.
Blonde L. et al.	Interim analysis of the effects of exenatide treatment on A1C, weight and cardiovascular risk factors over 82 weeks in 314 overweight patients with type 2 diabetes.	Diabetes, Obesity and Metabolism, 8, 436-447.
Gao Y. et al.	Efficacy and safety of exenatide in patients of Asian descent with type 2 diabetes inadequately controlled with metformin or metformin and a sulphonylurea.	Diabetes Research and Clinical Practice, 83, 69-76.
He YL. et al.	Bioequivalence of vildagliptin/metformin fixed-dose combination tablets and a free combination of vildagliptin and metformin in healthy subjects.	Int J Clin Pharmacol Ther. 2008;46:259-267.

Overall, the risk of bias in the trials was considered to be low. However, the PBAC noted Pan et al (2002) may have limited external applicability given the short duration and the fixed-dose regimen for pioglitazone used in the study. The PBAC also noted the Pan study was reported in Chinese and the translation was not sufficiently informative.

The PBAC agreed that the linagliptin and exenatide trials were sufficiently comparable to vildagliptin trial for an indirect comparison. The PBAC considered that the characteristics of the pioglitazone trials indicated that it was highly unlikely that the indirect comparison of vildagliptin versus the individual pioglitazone trials, or the pooling of the pioglitazone trial outcomes, could produce results of sufficient reliability to inform the relative effectiveness (in terms of % change in HbA_{1c} from baseline) and safety of vildagliptin in triple therapy. In addition to the differences in trial characteristics, the PBAC agreed that baseline HOMA-β function and the extent of weight gain in participants from Charpentier 2009 may bias the indirect comparison in favour of pioglitazone.

The PBAC noted that an equivalent comparison of the above factors could not be conducted with the other pioglitazone trials as these variables were not reported in sufficient detail. Rather, these potential differences emphasised the unreliability of the indirect comparison.

8. Results of Trials

The table below presents the results of the indirect comparison and meta-analyses for percentage change from baseline HbA1c.

Change from baseline HbA_{1c}: Indirect Comparison of vildagliptin versus pioglitazone; linagliptin; and exenatide

Trial	Trial Duration (weeks)	Active Treatment Group^				Placebo Group^			Indirect Comparison^
		Intervention	n	Mean Δ baseline HbA_{1c}	SD	N	Mean Δ baseline HbA_{1c}	SD	Mean difference: Vildagliptin vs. Active Treatment (95% CI)
Vildagliptin trial									
Study 23152	24	V50mg bd	152	-1.01	[redacted]	[redacted]	[redacted]	[redacted]	-

Pioglitazone trials									
Scheen 2009	138	P15-45mg d	654	-0.90	1.30	660	-0.30	1.40	-0.16 (-0.45, 0.13)
Charpentier 2009	28	P30-45mg d	135	-0.90	0.90*	141	0.28	0.90*	***0.42 (0.10, 0.74)***
Pan 2002	12	P30mg d	141	-0.70	0.96	142	-0.40	0.83	**-0.46 (-0.79, -0.13)**
Vildagliptin 50mg vs. Pioglitazone (15-45mg)									-0.07 (-0.59, 0.45)
Linagliptin trial									
Owens 2011	24	L5mg d	778	-0.72	0.84	262	-0.10	*0.81*	-
Vildagliptin 50mg vs. Linagliptin 5mg									-0.14 *(-0.42, 0.14)*
Exenatide trials									
Gao 2009	16	*E5-10µg bd*	234	-1.20	0.78	232	-0.40	*1.17*	0.04 (-0.27, 0.35)
Kendall 2005	30	E5µg bd	245	-0.55	*1.10*	247	0.23	*1.10*	*0.20 (-0.30, 0.34)*
		E5-10µg bd	241	-0.77	*1.24*	247	0.23	*1.10*	*0.24 (-0.08, 0.56)*
Vildagliptin 50mg vs. Exenatide (5-10µg) ‡									*0.13 (-0.18, 0.45)*

* SD reported in linagliptin PSD 2012

‡ Meta-analysis for exenatide used results from the 5-10µg treatment arms of Gao 2009 and Kendall 2005. Exenatide 5µg bd is considered to be a titration dose, with the majority of patients transitioning to 10µg bd to achieve enhanced glycaemic control.

^ Estimated during the evaluation using Stats Direct 2.7.9. Figures in italics were updated during the evaluation

Abbreviations: E = exenatide; L = linagliptin; P = Pioglitazone; V = Vildagliptin

The indirect comparisons with pioglitazone demonstrated variable results for percentage change in baseline HbA_{1c} across the trials. Study 23152 (vildagliptin) versus Pan 2002 (pioglitazone) showed a statistically significant advantage for vidalgliptin, while Study 23152 (vildagliptin) versus Charpentier 2009 (pioglitazone) showed significant advantage for pioglitazone. No difference was seen between Study 23152 (vildagliptin) and Scheen 2009 (pioglitazone).

Indirect comparisons of vildalglptin with linagliptin and exenatide, using placebo as the common reference in triple therapy, did not demonstrate a statistically significant difference in the estimated mean difference of change from baseline HbA_{1c} using placebo as the common reference.

The PBAC noted that significant statistical heterogeneity existed within the meta-analysis for the three pioglitazone trials ($Chi^2 = 36.10$, DF=2, $I^2 = 94\%$). Further, differences in study design/participants and treatment effects across the placebo arms, the value of the indirect comparisons and the meta-analysis of the pioglitazone trials for the assessment of effectiveness were highly questionable.

With regard to comparative harms, the PBAC noted comparisons of adverse events profiles were not possible across the vildagliptin, pioglitazone, linagliptin and exenatide trials as a consequence of the heterogeneity of the trials and different reporting of adverse events.

Study 23152 (vildagliptin) demonstrated significant differences in nervous system disorders and skin and subcutaneous tissue disorders, shown by differing incidences of dizziness, tremor events and hyperhidrosis. Gastrointestinal events (nausea and diarrhoea) were common adverse events found in the exenatide trials.

All of the linagliptin and exenatide trials and two of the pioglitazone trials (Scheen 2009, Charpentier 2009) reported an increased incidence of hypoglycaemic events in the treatment arm that was statistically significant. There was no statistically significant difference in Study 23152 (vildagliptin) and Pan 2002 (pioglitazone). The PBAC noted that the statistical comparison of hypoglycaemic events and further noted that the definition of hypoglycaemic events in Study 23152 (blood glucose concentration less than 3.1 mmol/l compared to 3.3 mmol/l as per the Therapeutic Guidelines, Endocrinology) could result in an underestimate in reported hypoglycaemic event rates.

The current FDA evaluation of unpublished reports of a possible increased risk of pancreatitis and pre-cancerous cellular changes of the pancreas in patients with T2DM treated with incretin mimetic drugs was noted by the PBAC.

9. Clinical Claim

The submission described vildagliptin 50 mg twice a day as being equivalent in terms of comparative effectiveness and comparative safety to pioglitazone (15-45 mg daily) when used in triple therapy with metformin and sulfonylurea. The PBAC did not consider this claim to be adequately supported.

The submission described vildagliptin, 50 mg twice a day, as equivalent in terms of comparative effectiveness and comparative safety compared to linagliptin, 5 mg once daily when used in triple therapy with metformin and a sulfonylurea. The PBAC did not consider that this claim was adequately supported by the results of the indirect comparison.

The submission described vildagliptin 50 mg twice a day as equivalent in terms of efficacy and safety compared to exenatide, 5 to 10 microgram twice a day. The PBAC noted that although the trial results for exenatide twice daily demonstrated greater percentage change in HbA_{1c} from baseline, when compared to vildagliptin, the indirect comparison demonstrated there was no statistically significant difference between vildagliptin and the individual exenatide trials. Overall, in view of the unreliable nature of the indirect comparison, the PBAC did not consider that this claim was adequately supported.

10. Economic Analysis

The submission presented a cost-minimisation analysis on the basis of non-inferiority between vildagliptin and pioglitazone in triple oral therapy. The PBAC noted that the cost-minimisation analysis did not include other comparators. The PBAC considered this approach was appropriate but contingent on claims of non-inferiority between vildagliptin and pioglitazone in triple therapy, being accepted. As the non-inferiority claims were rejected, the cost-minimisation analysis was also rejected.

The submission used a weighted average of the maximum pioglitazone dose from each of the trials, resulting in an equi-effective dose of 42.75mg daily, based on the number of participants in the pioglitazone trials. This was considered to be inappropriate by the PBAC in view of the unreliability of the indirect comparison.

11. Estimated PBS Usage and Financial Implications

The submission presented estimates for vildagliptin use based on a market share model. Recognising that vildagliptin and vildagliptin/metformin FDC are both PBS listed already, the submission included an estimated change in vildagliptin/metformin FDC use as a result of extending listing to triple therapy.

The PBAC noted concerns about the estimates because of perceived flaws in the methodology used to project the expected use of vildagliptin in the triple oral therapy.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC rejected the listing of viladagliptin 50 mg tablet in triple therapy on the PBS due to the inappropriate comparator. The PBAC did not accept pioglitazone as the appropriate comparator in view of concerns about adverse cardiovascular events and its diminishing use in the clinical treatment algorithm for type 2 diabetes.

The PBAC considered insulin may be an appropriate comparator. The PBAC recalled that it rejected a submission in July 2012 for combination with metformin and a sulfonylurea (triple oral therapy). The PBAC considered that although there is evidence of utilisation of gliptins in triple oral therapy, the cost effectiveness of this combination is not supported by evidence. The PBAC therefore considered that linagliptin is not a comparator.

The PBAC considered that although exenatide is PBS listed for triple therapy with metformin and a sulfonylurea and may therefore be viewed as a comparator, the rapid evolution of treatment algorithms for diabetes meant that it was not possible to be certain that vildagliptin would replace exenatide in practice. It would therefore not be appropriate as the sole comparator.

Given the rapidly changing treatment patterns, the PBAC considered that overall an appropriate comparator for third line treatment with an oral product would need to be a mixed comparator of sulfonylurea, acarbose, insulin and exenatide. The PBAC also noted the advice from the professional societies suggested that this approach was likely to be more consistent with the current and evolving management strategies for Type 2 Diabetes Mellitus.

The PBAC considered also that there was insufficient evidence to support a claim of non-inferiority to the nominated comparator, pioglitazone. Based on the Drug Utilisation Sub-Committee (DUSC) February 2013 diabetes utilisation analysis, the PBAC considered pioglitazone is no longer a reference for third line therapy and cannot be used as the basis for price comparison for triple therapy.

The PBAC noted the extent of use of gliptins beyond the dual therapy restriction (February 2013 DUSC review), and recalled that the cost effectiveness of gliptins in this setting has not been established. The PBAC agreed that recently completed placebo controlled trials

investigating the use of sitagliptin[1] and saxagliptin[2] in triple therapy would potentially inform the comparative effectiveness of vildagliptin in triple therapy.

Due to differing trial characteristics, the PBAC considered the indirect comparisons were unreliable and did not inform an assessment of the effectiveness and safety of vildagliptin in triple therapy. The PBAC noted the vildagliptin and exenatide trial population were younger and had higher HbA_{1c} at baseline when compared to the Australian studies. The inclusion of patients with higher HbA_{1c} and younger age may represent a population that are more sensitive to the effects of anti-diabetic agents compared to the Australian population. The PBAC considered it was not possible to determine whether the differences in the vildagliptin and exenatide trials would have a significant impact on treatment effect in the proposed PBS population. The PBAC did not consider it possible to make a definitive safety comparison between vildagliptin and pioglitazone in triple therapy based on the indirect comparison.

The PBAC recalled Table 1 of the DUSC Feb 2013 diabetes utilisation analysis and Figure 2 of the DUSC advice and acknowledged the trends in the current clinical management of diabetes. Table 1 is presented below:

Triple regimens	**Patients**	**%**
Met+SU+Insulin	10,232	26.6%
Met+SU+Pio	8,567	22.3%
Met+SU+Glip	4,197	10.9%
SU+Glip&Met	4,179	10.9%
(Met+Glip&Met)	1,581	4.1%
Met+SU+Exen	1,468	3.8%
Met+Acar+SU	1,317	3.4%
Glip&Met+Insulin	1,086	2.8%
Met+Glip+Insulin	933	2.4%
Met+Pio+Insulin	903	2.3%
SU&Met+Pio	700	1.8%
SU&Met+Insulin	619	1.6%
SU+Glip+Insulin	497	1.3%
SU+MetR	441	1.1%
Met+SU+Rosi	391	1.0%
SU&Met+Glip	353	0.9%
Met+Exen+Insulin	274	0.7%

[1] Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P. 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. Diabetes, Obesity and Metabolism. 2007:9;733-745.
[2] ClinicalTrials.gov. Saxagliptin Triple Oral Therapy. http://clinicaltrials.gov/ct2/show/results/NCT01128153 , Last Accessed 20 March 2013.

Met+Acar+Insulin	264	0.7%
(Met+SU&Met)	254	0.7%
SU+Pio+Insulin	229	0.6%
Grand Total	38,485	100%
Concessional Patients	18,828	48.9%
Extrapolated total Patients	26,897	

At the PBAC April 2013 Special meeting, the PBAC noted the use of gliptin FDC products substantially exceeded projected utilisation. The Committee observed that the gliptin FDC products were driving growth in the market, causing increased cost to the Commonwealth in triple oral therapy treatment which was outside the restriction, and for which cost-effectiveness had not been established. With specific regard to gliptins, the PBAC recalled the DUSC data showed for all regimens containing a gliptin, the total non-compliance with the PBS criteria for co-administered therapies was 34.6%, 18.5% of which was a gliptin in combination with both metformin and a sulfonylurea. The PBAC considered that although triple oral therapy is being used in practice, the clinical appropriateness and benefit of this combination is poorly supported by the evidence and therefore there is no basis to construct a cost effective price for gliptins in this context.

The PBAC further recalled the diminishing use of pioglitazone in the treatment regimens presented in the DUSC report and noted DUSC advice that pioglitazone was replaced most often by a gliptin despite pioglitazone having additional indications and therefore potentially a larger eligible patient population. The decline was attributed to ongoing safety concerns with pioglitazone.

With regard to the place in therapy in relation to sulfonylureas, vildagliptin was viewed in practice as an alternate therapy to sulfonylureas, rather than being reserved for patients who cannot tolerate sulfonylurea. Noting the utilisation of gliptins outside the PBS restrictions, the PBAC considered that the place of vildagliptin in clinical practice was not clear.

The cost minimisation analysis presented by the submission was deemed to be unreliable as non-inferiority of vildagliptin to pioglitazone was not established. The PBAC considered that the assumption that an extension to the listing of vildagliptin and vildagliptin FDC for triple oral therapy will not grow the triple therapy market was not justified.

The PBAC considered the use of the weighted average of the maximum doses from the pioglitazone trials (Charpentier 2009, 30-45 mg; Scheen, 2009, 15-45 mg and Pan 2002, 30 mg) to inform the equi-effective doses was inappropriate as the indirect comparison had failed to reliably demonstrate non-inferiority for vildagliptin and pioglitazone.

The PBAC noted that substitution of vildagliptin for lower doses of pioglitazone would result in a cost to the PBS; the proportions of pioglitazone 15mg, 30mg and 45 mg used in triple therapy were not provided in the submission. The PBAC noted the sponsor's willingness to negotiate a weighted price across the dual and triple therapy. The PBAC considered that the estimates as presented in the submission did not provide sufficient basis to establish a

weighted price. The PBAC did not accept the submission's claim of net cost savings to the PBS/RPBS.

With regards to quality use of medicines, vildagliptin when used as dual therapy with a sulfonylurea is recommended at 50 mg per day. For the proposed triple therapy, the recommended dose of vildagliptin is 50 mg twice daily, giving rise to concerns of confusion in the quality use of medicines context.

The PBAC acknowledged the clinical need for effective treatments for diabetes, however considered that the submission did not establish that vildagliptin represented a cost effective treatment in this context.

Outcome
Rejected

13. 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.

14. Sponsor's Comment

The sponsor had no comment.