

Public Summary Document

Product: Vildagliptin with metformin, tablets, 50 mg-500 mg, 50 mg-850 mg and 50 mg-1,000 mg, Galvumet[®]

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 of vildagliptin with metformin as a fixed dose combination (FDC), and a sulfonylurea given concomitantly.

2. Background

The PBAC had not previously considered vildagliptin/metformin FDC as part of triple oral combination therapy in type 2 diabetes mellitus (T2DM).

In November 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/metformin FDC was TGA registered on 13 December 2010 for patients with T2DM as an adjunct to diet and exercise to improve glycaemic control in patients whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment should not be initiated with this fixed-dose combination.

Vildagliptin/metformin FDC was TGA registered on 12 June 2013 for the extended indication: in combination with a sulphonylurea (ie. Triple oral combination therapy) as an adjunct to diet and exercise in patients inadequately controlled with metformin and a sulfonylurea.

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 HbA_{1c} 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 HbA_{1c} 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 for third line treatment of T2DM in patients who meet certain criteria.

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/metformin FDC was proposed as an additional oral therapy to pioglitazone in combination therapy with a sulfonylurea.

6. Comparator

The submission relied on the individual vildagliptin and metformin components given concomitantly as the comparator. Claims of comparative efficacy in triple therapy regimen were based on evidence presented for the individual vildagliptin formulation compared to pioglitazone in triple therapy. The submission did not present evidence of vildagliptin/metformin FDC use in triple therapy.

Linagliptin and exenatide in triple therapy were presented as secondary comparators.

The PBAC noted TGA's listing of vildagliptin/metformin FDC for dual and triple therapy. The PBAC did not accept pioglitazone as the appropriate comparator for triple therapy based on the Drug Utilisation Sub-Committee (DUSC) diabetes utilisation report 2013, due to its declining use in the diabetes clinical management algorithm and safety concerns.

7. Clinical Trials

The submission provided three open label bioequivalence trials, (LMF2303, LMF2307, LMF 2301) which compared different doses of vildagliptin/metformin FDC with the co-

administration of equivalent free doses of vildagliptin and metformin in 128 healthy patients. These studies were previously presented to the PBAC for consideration in November 2010 in the vildagliptin dual therapy submission, which was recommended by the PBAC.

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

Trial ID/ First author	Protocol title/ Publication title	Publication citation
LMF2303 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.
LMF2307 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.
LMF2301 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.

8. Results of Trials

The submission did not present direct evidence to support claims of comparative efficacy but depended on claims of bioequivalence as a surrogate for comparative efficacy and safety.

The mean plasma concentration-time profiles of vildagliptin and metformin (at 3 doses) were similar following single oral doses of vildagliptin and metformin in fixed combination or vildagliptin and metformin as free combination in healthy subjects. Bioequivalence between the two administrative forms was also demonstrated in the key parameters of C_{max}, AUC_{0-t} and AUC_{0-∞}.

The table below presents the geometric mean ratio of the pharmacokinetic properties of vildagliptin/metformin FDC relative to the individual components.

Geometric Mean Ratio (GMR) of the pharmacokinetic properties of vildagliptin/metformin FDC relative to the individual components

Trial	Intervention	n	Estimated GMR (FDC/Co-Administration) (90% CI)					
			Vildagliptin			Metformin		
			C _{max}	AUC _{0-t}	AUC _{0-∞}	C _{max}	AUC _{0-t}	AUC _{0-∞}
LMF2303	V50/MET500	37	0.92 (0.83- 1.02)	0.98 (0.94, 1.02)	0.98 (0.94, 1.02)	0.96 (0.89, 1.04)	1.00 (0.95, 1.05)	1.00 (0.95, 1.05)
LMF2307	V50/MET850	43	1.05 (0.99, 1.11)	1.01 (0.99, 1.04)	1.01 (0.99, 1.04)	1.05 (1.01, 1.10)	1.03 (0.99, 1.07)	1.02 (0.99, 1.06)

LMF2301	V50/MET1000	43	1.00 (0.95, 1.06)	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)	1.02 (0.98, 1.07)	1.01 (0.97, 1.04)	1.01 (0.97, 1.04)
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Bolded typography indicates results that are in accordance with EMEA/TGA Guidelines for bioequivalence.

Abbreviations: GMR = Geometric mean ratio; MET = Metformin; V = Vildagliptin.

The PBAC noted no evidence was provided by the submission to inform efficacy of vildagliptin/metformin FDC in triple therapy, but recalled accepting bioequivalence data relating to vildagliptin/metformin FDC in dual therapy at its November 2010 meeting. The PBAC noted the healthy subjects participating in the bioequivalence trials were not representative of the T2DM population for the PBS listing sought. However, the PBAC noted that the trials have been accepted by the TGA for the purposes of determining bioequivalence.

With regard to comparative harms, the submission did not present safety data specific to vildagliptin/metformin FDC in triple therapy. Outcomes from the bioequivalence studies did not highlight serious adverse events or clinically significant changes in vital signs. On this basis, the PBAC considered the safety profile as being similar to the concomitant administration of vildagliptin and metformin.

The PBAC also noted 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.

9. Clinical Claim

The submission claimed the vildagliptin/metformin fixed dose combination tablets, containing vildagliptin/metformin at doses of 50/500 mg, 50/850 mg and 50/1000 mg as bioequivalent to the free combination of the respective component agents when used at corresponding doses. Although the bioequivalence of vildagliptin/FDC versus the free combination was adequately demonstrated, the PBAC noted that the submission did not present evidence regarding the use of vildagliptin/metformin FDC in triple therapy.

10. Economic Analysis

A cost-minimisation analysis was presented on the basis of

- (i) bioequivalence of vildagliptin/metformin FDC and free combination of vildagliptin and metformin in triple oral therapy, and
- (ii) the claims of non-inferiority of vildagliptin compared to pioglitazone in triple therapy would apply equally to the FDC formulation.

The PBAC noted that the cost-minimisation analysis was dependent on the acceptance of bioequivalence as a surrogate for efficacy/safety in triple therapy, and that the effectiveness of vildagliptin in triple therapy would apply to the FDC. As the submission had not presented any evidence to inform the efficacy/safety of vildagliptin/metformin FDC, it was unclear whether cost minimisation analysis was appropriate. Further, because pioglitazone was rejected as a comparator in triple therapy involving vildagliptin as a single component product, the PBAC did not accept pioglitazone as a relevant comparator in a FDC.

11. Estimated PBS Usage and Financial Implications

A market share approach was undertaken to estimate the extent of use. The submission also estimated the potential change in vildagliptin/metformin FDC utilisation as an outcome of extending the listing.

The proposed ex-manufacturer price for vildagliptin was calculated according to an equi-effective dose of vildagliptin 50mg bd and pioglitazone 42.75mg daily, which was derived from a weighted average of maximum doses used from the pioglitazone trials. The PBAC considered this inappropriate as the indirect comparison failed to demonstrate non-inferiority for vildagliptin and pioglitazone.

12. Recommendation and Reasons

The PBAC rejected the listing of vildagliptin/metformin FDC tablets (50 mg-500 mg, 50 mg-850 mg and 50 mg-1000 mg) on the PBS for triple oral combination therapy, with a sulfonylurea because the cost-minimisation analysis was contingent on the PBAC accepting bioequivalence as a surrogate for efficacy/safety in triple therapy, and that the effectiveness of vildagliptin in triple therapy would apply to the FDC. The PBAC considered that since no evidence was presented to inform the efficacy/safety of vildagliptin/metformin FDC in triple therapy, it was unclear whether the cost minimisation analysis was appropriate.

The PBAC noted that it had previously considered FDC submissions based solely on bioequivalence data. The PBAC noted however that the basis of the submission to list the vildagliptin/metformin FDC was the acceptance of the non-inferiority of vildagliptin as a single component product to pioglitazone in triple oral therapy. The PBAC noted that the sponsor had made a submission to this meeting for vildagliptin in triple oral therapy on that basis (*refer to item 6.5 of this meeting*).

In addition to rejecting pioglitazone as the comparator, the PBAC considered the indirect comparisons presented in the submission for vildagliptin in triple oral therapy were unreliable and were therefore did not inform assessment of the effectiveness and safety of any form of vildagliptin in triple therapy.

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 has no comment.