Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Vildagliptin/Metformin hydrochloride

Proprietary Product Name: Galvumet/Sobrea

Sponsor: Novartis Pharmaceuticals Australia Pty Ltd

January 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Fixed Combination
Decision:	Approved
Date of Decision:	7 December 2010
Active ingredient(s):	Vildagliptin/Metformin hydrochloride
Product Name(s):	Galvumet 50/500, 50/850 and 50/1000 Sobrea 50/500, 50/850 and 50/1000
Sponsor's Name and Address:	Novartis Pharmaceuticals Australia Pty Limited 54 Waterloo Road North Ryde NSW 2113
Dose form(s):	Film coated tablets
Strength(s):	vildagliptin/metformin hydrochloride 50 mg/500 mg, 50 mg/850 mg and 50 mg/1000 mg
Container(s):	PVC/Al/PVDC/Al blisters packed in cartons
Pack size(s):	10, 30, 60, 120, 180 and 360 tablets
Approved Therapeutic use:	As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes 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 of type 2 diabetes should not be initiated with this fixed-dose combination.
Route(s) of administration:	Oral
Dosage:	Twice daily with meals
ARTG Number (s)	161216, 161217, 161218, 164358, 164359 and 164360

Product Background

The pathophysiology of Type 2 diabetes mellitus (T2DM) is characterised by deficient insulin activity arising from decreased insulin secretion secondary to beta cell failure, and/or compromised insulin action in peripheral target tissues (insulin resistance). This abnormal metabolic state is exacerbated by excess hepatic glucose production and altered metabolism of proteins and lipids, which along with hyperglycaemia, contribute to microvascular and macrovascular complications.

T2DM accounts for approximately 85% to 95% of diabetes cases in developed regions like the European Union (EU). Age and weight are established risk factors for T2DM. The majority of patients with T2DM are overweight or obese. Diet modification and exercise is the first line of treatment for T2DM. Pharmacologic intervention with one oral antidiabetic drug (OAD) is usually the next step in treatment. After 3 to 9 years of OAD monotherapy, patients typically require an additional intervention. The recommended first line treatment is metformin which restrains hepatic glucose production and decreases peripheral insulin resistance. Sulphonylureas, which are insulin secretagogues, may be used as an alternative to

patients intolerant to metformin or as an addition to metformin. Other second line oral treatment alternatives include alpha-glucosidase inhibitors, meglitinides and thiazolidinediones. Although being efficient in attenuating hyperglycaemia, all of the treatment alternatives have more or less serious side effects and there is a need for development of efficient drugs without metabolic or other side effects.

Vildagliptin is one of a relatively new class of antidiabetic agents with potential for use in the treatment of T2DM. Vildagliptin is an inhibitor of dipeptidyl peptidase-IV (DPP-IV), an enzyme that inactivates *inter alia* the incretin peptides glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

This AusPAR described the evaluation process of an application by Novartis Pharmaceuticals Australia Pty Ltd to register three new fixed combination products containing vildagliptin and metformin hydrochloride, a well established biguanide and hypoglycaemic agent. The film-coated tablets are proposed to contain 50/500, 50/850 and 50/1000 mg of vildagliptin /metformin respectively. There are two tradenames proposed for each combination, Galvumet and Sobrea, but the product will be referred to as Galvumet for the remainder of this AusPAR.

An application for marketing of vildagliptin for use in T2DM in combination with metformin, a sulphonylurea, a thiazolidinedione or insulin, has recently been approved and this present application should be considered in conjunction with the information in that document.[1] It can be regarded as relating to a subgroup of patients meeting one therapeutic indication being sought in that application for vildagliptin, that is, addition to the regimen of patients inadequately controlled with metformin. Data related to concomitant use of these two agents for this indication is presented in the vildagliptin submission. The evaluation of the current submission concerned only those data not previously submitted. The proposed indication is as follows:

To improve glycaemic control in conjunction with diet and exercise, of patients with Type 2 diabetes mellitus who are already treated with metformin and vildagliptin or who are not adequately controlled on metformin alone.

The recommended dosing regimen is one tablet taken twice daily. All tablets proposed will thus provide a dose of 100 mg/day vildagliptin but from 1,000mg, 1,700 mg or 2,000mg metformin per day. For patients already taking metformin, any strength may be selected, to be taken twice daily. For patients already taking the separate actives in combination, the appropriate fixed combination tablet is taken.

Regulatory Status

A similar application to the current Australian submission was approved in the EU as Eucreas on 14 November 2007. The EU indication is:

Eucreas is indicated in the treatment of type 2 diabetes mellitus patients who are unable to achieve sufficient glycaemic control at their maximally tolerated dose of oral metformin alone or who are already treated with the combination of vildagliptin and metformin as separate tablets.

In New Zealand, the product was approved on 14 May 2009 with the indication:

Galvus Met is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus whose diabetes is not adequately controlled on

[1] TGA. Vildagliptin – AusPAR. Available at http://www.tga.gov.au/pmeds/auspar/auspar-galvus.pdf, accessed 20 October 2010.

metformin hydrochloride or vildagliptin alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets.

In Switzerland, the product was approved on 6 November 2009 with the indication:

Galvumet is indicated as an adjunct to diet and exercise in patients with type 2 diabetes mellitus whose blood glucose is not adequately controlled on metformin hydrochloride or vildagliptin alone, or in patients already being treated with a free combination of metformin hydrochloride and
vildagliptin.

In the United States, an approvable letter for Galvus Met was received on 27 September 2007.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

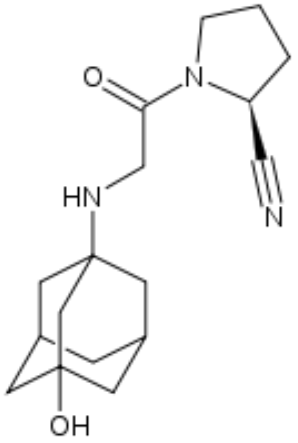
II. Quality Findings

Introduction

Novartis currently markets 50 mg vildagliptin tablets under the trade names Galvus and Xiliarx, which were approved for registration in Australia in February 2010.[1]

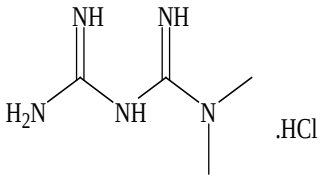
Drug Substances (active ingredients)

The structure and properties of vildagliptin are shown below:

Chemical name:	(S)-1-[2-(3-Hydroxyadamantan-1-ylamino)acetyl]pyrrolidine-2-carbonitrile; 1-[(3-hydroxyadamant-1-ylamino)-acetyl}-pyrrolidine-2(S)-carbonitrile	
AAN:	Vildagliptin.	
Molecular formula:	$C_{17}H_{25}N_3O_2$	
Molecular weight:	303.4	
CAS number:	274901-16-5	
Crystallinity:	White to slightly yellowish, slightly greenish crystalline powder	
Chirality:	One chiral centre	

The vildagliptin used in the proposed products is manufactured and controlled in the same manner as the vildagliptin used in the Galvus tablets.

The structure and properties of metformin hydrochloride are shown below:



Chemical name (IUPAC):	1,1-Dimethylbiguanide hydrochloride

AAN:	Metformin hydrochloride
Molecular formula:	$C_4H_{11}N_5.HCl$
Molecular weight:	165.6
CAS number:	1115-70-4
Crystallinity:	A white to off-white powder
Melting point:	222°C to 226°C
Solubility:	Freely soluble in water at 15°C - 25°C (10-100% w/v)
Polymorphism:	No polymorphs are known
Chirality:	achiral

The quality control of the metformin hydrochloride used in the proposed product is covered by a European Directorate for the Quality of Medicines certificate of suitability.

The sponsor does not market a tablet containing metformin, however metformin hydrochloride 500 mg, 850 mg and 1000 mg tablets are currently registered by a number of sponsors, including the innovator company Alphapharm Pty Ltd. The Australian innovator brand name is Glucophage for the 500 mg and 850 mg tablets and Diabex or Diaformin for the 1000 mg tablets. In addition, modified release 500 mg metformin tablets and several fixed combination tablets (containing a combination of metformin and either glibenclamide, rosiglitazone or sitagliptin) are registered. Metformin hydrochloride is referred to as metformin for the remainder of this AusPAR.

Drug Product

The proposed drug products are unscored, film-coated, immediate release tablets. They are distinguished by colour, size and markings. The different strengths do not have directly scaled cores, nor do they use a fixed matrix. The excipients in the products are conventional.

The proposed tablets were developed with the aim of being bioequivalent to equivalent doses of the single entity vildagliptin and metformin tablets when co-administered.

The finished product specification controls the identities, assays, purities and other physical, chemical and microbiological properties relevant to the clinical use of the product.

The proposed shelf life for the unopened product is 18 months when stored below 30°C when packaged in aluminium blisters. Adequate stability data have been provided to support the proposed shelf life.

Biopharmaceutics

The following bioavailability and bioequivalence data were submitted:

- One crossover study (LMF237A2304) was aimed at examining the relative bioavailability of two different pilot formulations of the 50/1000 mg fixed dose combination and a free combination of 50 mg vildagliptin and 1000 mg metformin tablets. Both the maximal plasma concentration (C_{max}) and the area under the plasma concentration time curve (AUC) were comparable between the free combination and fixed dose combination tablets with regard to both test formulations.
- Three crossover studies (designated LMF237A2303, LMF237A2307 and LMF237A2301) were designed to assess whether the proposed fixed dose formulations of 50/500 mg, 50/850 mg and 50/1000 mg vildagliptin/metformin are bioequivalent to the respective free combination of 50 mg vildagliptin and 500 mg, 850 mg and 1000 mg metformin comparator products.

  In each study, the pharmacokinetic parameters with regard to both vildagliptin and metformin were similar between the two treatments. The ratios of the geometric means

for both vildagliptin and metformin parameters were close to unity and the 90% confidence intervals for C_{max} and AUC were within 0.8-1.25 limits.

- One crossover study (LMF237A2101) was designed to assess the effect of food on the absorption of the proposed product, in which participants were dosed with the proposed 50/1000 mg vildagliptin/metformin product in the fasting state and after receiving a high fat breakfast.

  There was no significant difference between C_{max} and AUC for vildagliptin when the tablets were administered with food as compared to those observed under fasting conditions.

  A significant food effect was observed for metformin. The C_{max} was reduced by 26% and the time to maximal plasma concentration (T_{max}) was delayed from 2.20 to 4.0 hours when the tablets were given with food. However, there was no significant difference in the overall extent of absorption between the fed and fasted states.

  The effects of food on the metformin pharmacokinetic parameters are consistent with but of lesser magnitude than those observed for metformin alone.

Only the 50/1000 mg fasted study was evaluated in full. This allowed evaluation of the assay method, which was also used in the fasted 50/500 mg (LMF237A2303), 50/850 mg (LMF237A2307) studies and food effect bioequivalence studies.

The major concern with regard to the bioequivalence studies was that the metformin reference product (Merck's Glucophage) was obtained from the United Kingdom. The sponsor has not justified the use of an overseas reference product according to Appendix 15 (section 7) of the ARGPM.[2] It has, instead, provided evidence to show that the overseas and Australian innovator products have similar dissolution characteristics.

However, direct comparison to the Australian innovator product is not considered critical in this instance (in contrast to an application to register a simple generic product, after which the Australian innovator and generic product may be used interchangeably). In the current application, a patient will transfer from taking individual doses of vildagliptin and metformin tablets to taking the corresponding fixed dose combination of the drug substances. The evidence presented by the sponsor will therefore be accepted.

Quality Summary and Conclusions

Details of the submission were considered at the 133rd meeting of the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM). The PSC endorsed all of the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues and had no objection to the registration of the products, provided that all outstanding issues were addressed to the satisfaction of the TGA.

All matters raised with the sponsor were satisfactorily addressed and registration was recommended with respect to chemistry, quality control and biopharmaceutics.

III. Nonclinical Findings

Introduction

At the time this nonclinical evaluation report was written, an application for registration of vildagliptin (as a new chemical entity) in free combination with metformin was currently under consideration by the TGA.[1] Newly submitted data in the current application comprised additional pharmacology studies (with vildagliptin and metformin alone), pharmacokinetic studies examining interactions between vildagliptin and metformin (in rats and dogs), general

[2] TGA. Australian Regulatory Guidelines for Prescription Medicines (ARGPM). Available at http://www.tga.gov.au/pmeds/argpm.htm, accessed 20 October 2010.

repeat-dose toxicity studies with the combination (in rats and dogs) and embryofetal toxicity studies with the combination (in rats and rabbits). All studies were of a high quality. The package of nonclinical studies was in accordance with recommendations in the TGA-adopted EU guideline on the nonclinical development of fixed combinations of medicinal products.[3]

Pharmacology

Vildagliptin inhibits the enzyme dipeptidyl peptidase IV (DPP-IV), responsible for inactivation of the incretin hormones GLP-1 and GIP. Newly submitted primary pharmacology studies showed improved glucose tolerance and decreased basal plasma glucose levels in insulin-resistant obese mice, and increased levels of GLP-1 and enhanced hepatic glucose uptake in dogs, following treatment with vildagliptin. The efficacy of vildagliptin and metformin in combination has not been studied in nonclinical models of diabetes. Metformin itself was shown to be able to inhibit DPP-IV, but this was very weak and not clinically relevant (that is, only 20% inhibition was observed at 1000 µM, a concentration >50-times greater than the clinical C_{max} for the drug at the maximum recommended human dose).

Pharmacokinetics

Plasma AUC for vildagliptin was not affected by co-administration of metformin in rats, dogs or humans, though reductions in vildagliptin C_{max} were observed at the upper dose range tested in rats (~2–3-fold lower; ≥60 mg/kg/day vildagliptin ± metformin at a 1:10 dose ratio) and to a small degree in humans (18%). The plasma kinetics of vildagliptin's carboxylic acid metabolite (LAY151; M20.7) were also shown to not be affected by metformin in dogs. In both laboratory animal species, plasma AUC (but not C_{max}) for metformin increased with co-administration of vildagliptin (by 1.4–2.1-times); vildagliptin did not affect the plasma kinetics of metformin in humans however.

Toxicology

General Toxicity

Repeat-dose studies of up to 13 weeks duration were performed with vildagliptin and metformin in combination in rats and dogs. The studies used the clinical route (oral [PO]) and vildagliptin:metformin dose ratios of 1:10 (or, in dogs following dose adjustments due to metformin toxicity, 1:5). Parallel single-agent control groups were used in the pivotal (13-week) studies and earlier 2-week ones. Doses used in the rat studies resulted in exposures of up to 18 times and 12 times the maximum anticipated clinical exposure (based on AUC) of vildagliptin and metformin, respectively (Table 1). Doses up to the maximum tolerated metformin dose were used in the dog studies, resulting in lower exposures (up to 4-fold the clinical AUC for each agent) compared with the rat studies.

Female dogs appeared to be particularly sensitive to metformin, with mortalities attributed to drug-induced hypoglycaemia occurring at≥50 mg/kg/day. The levels of mortality in the submitted studies were similar to those reported previously in beagles at equivalent doses.

[3] EMEA, Committee for Medicinal Products for Human Use (CHMP), 24 January 2008. Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products, CHMP/SWP/258498/2005.

Table 1: Relative exposures of vildagliptin and metformin achieved in repeat-dose toxicity studies.

Species (Strain)	Study; [Treatment duration]	Dose (mg/kg/day)		$AUC_{0–24h}$ (µg·h/mL)			Exposure ratio[a]		
		Vildagliptin	Metformin	Vildagliptin	Metformin		Vildagliptin	Metformin	
				♂/♀	♂	♀	♂/♀	♂	♀
Rat (Wistar)	0570004 [2 weeks]	10	100	2.5	39		1.3	1	
		20	200	7.1	109		4	3	
		60	600	10	112		5	4	
		0	600	–	177		–	6	
		60	0	8.9	–		5	–	
	0670033 [13 weeks]	10	100	2.7	37		1.4	1.2	
		30	300	9.4	103		5	3	
		100	1000	36	391		18	12	
		0	1000	–	271		–	9	
		100	0	35	–		18	–	
Dog (Beagle)	0570005 [2 weeks]	1.25	12.5	0.5	11	17	0.2	0.3	0.5
		2.5	25	1.5	28	32	0.8	0.9	1.0
		5	50	2.7	57	80	1.4	1.8	2.5
		0	50	–	40	41	–	1.3	1.3
		5	0	2.7	–	–	1.4	–	–
	0670034 [13 weeks]	2.5	25	1.7	23	32	0.9	0.7	1.0
		5	50	3.2	47	113	1.6	1.5	4
		10	50	8.1	45	106	4	1.4	3
		0	50	–	26	51	–	0.8	1.6
		10	0	6.5	–	–	3	–	–
Human[b]	LMF237 A2301	2×50 mg	2×1000 mg	2.0	32		–	–	

ÿ *[a] calculated as animal:human $AUC_{0–24h}$; [b] maximum recommended clinical dose is 50/1000 mg vildagliptin/metformin twice daily (bd), plasma $AUC_{0–24h}$ values for a single dose obtained in the study were multiplied by 2 to account for bd dosing*

Toxicities observed in rats and dogs were as expected for vildagliptin and metformin with no novel toxicities occurring in animals that had received the combination. Toxicities noted in animals that had received the vildagliptin/metformin combination did not appear to occur with greater incidence or severity than in animals that had received identical doses in the single-agent control groups with one exception: intra-alveolar accumulations of foamy macrophages in rats, an effect attributed to vildagliptin treatment. In the 13-week study, the incidence and severity of the finding was higher in both male and female animals treated with 100 mg/kg/day vildagliptin together with 1000 mg/kg/day metformin compared with vildagliptin alone (males: 9/10 compared with 4/10; females: 5/10 compared with 1/10;

always of minimal severity with the single agent compared with up to slight severity with the combination). Relative exposure at the No Observable Effect Level (NOEL) is moderately large (5), and the finding has not been observed with vildagliptin in non-rodent species (dog and monkey).

Gastrointestinal effects (soft, mucoid faeces and diarrhoea) were observed in dogs, and can be attributed to both vildagliptin and metformin. Cardiovascular findings included sporadic electrocardiogram (ECG) changes (intermittent left bundle branch block, tall R waves and deep T waves) in female dogs that had received 50 mg/kg/day metformin (either alone or in combination with vildagliptin) and myocardial necrosis in the rising dose dog study. The latter finding was attributed to underperfusion of the myocardium related to hypoglycaemic shock and may further reflect the sensitivity of this species to the pharmacological action of metformin.

Reproductive toxicity

Embryofetal development studies were conducted in rats and rabbits with the vildagliptin/ metformin combination. A metformin-only concurrent control was also included. Teratogenicity was not observed in either species, consistent with findings for the single agents. An increase in the incidence of incomplete ossification observed in the fetuses of rats treated at 1000 mg/kg/day metformin with and without 100 mg/kg/day vildagliptin and an increase in early resorptions in rabbits at 10/100 mg/kg/day vildagliptin/metformin are likely to be secondary to maternal metformin-associated toxicity. These doses resulted in exposures 14-fold and approximately equivalent to the anticipated clinical exposure (based on AUC) in rats and rabbits, respectively (Table 2).

Table 2: Relative exposures in reproductive toxicity studies

Study	Species, Strain	Dose (mg/kg/day)		Vildagliptin		Metformin	
		vildagliptin	metformin	$AUC_{0–24h}$ (µg·h/mL)	Exposure ratio[a]	$AUC_{0–24h}$ (µg·h/mL)	Exposure ratio[a]
0670172	**Rat** (Wistar)	10	100	4.1	2	67	2
		30	300	12	6	135	4
		100	1000	40	20	448	14
		0	1000	–	–	394	12
0670015	**Rabbit** (NZW)	1	10	0.22	0.11	5	0.2
		3	30	0.99	0.5	14	0.4
		10	100	3.7	2	40	1.3
		0	100	–	–	46	1.4
LMF237 A2301	**Human** Healthy	2×50 mg	2×1000 mg	2.0	–	32	–

ÿ [a] *calculated as animal:human* $AUC_{0–24h}$

Impurities

The proposed specifications for identified impurities/degradants in the drug substance and drug product for Galvumet were found to be acceptable. As there were no toxicities that could be attributed to the impurities at doses far exceeding the maximum human dose on a body-surface area basis (Table 3), there are unlikely to be safety concerns with the higher limits

proposed for the degradants 207-01 and 209-01. Previously evaluated genotoxicity studies with TOX1/LAF237 (bacterial mutagenicity and *in vitro* clastogenicity) were negative.

Table 3: Dose ratio of degradants in Study 0170512 (4-week rat study)

Degradation product	Maximum human dose		Dose in Study 0170152		Animal:human dose ratio based on BSA
	mg/day	mg/m^2/day[a]	mg/kg/day	mg/m^2/day[b]	
207-01	1	0.66	19.67	118	179
209-01	1	0.66	19.67	118	179

ÿ [a]*Based on a 50 kg individual and using a mg/kg to mg/m^2 conversion factor of 33 for humans*
[b]*Using a mg/kg to mg/m^2 conversion factor of 6 for rats*

The only metformin-related impurity in the drug substance is 1-cyanoguanidine which is specified at 0.02%. This is below the qualification threshold.

Therefore, the proposed specification limits for impurities/degradants in Galvumet are considered to be acceptable on toxicological grounds.

Nonclinical Summary and Conclusions

Two newly submitted primary pharmacology studies, conducted in mice and dogs and using single-agent vildagliptin, add further support for the drug's expected efficacy to improve glycaemic control in patients with type 2 diabetes.

Metformin did not affect the plasma AUC for vildagliptin in rats, dogs or humans, but reduced the C_{max} for vildagliptin in rats (at high doses) and (to a minor degree) in humans. Exposure to metformin increased with co-administration of vildagliptin in both rats and dogs (by 1.4–2.1 times), but vildagliptin did not affect metformin's kinetics in humans.

Toxicity studies were appropriately designed and conducted.

Repeat-dose toxicity studies of up to 13 weeks duration in dogs and embryofetal toxicity studies in rats and rabbits revealed no novel or exacerbated toxicity with vildagliptin/metformin co-administration. An increase in the incidence and severity of intra-alveolar accumulations of foamy macrophages was observed in rats treated with vildagliptin and metformin in combination (at 100 and 1000 mg/kg/day, respectively) compared with animals treated with vildagliptin alone. This rodent-specific effect of vildagliptin is not considered to be of clinical significance.

There were no objections on nonclinical grounds to the registration of Galvumet.

IV. Clinical Findings

Pharmacokinetics

Five biopharmaceutical studies of similar, satisfactory design are presented. One was to choose which of two formulations to develop, three were to evaluate bioequivalence of the component drugs given alone or as each of the three combined-dose tablets applied for, and one examined the effect of food on bioavailability of the components of a vildagliptin/metformin 50/1000 mg tablet.

There was, in addition, a randomised crossover comparison of the multiple dose pharmacokinetics of vildagliptin (100 mg) and of metformin (1000 mg), each given either alone or as a combined tablet (not currently applied for in this dose combination), in patients with Type 2 diabetes mellitus.

Study LMF 2304 was a pilot study comparing the bioavailability of vildagliptin and metformin given as two formulations of 50/1000 mg fixed-dose combinations including differing percentages of an excipient with that of vildagliptin 50 mg and metformin 500 mg,

given as separate tablets as the "gold standard." Essentially no difference was found between the two fixed-dose formulations and the "gold-standard." This study was discussed in Section II.

Study LMF 2301 was a crossover evaluation of bioequivalence of a single dose of vildagliptin/metformin 50/1000 mg given as either a combined formulation or as separate tablets in 44 healthy female and male (F:M = 28:16) subjects aged 18-50 years. All but one enrolled subject completed both arms of the study without significant protocol deviations. This study was discussed briefly in Section II.

The study design was as follows:

Treatment Sequence Group	Period 1	Period 2	Period 3*
I	A	B	C
II	B	C	A
III	C	A	B

Treatment A: LMF237 50 mg/ 1000 mg formulation A tablet
Treatment B: LMF237 50 mg /1000 mg formulation B tablet
Treatment C: Free combination of LAF237 50 mg and metformin 1000 mg tablets

Results

Vildagliptin

The mean plasma concentration-time profiles of vildagliptin were similar following single oral doses of vildagliptin as vildagliptin 50 mg/metformin 1000 mg in fixed combination (Treatment A) or vildagliptin 50 mg and metformin 1000 mg as separate tablets (Treatment B).

The vildagliptin pharmacokinetic parameters were similar between the two treatments. One subject had a vildagliptin half-life ($t_{½}$) of 40.2 hours during Treatment B; this $t_{½}$ value was longer than that for any other subject in either Treatment A or B and the $t_{½}$ for this subject during Treatment A was 2.06 hours. The main reason for the prolonged $t_{½}$ for this subject during Treatment B was that there were measurable vildagliptin plasma concentrations until 48 hours. The exclusion of data from this subject resulted in mean±SD (standard deviation) (CV [coefficient of variation]%) $t_{½}$ values of 2.47±0.78 (31%) hours for Treatment B compared with 2.56±0.90 hours for Treatment A.

Metformin

Results for metformin exhibited similar concordance between the two drug presentations and statistical evaluation demonstrated acceptable bioequivalence of the two presentations.

Study LMF 2303 was of the same purpose and design as Study LAF 2301 but evaluating a dose of 50/500 mg vildagliptin/metformin. Of the 40 subjects enrolled, 37 completed both arms of the study and 3 withdrew their consent. The entry criteria were the same for both studies but mean age was greater in Study 2303 (37.8 vs 29.1 years). This study was discussed briefly in Section II.

Results

The 37 subjects who completed both study periods were included in the pharmacokinetic data analysis.

Vildagliptin

Pharmacokinetic parameters and the concentration/time profiles were similar for the two drug presentations.

Metformin

Results for metformin were similar and statistical evaluation indicates bioequivalence of the different presentations for both component drugs.

Study LMF 2307 was of the same purpose and design as Studies LAF2301 and 2303 but for a dose of vildagliptin/metformin of 50/850 mg. Of the 44 subjects enrolled, all but one completed the study and provided data for analysis. This study was discussed briefly in Section II.

Results

Vildagliptin

Pharmacokinetic parameters and the concentration/time profiles were similar for the two drug presentations.

Metformin

Results for metformin exhibited similar concordance between the two drug presentations and statistical evaluation of the two presentations demonstrated bioequivalence of the two presentations of the two drugs for both drugs.

Study LMF2101 was a randomised crossover examination of the effect of food on the bioavailability of vildagliptin and of metformin given as a single dose of the combined formulation of vildagliptin/metformin 50/1000 mg. The study design was essentially the same as the above bioequivalence studies except that the two schedules compared were of the formulation given in the fasting state or within 5 minutes of an FDA standard fatty breakfast. Twenty four subjects aged 18-45 years (F:M =5:19) were enrolled in the study but one did not attend for the "fed" sequence. This study was discussed in Section II.

Results

Vildagliptin absorption was not affected by administration in the fed state.

Metformin absorption was slowed, resulting in increase in median T_{max} from 2 to 4 hours and reduction in mean C_{max} by 26% but mean AUC was reduced by only ~8% (Table 4).

Table 4: PK data for Study LMF2101

Summary of metformin pharmacokinetic parameters after a single dose of one vildagliptin/metformin 50/1000 mg tablet in the fasting state (Treatment A) and in the fed state (Treatment B) to healthy subjects

Treatment	T_{max} (hr) Median (min, max)	C_{max} (ng/mL) Arithmetic mean ± SD (CV%)	AUC_{0-t} (hr*ng/mL) Arithmetic mean ± SD (CV%)	$AUC_{0-\infty}$ (hr*ng/mL) Arithmetic mean ± SD (CV%)
A (Fasting)	2.00 (0.50, 4.00)	1740 ± 451 (25.9)	11167 ± 2867 (25.7)	11371 ± 2896 (25.5)
B (Fed)	4.00 (1.50, 6.00)	1290 ± 374 (29.1)	10273 ± 2675 (26.0)	10507 ± 2693 (25.6)

Statistical evaluation of these results indicated that food did not affect bioavailability of vildagliptin beyond conventionally accepted limits, although the decrease in C_{max} of metformin (but not AUC) did so.

Study LAF2104 was a randomised crossover comparison of the multiple dose pharmacokinetics of vildagliptin (100 mg) and of metformin (1000 mg), each given either alone or as a combined tablet, in patients with Type 2 diabetes mellitus previously under treatment with metformin 500-2000 mg/day. Note that the combined tablet studied here was not one of those applied for in this application.

The patient's metformin was stopped 72 hours before commencing the trial administration and there was a 72 hour washout between treatment periods.

Test administrations given fasting, were as follows:

- Treatment A: 100 mg vildagliptin daily for 5 days
- Treatment B: 1000 mg metformin daily for 5 days
- Treatment C: 1000 mg metformin /100 mg vildagliptin daily for 5 days

All 17 enrolled patients completed the study.

Results

Vildagliptin

On Days 3, 4 and 5, trough levels of vildagliptin given either alone or as the combined tablet with metformin were for the most part below or just above the lowest level of quantification (LLOQ) and showed no evidence of accumulation.

When given with metformin, median T_{max} was greater and C_{max} reduced and the geometric mean C_{max} ratio limits for vildagliptin exceeded the conventionally accepted lower limit. AUC was not significantly altered.

Metformin

On Days 3, 4 and 5 trough levels of metformin, given either alone or in the combined tablet with vildagliptin, were measurable but showed no evidence of accumulation.

The mean area under the plasma concentration time curve from 0 to 24 hours (AUC_{0-24}) was ~15% greater when metformin was given as the combined tablet, but the geometric mean ratio of C_{max} was within conventionally accepted limits.

Summary of pharmacokinetics

Randomised crossover studies of satisfactory design and execution in healthy young adults have demonstrated bioequivalence of exposure following a dose of both vildagliptin and metformin given either as separate marketed formulations or as the combined tablets that are the subject of this application. The doses evaluated were vildagliptin/metformin 50/500 mg, 50/850 mg and 50/1000 mg.

A crossover study of the effect of food on the bioavailability of the constituent drugs in a vildagliptin/metformin 50/1000 mg tablet found no influence of food on vildagliptin but a significant increase of metformin T_{max} from 2 to 4 hours, a significant reduction of 26% in C_{max} and a non-significant decrease of 8% in AUC.

Multiple dose pharmacokinetics of vildagliptin and metformin administered together, either as separate marketed formulations or as a combined tablet have been compared in patients with Type 2 diabetes mellitus being treated with metformin 500-2000 mg daily. When studied after withdrawal of their regular metformin medication for three days, absorption of vildagliptin was slowed and C_{max} decreased, but the mean AUC was not significantly reduced.

Efficacy

Introduction

Five controlled studies of efficacy in patients with Type 2 Diabetes Mellitus (T2DM) were submitted. One of them involved comparison of a combination tablet with the individual drug components. The remainder concern this application by inference only, as they studied various dosage regimens of the two drugs given separately. There are in addition two uncontrolled studies one of which was of the combined tablet in patients with very poor glycaemic control with metformin alone and thus not eligible for the combined tablet placebo controlled trial.

Study CLMF237A2302

Study CLMF237A2302 compared four methods of commencing and escalating the intensity of 24 weeks treatment with metformin and/or vildagliptin, of drug-naïve patients with T2DM and glycosylated haemoglobin (HbA1c) of 7.5-11%.[4]

The treatments administered are summarised in Figure 1.

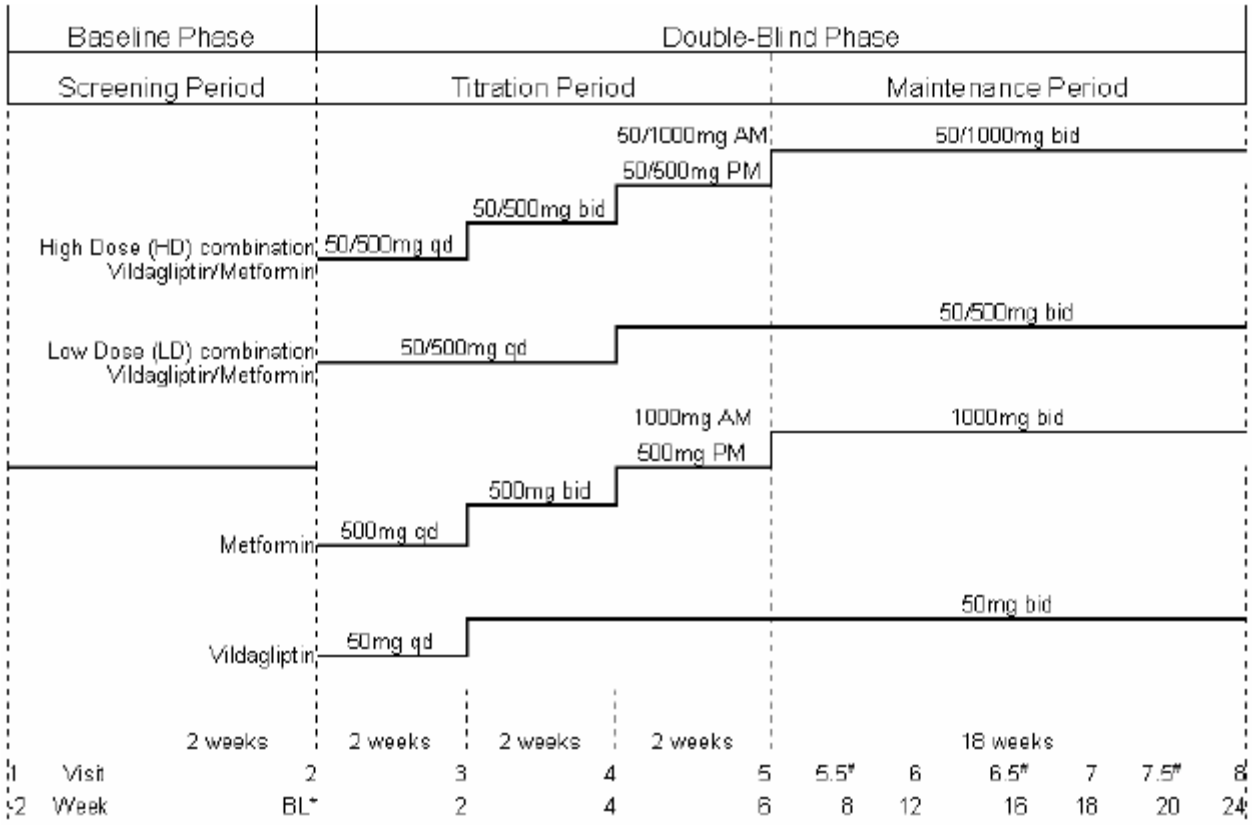
Demographic and disease characteristics of the 1179 randomised patients were acceptably distributed between the four arms of the study.

Of those randomised, 995 completed the study. The major reasons for failure to complete the study were withdrawal of consent (79 patients, 6.7%), adverse events (38, 3.2%) lost to follow up (31, 2.6%) and unsatisfactory response (20, 1.7%).

The primary efficacy variable was the change from baseline in HbA1c at Week 24 or at the final post-baseline visit with an HbA1c measurement for those patients for whom the Week 24 HbA1c measurement was missing (that is, using the Last Observation Carried Forward [LOCF] algorithm).

Figure 1: Study Design

[4] For the purposes of this and other protocols, “drug-naïve” patients were defined as those who had never been treated with an antidiabetic agent or subjects who had not taken any antidiabetic agent for at least 12 weeks prior to study entry (Visit 1) and if they had received oral antidiabetic agents, then never for > 3 months at any time in the past.



* Baseline, Day 1; randomization and first day of study medication.

#At visits 5.5, 6.5 and 7.5 only blood samples were taken in order to monitor liver function, accordingly the visits were named as such in order to avoid confusion with existing study aids where visit numbers were preprinted

The primary analysis was the comparison of the change from baseline in HbA1c in the fixed combinations (high dose [HD] and low dose [LD] of vildagliptin and metformin) versus each of the monotherapy components. Results for this variable are also expressed as responder rates using six pre-specified definitions of response, as shown below.

Responder analysis: Six definitions of responder at endpoint are defined:

1. Endpoint HbA_{1c} <7%
2. Endpoint HbA_{1c} <7% in patients with baseline HbA_{1c} ≤8%
3. Endpoint HbA_{1c} ≤6.5%
4. HbA_{1c} reduction from baseline at endpoint ≥1%
5. HbA_{1c} reduction from baseline at endpoint ≥1% in patients with baseline HbA_{1c} >9%
6. HbA_{1c} reduction from baseline at endpoint ≥0.7%

Secondary efficacy variables were change from baseline of fasting plasma glucose level (FPG), fasting lipid profile and body weight.

Results

The change in HbA1c from baseline is detailed in Table 5. In the intent-to-treat (ITT) population, HbA1c declined from baseline with all four treatments (-1.61%, -1.82%, -1.09% and -1.36% for low dose combination, high dose combination, vildagliptin and metformin respectively).

Table 5: Study CLMF237A2302 – ANCOVA results for the change in HbA1c (%) from baseline to endpoint

Treatment	n	Baseline Mean (SE)	Adjusted Mean Change (SE)	Treatments Compared	Difference in Adjusted Mean Change		
					Mean (SE)	95% CI	p-value*
ITT Population							
A. Vilda + Low dose Met	277	8.56 (0.061)	-1.61 (0.063)	(A-C)	-0.52 (0.087)	(-0.69, -0.34)	<0.001*
				(A-D)	-0.25 (0.087)	(-0.42, -0.08)	0.004*
B. Vilda + High dose Met	285	8.71 (0.061)	-1.82 (0.062)	(B-C)	-0.72 (0.086)	(-0.89, -0.56)	<0.001*
				(B-D)	-0.46 (0.086)	(-0.63, -0.29)	<0.001*
C. Mono Vilda	287	8.67 (0.060)	-1.09 (0.061)				
D. Mono Met	285	8.60 (0.055)	-1.36 (0.062)				
Per Protocol Population							
A. Vilda + Low dose Met	244	8.53 (0.064)	-1.68 (0.064)	(A-C)	-0.54 (0.089)	(-0.71, -0.36)	<0.001*
				(A-D)	-0.20 (0.090)	(-0.38, -0.03)	0.025*
B. Vilda + High dose Met	258	8.70 (0.061)	-1.89 (0.062)	(B-C)	-0.75 (0.088)	(-0.92, -0.58)	<0.001*
				(B-D)	-0.41 (0.089)	(-0.59, -0.24)	<0.001*
C. Mono Vilda	254	8.65 (0.063)	-1.14 (0.063)				
D. Mono Met	238	8.56 (0.059)	-1.48 (0.065)				

Baseline is measurement obtained on the day of randomization, or on the sample obtained on an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if the Day 1 (Visit 2) measurement is missing.

Week 24 endpoint is the measurement obtained at the last scheduled or unscheduled post-baseline study visit prior to or at the last scheduled visit (Week 24, Visit 8).

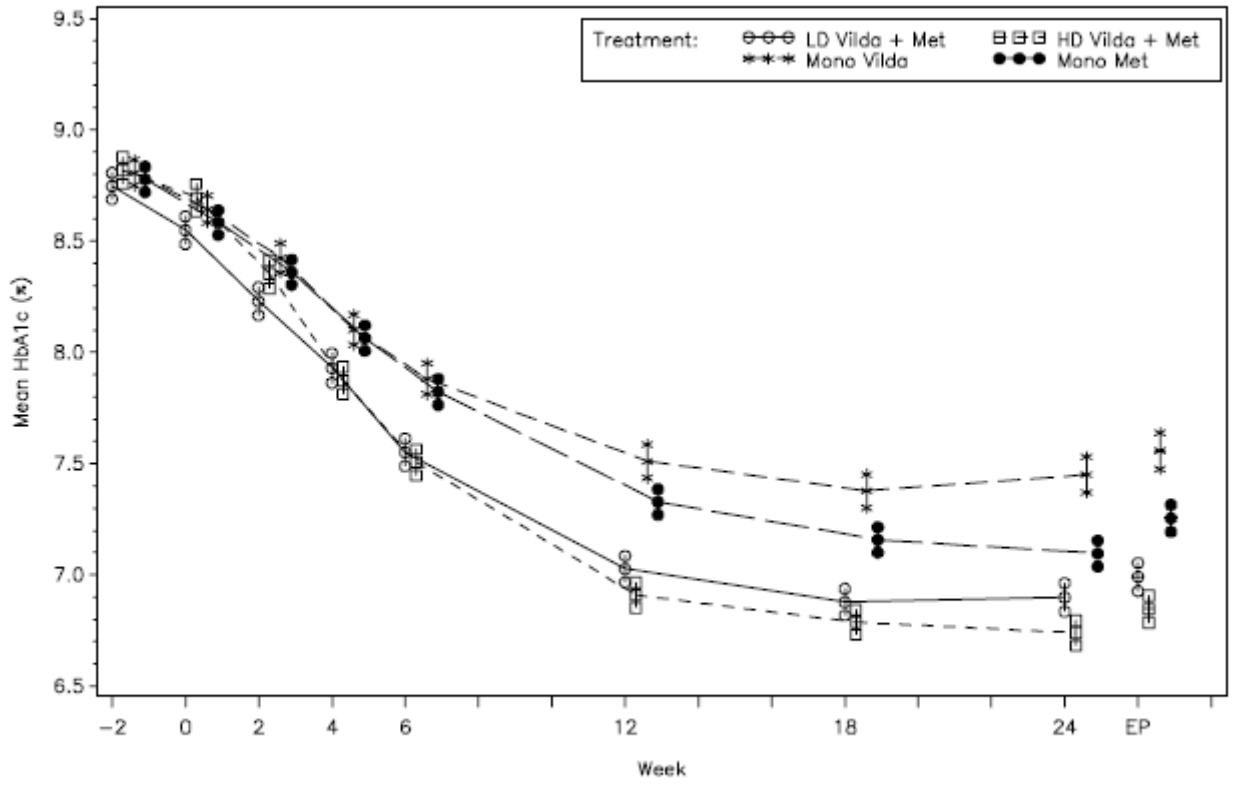
n is the number of patients with observations at both baseline and endpoint.

Adjusted means and the associated standard errors (SE), confidence intervals (CI) and p-values were obtained from an ANCOVA model containing terms for treatment, pooled study center and baseline HbA_{1c}.

* indicates statistical significance at 5% level according to the Hochberg step-up procedure.

The same pattern was seen in the per-protocol population. Mean HbA1c levels during the course of the study are shown in Figure 2. Decline from baseline was significantly greater with both low and high dose combined treatment than with each of the two monotherapy dosing schedules ($p \leq 0.004$). The statistical analysis allowed for multiplicity of comparisons.

Figure 2: Study CLMF237A2302 – Mean HbA1c (%) by treatment and visit



Unadjusted means and standard errors (vertical bars) are given.
EP (Endpoint) is the final available post-randomization assessment up to the last regular scheduled visit.

When the change in HbA1c was expressed as responder rate, both combined tablet schedules were significantly superior to both monotherapy treatments with some exceptions.

The change from baseline for FPG followed the same overall pattern as for HbA1c.

Changes in fasting lipid profile were for the most part, neither statistically nor clinically significant.

Mean body weight decreased in all groups with the greatest decrease observed in the metformin monotherapy group (-1.62 kg) and the smallest decrease in the vildagliptin monotherapy group (-0.59 kg).

Study CLAF237A2204

Study CLAF237A2204 was a randomized, parallel group, placebo-controlled trial comparing the addition of vildagliptin or placebo in the treatment of 132 patients with T2DM who were receiving metformin at a stable dosage of 1500–3000 mg daily. Initially two vildagliptin dosage arms, 50 and 100 mg once daily, were planned but the higher dose was subsequently omitted due to safety concerns arising from pre-clinical studies. Patients continued their prior metformin dose during the whole study. They received placebo during a 4-week run-in phase and thereafter either commenced vildagliptin or continued placebo for 12 weeks.

The primary efficacy variable was the change from baseline in HbA1c at the end of the study. For subjects who did not have a Week 12 HbA1c measurement, the LOCF algorithm was used. Response rates by pre-defined criteria were also presented.

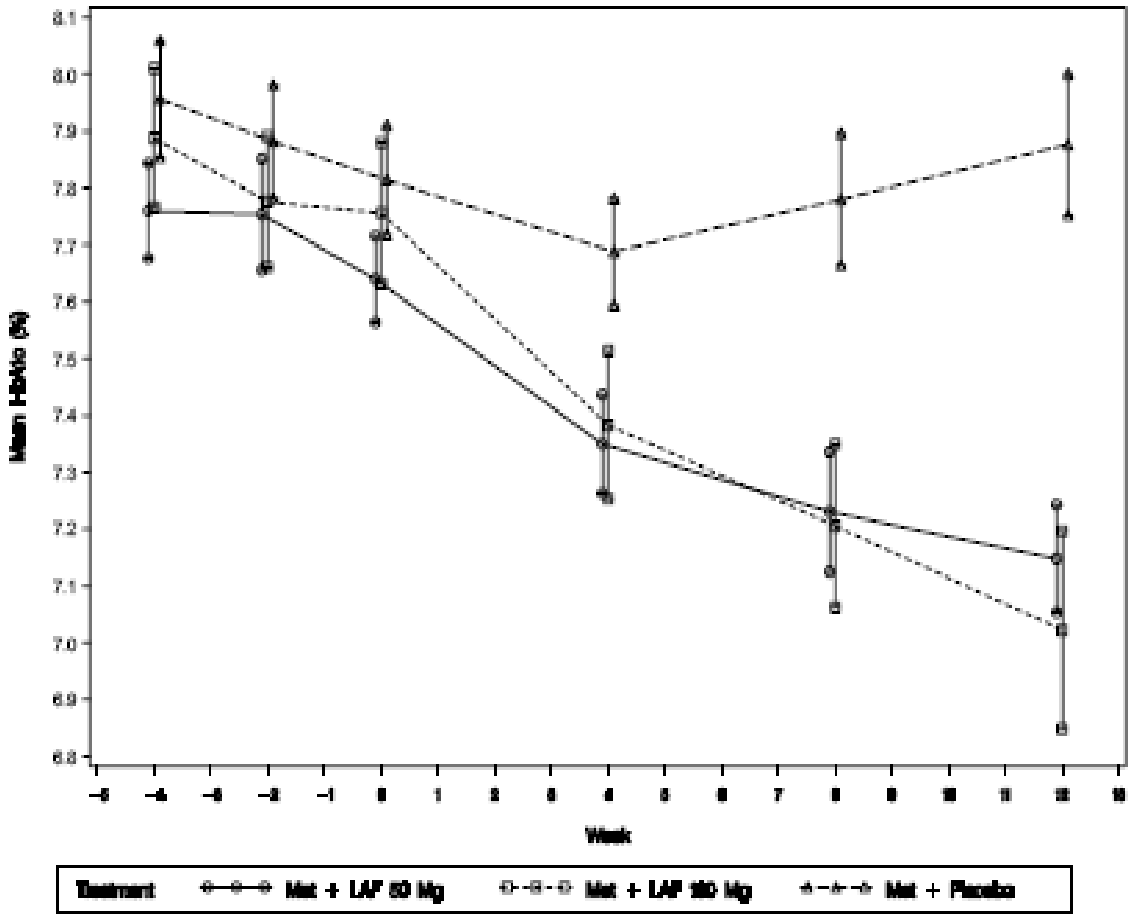
Secondary variables (including FPG, fasting insulin, pro-insulin, C-peptide, lipids, body weights and prandial glycaemic parameters) were also measured.

The placebo and vildagliptin 50 mg groups were reasonably matched in terms of demographic and disease characteristics except that 58.8% of the placebo group had a body mass index (BMI) $\geq$30 kg/m^2 compared with 44.6% of the vildagliptin group. The metformin dose at randomisation was comparable in these two groups. Approximately 90% of both the placebo and vildagliptin groups completed the study.

Results

The primary variable, the change in HbA1c from baseline, showed a small increase in mean level in the placebo group (+0.09%) but a decrease in the vildagliptin group (-0.56%). The difference was significant ($p<0.0001$). The movement of mean HbA1c over the course of the trial is shown in Figure 3.

Figure 3: Study CLAF237A2204 – Mean HbA1c (%) by treatment group and visit



The proportion of responders by various definitions of response, are shown in Table 6. All were substantially higher for the vildagliptin group.

Table 6: Study CLAF237A2204 – Number of patients who responded at the endpoint

Responder criterion	Met+ LAF 50mg N=56	Met+ LAF 100mg N=25	Met+ Placebo N=51
n*	53 (100%)	25 (100%)	50 (100%)
HbA_{1c} < 7%**	22/47 (46.8%)	11/24 (45.8%)	6/48 (12.5%)
HbA_{1c} ≤ 6.5%	7 (13.2%)	3 (12.0%)	1 (2.0%)
Reduction of HbA_{1c} ≥ 1%	12 (22.6%)	7 (28.0%)	1 (2.0%)
Reduction of HbA_{1c} ≥ 0.5%	26 (49.1%)	12 (48.0%)	8 (16.0%)

* = number of patients with both baseline and endpoint HbA1c measurements.

** Denominator are patients with baseline HbA1c ≥7% and endpoint HbA1c measurement.

Of the secondary variables, the change from baseline FPG mimicked the primary variable: there was ~2% mean rise in the placebo group and ~10% fall in the vildagliptin 50 mg group, the difference being significant (p=0.0057). The only other fasting level secondary variable that differed significantly between the two groups was pro-insulin which decreased significantly in the vildagliptin group, p=0.0006.

Secondary variables derived from the test meal in the vildagliptin 50 mg group showed statistically significant decreases of mean plasma glucose, mean glucose excursions and of mean pro-insulin compared to changes in the placebo group. Mean C-peptide revealed a statistically significant increase at endpoint in the vildagliptin 50 mg group compared to placebo. Noteworthy changes or between-group differences in mean insulin time profiles were not observed in the ITT population.

Treatment effects on beta-cell function indicated improved insulin secretion and insulin sensitivity in the vildagliptin group compared to the placebo group.

Study CLAF237A2204-E

Study CLAF237A2204-E was a 40-week extension of the above Study 2204 maintaining the double-blind structure and continuing the observations.

Of those completing the initial trial, 42/60 (70%) and 29/47 (62%) entered the extension in the placebo and vildagliptin arms respectively of whom 10 (24%) and 3(10%) respectively, withdrew before completion.

Demographic and disease characteristics were similar at initial and extension entry for the vildagliptin arm but in the placebo arm the latter had lesser duration of diabetes (3.6 vs 5.5 years) and duration of metformin treatment (23.7 vs 29.8 months).

Results

In the vildagliptin arm, the mean change in HbA1c from baseline at extension endpoint (52 weeks) was similar to the change from baseline at core endpoint (12 weeks) [-0.50% vs -0.56%], whereas in the placebo arm mean HbA1c increased further during the 40 week extension (mean changes in HbA1c from baseline of +0.60% vs +0.09% at Week 52 and Week 12, respectively). The difference between the two treatments was significant (p<0.0001).

The percentage of responders according to four definitions of response was considerably greater in the vildagliptin treated group (Table 7).

The effect on FPG exhibited similar durability to that on HbA1c. There were no statically significant differences in fasting levels of other secondary variables except for a small difference in reduction in mean total cholesterol, in favour of vildagliptin, of -0.30 mmol/L at endpoint (p =0.0340).

Table 7: Study CLAF237A2204-E - Number of patients who responded at the endpoint

Responder criterion	Met+LAF 50mg N=42 n (%)	Met+Placebo N=29 n (%)
Extension ITT population		
N*	42 (100)	29 (100)
$HbA_{1c} < 7\%$**	15/36 (41.7)	3/28 (10.7)
$HbA_{1c} \leq 6.5\%$	9 (21.4)	0
Reduction of $HbA_{1c} \geq 1\%$	10 (23.8)	2 (6.9)
Reduction of $HbA_{1c} \geq 0.5\%$	18 (42.9)	5 (17.2)
Extension Per-Protocol population		
N*	31 (100)	25 (100)
$HbA_{1c} < 7\%$**	11/26 (42.3)	3/24 (12.5)
$HbA_{1c} \leq 6.5\%$	7 (22.6)	0
Reduction of $HbA_{1c} \geq 1\%$	7 (22.6)	2 (8.0)
Reduction of $HbA_{1c} \geq 0.5\%$	12 (38.7)	5 (20.0)

* Number of patients with both baseline and endpoint HbA_{1c} measurements in the specified population.
** Denominator are patients with baseline $HbA_{1c} \geq 7\%$ and endpoint HbA1c measurement.

The pattern seen at endpoint for this trial, in test meal responses, was similar to that seen at 12 weeks, except that the 4-hour mean insulin was greater and was significantly larger with vildagliptin than with placebo and the 4-hour mean pro-insulin levels did not differ significantly between treatments.

Assessments of insulin resistance were to some degree at variance with those at 12 weeks perhaps because the populations were different due to dropouts following completion of the core study.

Study LAF237A 2303

Study LAF237A 2303 was of similar basic purpose and design to the unamended Study CLAF237A2204 with the following differences:

- The three arms were placebo, vildagliptin 50 mg once daily (qd) and 50 mg twice daily (bd)
- Duration of the double-blind period was 24 weeks
- A fifth criterion for responder status was added - reduction of HbA1c at endpoint $\geq 0.7\%$.

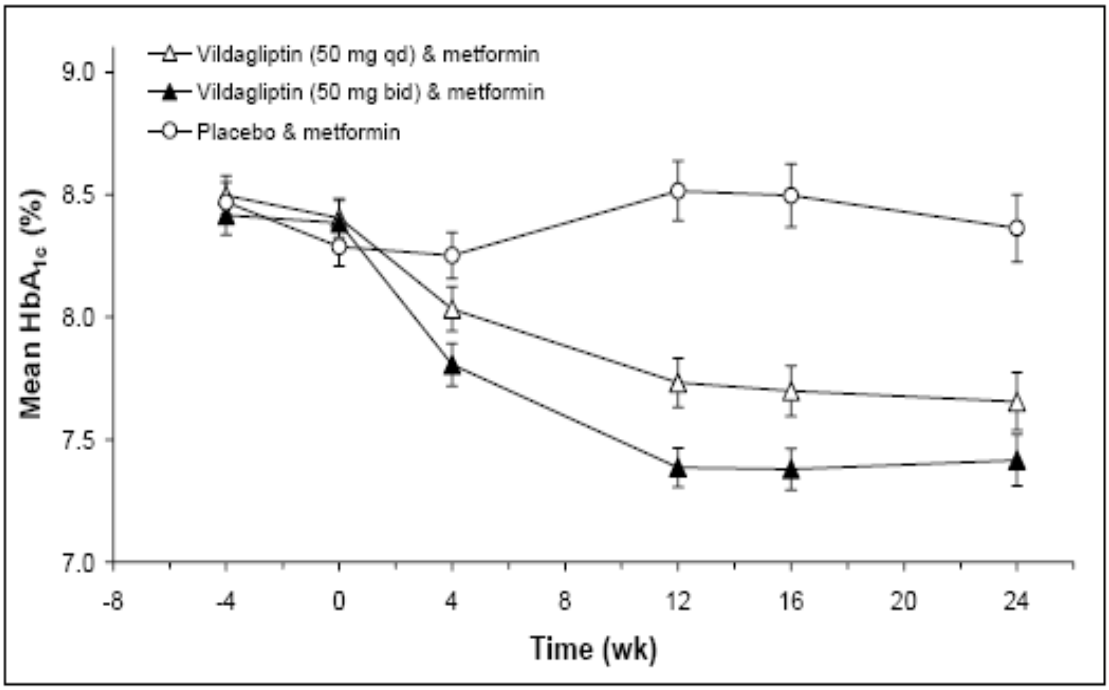
Of the 544 patients randomised, 462 completed the study but only 416 were included in the ITT population. In 40 of the 128 patients excluded, it was due to lack of reliable baseline HbA1c levels and 64 were incorrectly randomised, both deficiencies being as a result of an HbA1c assay problem.

Demographic and disease characteristics and metformin dosage were reasonably distributed across the groups.

Results

Mean HbA1c at endpoint had declined from baseline in both vildagliptin arms but had risen in the placebo arm (-0.88, -0.51 and +0.23% in vildagliptin 50 mg bd, qd and in the placebo arms respectively). Comparisons of both vildagliptin dose arms with placebo, adjusted for multiplicity, were statistically significant. Progress through the 24 weeks of the study is shown in Figure 3.

Figure 3: Study LAF237A 2303 – Mean HbA1c (%) by treatment group and visit



Expressing the results as the proportion of responders according to various definitions showed that there were significantly more responders in each vildagliptin arm than in the placebo arm for all definitions of response.

Of the secondary variables, there was ~7% rise in the mean change from baseline FPG in the placebo group, ~10% fall in the vildagliptin 50 mg bd group and a small fall of ~1.7% in the 50 mg qd group. The differences from placebo were significant for each vildagliptin dosage.

Standard meal tests were conducted at baseline and endpoint in a subgroup of patients. Participation was optional and determined at study entry. Overall, 192 patients (35% of randomised patients) participated in these tests which included comparable numbers of patients from each treatment group. This subpopulation was similar in demographic and baseline characteristics to the main study population with the exception of a somewhat shorter time of metformin use (13.85 vs 17.74 months). However their HbA1c responses were greater (-0.90% vs -0.51% and -1.10% vs -0.88% for 50 mg qd and bd respectively). In this partly unrepresentative group, both vildagliptin dosages significantly reduced prandial glucose excursions and increased those of insulin and C-peptide.

The effect of addition of vildagliptin was to significantly decrease fasting pro-insulin/insulin ratio and increase corrected insulin response (CIR) and insulin secretion rate relative to

glucose for both vildagliptin dosages and to increase the insulinogenic index (0-peak glucose), although for the 50 mg qd dose this just missed significance (p= 0.053).

Study LAF237A 2309

Study LAF237A 2309 was a non-inferiority comparison of metformin and vildagliptin as monotherapy. Thus it addressed a question that is directly relevant neither to this application for the combined tablet nor to the revised application which is to be contemporaneously considered by the TGA that excludes vildagliptin as monotherapy.

Drug-naïve patients with T2DM and an HbA1c of 7.5-11% were randomised (2:1) to receive vildagliptin 50 mg bd or metformin up to 1000mg bd for 52 weeks.

Efficacy variables were essentially the same as for the studies already considered with the following exceptions:

This was a non-inferiority study; a pre-determined margin for the primary efficacy variable (decline of HbA1c from baseline to endpoint) was 0.4% and for the "critical" secondary variable (decline from baseline to endpoint of FPG) was 0.6 mmol/L and a secondary variable, coefficient of failure, was included as a measure of durability of response.[5]

Approximately 70% completed the trial; there were more withdrawals due to adverse events in the metformin group (6.3% vs 3.6%) but more in the vildagliptin arm due to inefficacy (6.7% vs 1.2%).

The two arms were reasonably balanced with regard to demographic and disease characteristics.

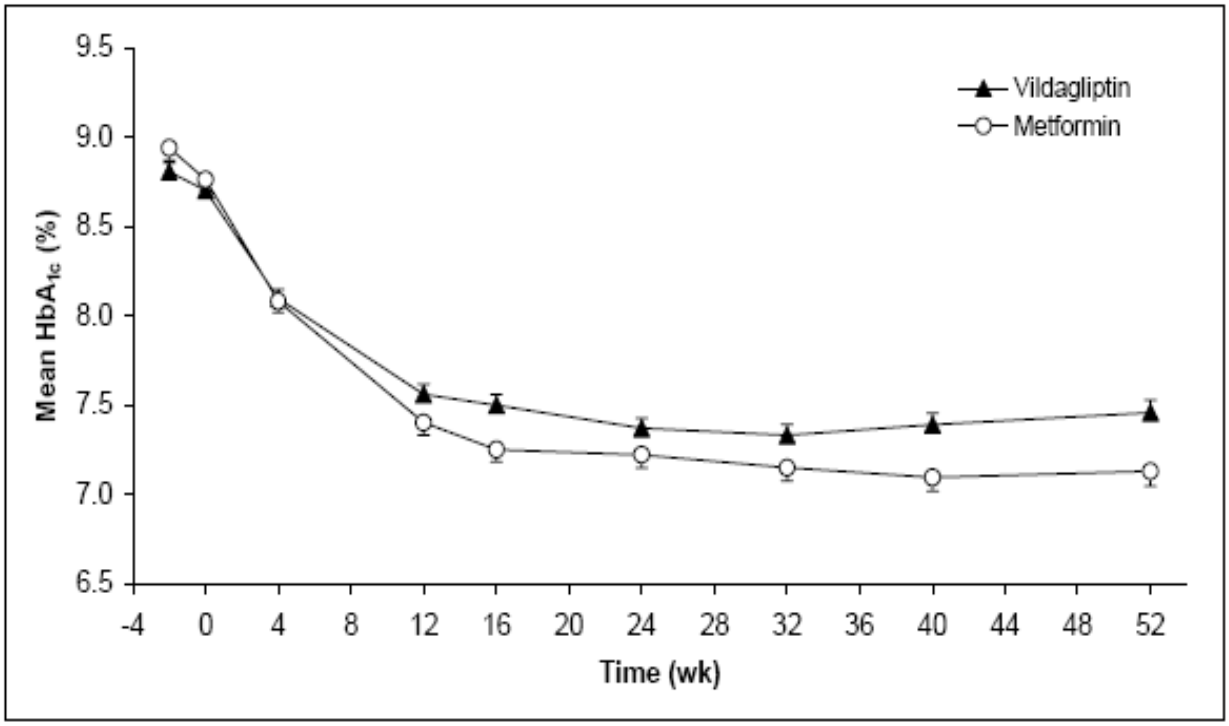
Results

Reduction from baseline HbA1c at endpoint was seen in both arms but was greater with metformin (-0.96% vs -1.44% for vildagliptin and metformin respectively). The upper bound of the 95% confidence interval (CI) of the difference of 0.48% (CI 0.28, 0.67) exceeded the pre-specified 0.4% and thus the stated criterion for non-inferiority was not met.

Figure 4 shows a prompt fall in HbA1c in both arms that is to a large extent maintained to endpoint. Such presentations can be misleading due to changing numbers at progressive time points, but retention rates to 52 weeks were quite high in both arms.

Figure 4: Study LAF237A 2309 – Mean HbA1c (%) by treatment group and visit

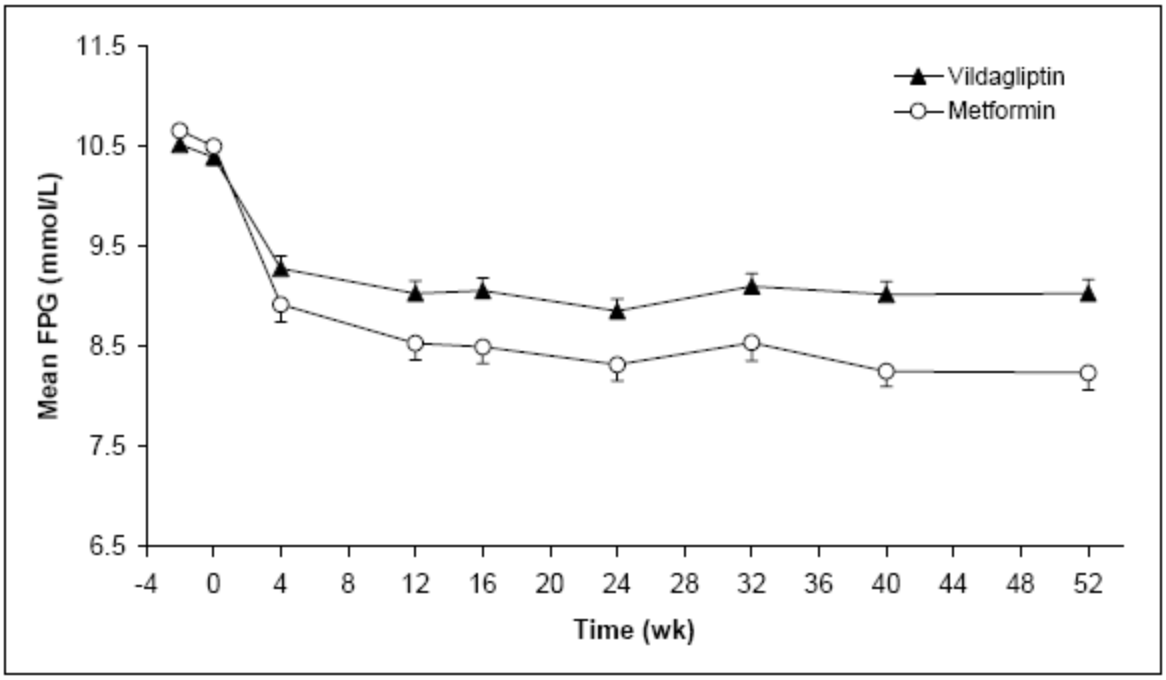
[5] The coefficient of failure (CF) was defined as the slope of the least-squares regression line of HbA1c versus time from Week 24 to the end of the study.



Responder rates were significantly greater with metformin for all criteria.

The critical secondary variable, the decline from baseline to endpoint of FPG, behaved similarly to the primary endpoint. Both treatments significantly reduced FPG from baseline but the mean difference in FPG reduction of 0.95 mmol/L (95% CI 0.53-1.36) indicated superiority of metformin using the pre-specified margin of 0.6mmol/L for non-inferiority. Figure 5 indicates a substantial response in FPG to both drugs by 4 weeks with maintenance of benefit to end of study.

Figure 5: Study LAF237A 2309 – Mean FPG (mmol/L) by treatment group and visit



Response to a test meal was determined in a self-chosen subgroup of patients (15.4% and 14.6% of vildagliptin and metformin arms respectively) who on average had greater response of HbA1c to their test drug than did the entire groups (-1.18% vs -0.99% with vildagliptin and
-1.71% vs -1.44% with metformin). Prandial glucose increase was diminished in both arms but to a significantly greater extent with metformin. Insulin response to the meal was increased from baseline by both drugs, more by vildagliptin but not significantly so. C-peptide rose with vildagliptin but fell with metformin, although this was not evident when adjusted.

Estimates of beta-cell function and insulin resistance revealed few significant differences between the two arms; metformin was associated with significant falls in fasting pro-insulin and pro-insulin/insulin ratio.

Uncontrolled studies

Study LAF237A 2303E1 was a 28-week extension of Study LAF237A 2303 in which the double-blind conditions were maintained for the two metformin plus vildagliptin (50 mg once daily or bd) arms but the metformin plus placebo arm was re-randomised to receive metformin plus vildagliptin 50 mg once daily. The principal object was to assess safety, but also efficacy over 52 weeks by comparing HbA1c at initial baseline and endpoint. Secondary variables were change in HbA1c from entry into the extension study to endpoint, change in FPG, measures of beta-cell function, fasting lipids and body weight at endpoint from both initial baseline and entry into the extension and changes in quality of life issues over the whole 52 weeks.

Of the 462 patients completing the core study, 417 entered the extension study which was completed by 363 patients with comparable proportions of patients discontinuing across study groups except for a tendency for higher discontinuations in the vildagliptin 50 mg qd (core+extension) group. Demographic and disease characteristics were reasonably balanced across the groups.

Results

In all three groups mean HbA1c at endpoint had declined significantly from baseline values but had risen significantly from those at entry into the extension phase in both groups treated with active drug during the core trial. In the group treated initially with placebo but changed to vildagliptin 50 mg qd, the mean HbA1c declined significantly thereafter but substantially less on vildagliptin 50 mg qd than had in the group taking that dose during the core trial.

The secondary variable FPG declined from initial baseline in all groups but this was significant for only those taking Vildagliptin 50 mg bd throughout the core and extension. As for HbA1c, part of the improvement was lost during the extension trial in those taking vildagliptin throughout and this rise from the Week 24 level was significant for the 50 mg bd group.

Study LMF237A 2302S1 was an accompaniment to Study **LMF237A 2302** in which patients fulfilling all its entry criteria except for baseline HbA1c level >11% and/or FPG >15% were recruited. The intention was to examine the possibility of combined vildagliptin and metformin treatment as initial therapy for patients with very poor glycaemic control. There was no placebo group and the trial was open-label. The metformin dose was titrated from an initial 500 mg bd to 1000 mg bd over 3 weeks. The primary efficacy variable was the change in HbA1c value from baseline at endpoint. Secondary efficacy parameters were fasting plasma glucose, body weight and responder rates.

Only ~60% completed the 24-week trial, the main reasons for withdrawal being patient choice.

Results

In both the ITT and Per Protocol populations there was a statistically and clinically significant reduction in mean HbA1c. Over 75% of the ITT population achieved >1.5 % reduction in HbA1c. Decline in FPG showed a similar significant response.

Summary of efficacy

Initiating and titrating treatment of drug-naïve patients with T2 DM, using combined tablets containing vildagliptin 50 mg and either metformin 500 mg or 1000 mg was shown to be superior to doing so with either vildagliptin or metformin used as monotherapy. This result is consistent with the premise that the efficacy of the two drugs is not impaired by administration as a combined formulation.

The other studies in the submission did not involve the combined tablets applied for, but supported evidence discussed in the earlier evaluation report that vildagliptin administration improved glycaemic control in patients with T2DM.

Vildagliptin 50 mg once daily was superior to placebo as supplementary treatment of patients taking metformin 1500-3000 mg per day, over a 52-week period. The improvement from baseline in HbA1c was well maintained at endpoint with vildagliptin but there was continuing increase in HbA1c in the placebo group.

Two studies demonstrated that the addition of vildagliptin to continuing prior metformin treatment was superior, over 52 weeks, to the addition of placebo.

An open-label, uncontrolled trial of vildagliptin 100 mg once per day and metformin titrated to 1000 mg bd in drug naïve patients with very poor glycaemic control found that >75% of patients achieved a reduction from baseline HbA1c≥ 1.5%.

Safety

Results from all the above trials were included in the sponsor's *Integrated Safety Summary* discussed in the previous clinical evaluation report for vildagliptin.[1] The two Periodic Safety Update Reports (PSURs) in this submission were also discussed in the previous submission.

The sole trial involving the combined tablet was Study CLMF237A2302. In that study, mean duration of exposure was ~22 weeks for all four groups. The mean daily dose of vildagliptin at endpoint was the same in both combined tablet and the vildagliptin monotherapy groups and of metformin was the same in high dose combined tablet and metformin monotherapy groups.

The overall incidence of adverse events in the four groups was 55.9 %, 57.5 %, 51.5% and 59.9% for low dose combined, high dose combined, vildagliptin and metformin monotherapy groups respectively. There were more gastrointestinal adverse effects (AEs) with treatments containing metformin but no other consistent difference across groups (Tables 8 and 9). There was no striking difference in the nature or overall incidence of adverse events from those noted in the *Integrated Summary*.

Table 8: Study CLAF237A2302 – Number (%) of patients with AEs up to and including Week 24 visit by primary System Organ Class (SOC)

Primary system organ class	Vilda + Low dose Met N=290 n (%)	Vilda + High dose Met N=292 n (%)	Mono Vilda N=297 n (%)	Mono Met N=292 n (%)
Any Primary system organ class	162 (55.9)	168 (57.5)	153 (51.5)	175 (59.9)
Blood and lymphatic system disorders	0 (0.0)	1 (0.3)	3 (1.0)	1 (0.3)
Cardiac disorders	6 (2.1)	10 (3.4)	3 (1.0)	10 (3.4)
Congenital, familial and genetic disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Ear and labyrinth disorders	8 (2.8)	8 (2.7)	2 (0.7)	4 (1.4)
Endocrine disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)
Eye disorders	9 (3.1)	8 (2.7)	6 (2.0)	10 (3.4)
Gastrointestinal disorders	57 (19.7)	64 (21.9)	49 (16.5)	73 (25.0)
General disorders and administration site conditions	24 (8.3)	30 (10.3)	21 (7.1)	35 (12.0)
Hepatobiliary disorders	1 (0.3)	0 (0.0)	5 (1.7)	2 (0.7)
Immune system disorders	0 (0.0)	3 (1.0)	2 (0.7)	2 (0.7)
Infections and infestations	57 (19.7)	68 (23.3)	65 (21.9)	57 (19.5)
Injury, poisoning and procedural complications	14 (4.8)	13 (4.5)	16 (5.4)	10 (3.4)
Investigations	2 (0.7)	4 (1.4)	4 (1.3)	8 (2.7)
Metabolism and nutrition disorders	2 (0.7)	5 (1.7)	7 (2.4)	6 (2.1)
Musculoskeletal and connective tissue disorders	32 (11.0)	31 (10.6)	30 (10.1)	35 (12.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (1.4)	1 (0.3)	1 (0.3)	3 (1.0)
Nervous system disorders	44 (15.2)	44 (15.1)	39 (13.1)	40 (13.7)
Psychiatric disorders	13 (4.5)	8 (2.7)	14 (4.7)	7 (2.4)
Renal and urinary disorders	5 (1.7)	2 (0.7)	5 (1.7)	8 (2.7)
Reproductive system and breast disorders	7 (2.4)	3 (1.0)	4 (1.3)	5 (1.7)
Respiratory, thoracic and mediastinal disorders	15 (5.2)	13 (4.5)	18 (6.1)	17 (5.8)
Skin and subcutaneous tissue disorders	23 (7.9)	17 (5.8)	23 (7.7)	16 (5.5)
Surgical and medical procedures	1 (0.3)	4 (1.4)	1 (0.3)	0 (0.0)
Vascular disorders	8 (2.8)	10 (3.4)	12 (4.0)	12 (4.1)

A patient with multiple occurrences of an AE is counted only once in the AE category.

Table 9: Study CLAF237A2302 – Number (%) of patients reporting common AEs (greater or equal to 2% in any group) up to and including Week 24 visit by Preferred Term (PT)

Preferred term	Vilda + Low dose Met N=290 n (%)	Vilda + High dose Met N=292 n (%)	Mono Vilda N=297 n (%)	Mono Met N=292 n (%)
Diarrhea	21 (7.2)	19 (6.5)	7 (2.4)	32 (11.0)
Headache	18 (6.2)	16 (5.5)	16 (5.4)	13 (4.5)
Nasopharyngitis	16 (5.5)	22 (7.5)	11 (3.7)	14 (4.8)
Dizziness	14 (4.8)	15 (5.1)	8 (2.7)	12 (4.1)
Nausea	14 (4.8)	19 (6.5)	7 (2.4)	17 (5.8)
Pain in extremity	9 (3.1)	4 (1.4)	5 (1.7)	7 (2.4)
Upper respiratory tract infection	9 (3.1)	4 (1.4)	10 (3.4)	8 (2.7)
Arthralgia	8 (2.8)	3 (1.0)	5 (1.7)	7 (2.4)
Bronchitis	7 (2.4)	6 (2.1)	6 (2.0)	2 (0.7)
Fatigue	7 (2.4)	7 (2.4)	6 (2.0)	15 (5.1)
Dyspepsia	6 (2.1)	10 (3.4)	3 (1.0)	5 (1.7)
Influenza	6 (2.1)	5 (1.7)	6 (2.0)	4 (1.4)
Tremor	6 (2.1)	5 (1.7)	5 (1.7)	3 (1.0)
Abdominal pain upper	5 (1.7)	8 (2.7)	5 (1.7)	7 (2.4)
Asthenia	4 (1.4)	9 (3.1)	4 (1.3)	4 (1.4)
Cough	4 (1.4)	5 (1.7)	8 (2.7)	9 (3.1)
Flatulence	4 (1.4)	4 (1.4)	4 (1.3)	6 (2.1)
Urinary tract infection	4 (1.4)	7 (2.4)	6 (2.0)	3 (1.0)
Vomiting	4 (1.4)	9 (3.1)	1 (0.3)	7 (2.4)
Abdominal distension	3 (1.0)	2 (0.7)	2 (0.7)	6 (2.1)
Back pain	3 (1.0)	11 (3.8)	6 (2.0)	11 (3.8)
Hyperhidrosis	3 (1.0)	3 (1.0)	6 (2.0)	5 (1.7)
Hypertension	3 (1.0)	6 (2.1)	7 (2.4)	10 (3.4)
Abdominal pain	2 (0.7)	2 (0.7)	6 (2.0)	10 (3.4)
Constipation	2 (0.7)	6 (2.1)	10 (3.4)	5 (1.7)
Neuropathy peripheral	0 (0.0)	0 (0.0)	2 (0.7)	6 (2.1)

A patient with multiple occurrences of an AE is counted only once in the AE category.

Preferred terms are sorted by descending order of incidence in the Vildagliptin and low dose metformin fixed combination 50/500mg qd (50/500mg bid) group.

Serious adverse events were more common in the two groups taking metformin 2000 mg per day (3.8% and 4.1% for combined and monotherapy vs 2.4% and 1.3% for low dose combined and vildagliptin monotherapy respectively). There was one death in the high dose vildagliptin group due to pneumonia following a traumatic femoral fracture in a 68 year-old woman.

Change in laboratory parameters from baseline to endpoint and the occurrence of pre-specified abnormalities during dosing were not beyond the expected frequency and there were no consistent differences between groups. Treatment-emergent elevations of hepatic enzymes were recorded in 16 patients, twice as often in the three groups taking vildagliptin as in the metformin monotherapy group, but in none of these was bilirubin >1.5 times the upper limit of normal (ULN). In one patient, after taking the low dose combined tablet for 86 days, elevated aspartate transaminase (AST) (215 U/L; ≥5xULN), alanine transaminase (ALT) (103U/L) and creatine phosphokinase (CPK) (10756 U/L; ≥10xULN) were noted. The patient

was asymptomatic. One day after completion of the study his ALT (25 U/L) and AST (23 U/L) were within the normal range but CPK was still increased (307 U/L).

After 24 weeks of treatment, the proportion of patients with at least one newly occurring or worsening notable abnormality of vital signs or body weight was low and comparable in all treatment groups (3.8% in the low dose combination, 5.5% for the high dose combination, 5.1% for vildagliptin monotherapy and 6.2% for metformin monotherapy). Most notable abnormal findings in this category were high body weight (1.4% of the low dose combination group, 2.7% for the high dose combination, 2.7% for vildagliptin monotherapy and 4.1% for metformin monotherapy).

The incidence of hypoglycaemia is of some interest since this study was examining the feasibility of using the combined tablet as initial therapy. The incidence of hypoglycaemia was low and encountered only in the two monotherapy groups.

Summary of Safety

The single study dealing with the combined tablet does not reveal any safety concerns peculiar to the combined formulation.

Clinical Summary and Conclusions

Randomised crossover studies of satisfactory design and execution in healthy young adults have demonstrated bioequivalence of exposure following a dose of both vildagliptin and metformin given either as separate marketed formulations or as the combined tablets that are the subject of this application. The doses evaluated were vildagliptin/metformin 50/500 mg, 50/850 mg and 50/1000 mg.

A crossover study of the effect of food on the bioavailability of the constituent drugs in a vildagliptin/metformin 50/1000 mg tablet found no influence of food on vildagliptin but a significant increase of metformin T_{max} from 2 to 4 hours, a significant reduction of 26% in C_{max} and a non-significant decrease of 8% in AUC.

Multiple dose pharmacokinetics of vildagliptin and metformin administered together, either as separate marketed formulations or as a combined tablet have been compared in patients with Type 2 diabetes mellitus being treated with metformin 500-2000 mg daily. When studied after withdrawal of their regular metformin medication for three days, absorption of vildagliptin was slowed and C_{max} decreased significantly but the mean AUC was not significantly reduced.

Initiating and titrating treatment of drug-naïve patients with T2 DM using combined tablets containing vildagliptin 50 mg and either metformin 500 mg or 1000 mg was shown to be superior to doing so with either vildagliptin or metformin used as monotherapy. This result is consistent with the premise that the efficacy of the two drugs is not impaired by administration as a combined formulation.

The other studies in the submission did not involve the combined tablets applied for, but supported evidence discussed in the earlier evaluation report, that vildagliptin administration improved glycaemic control in patients with T2DM.

Vildagliptin 50 mg once daily was superior to placebo as supplementary treatment of patients taking metformin 1500-3000 mg per day, over a 52-week period. The improvement from baseline in HbA1c was well maintained at endpoint with vildagliptin but there was continuing increase in HbA1c in the placebo group.

Two studies demonstrated that the addition of vildagliptin to continuing prior metformin treatment was superior over 52 weeks, to addition of placebo.

An open-label, uncontrolled trial of vildagliptin 100 mg once per day and metformin titrated to 1000 mg bd in drug-naïve patients with very poor glycaemic control found that >75% of patients achieved a reduction from baseline HbA1c≥ 1.5%.

The single study dealing with the combined tablet does not reveal any safety concerns peculiar to the combined formulation.

Recommendation

If vildagliptin is approved for the indication sought in the previously submitted application, there will be patients with T2DM for whom the addition of vildagliptin to metformin may be considered appropriate.[1] Using the combined tablets would be acceptable for some of these patients. In these circumstances, it was recommended that the three combined tablets of vildagliptin/metformin containing 50/500 mg, 50/850 mg and 50/1000 mg be approved for use to improve glycaemic control in conjunction with diet and exercise, of patients with type 2 diabetes mellitus who are already treated with metformin and vildagliptin or who are not adequately controlled on metformin alone.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM). The sponsor identified the following safety concerns with associated pharmacovigilance activities (Table 10):

Table 10: Pharmacovigilance activities and Risk Minimisation Plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Identified risks		
Transaminase elevations	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study	Vildagliptin/metformin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (ULN). (CDS Section 4.2 and Section 4.4 and local labels) Prescribing information includes precautions and liver enzyme monitoring. (CDS Section 4.4, Special warnings and precautions for use and local labels) The CDS "Undesirable effects" section describes the frequency and severity of hepatic dysfunction observed with vildagliptin. (CDS Section 4.8, Undesirable effects and local labels)
Angioedema	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study	Prescribing information includes angioedema as an adverse reaction. (CDS section 4.8, Undesirable effects and local labels)
Lactic acidosis	Cumulative analysis in PSUR Population-based post-marketing epidemiologic study	Prescribing information includes lactic acidosis in CDS.
Potential risks		
Skin lesions	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. Clinical mechanistic study LAF237A2113 European post-marketing long-term observational study	Skin lesions found in monkeys are described under CDS section 5.3. (CDS Section 5.3, Preclinical Safety data and local labels)
Drug-induced liver injury (DILI)	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study	Vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal (ULN). (CDS Section 4.2 and

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
		Section 4.4 and local labels) Prescribing information will includes precautions and liver enzyme monitoring. (CDS Section 4.4, Special warnings and precautions for use and local labels) The CDS "Undesirable effects" section and local labels describes the frequency and severity of hepatic dysfunction observed with vildagliptin. (CDS Section 4.8, Undesirable effects)
Infections	Routine pharmacovigilance activities European post-marketing long-term observational study	None
Cardiac conduction disturbances	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist.	None
Muscle events/ myopathy with and without concurrent statin use	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. Detailed analysis in PSUR	None
Hypoglycemia	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. All post-marketing reports and clinical trial SAE reports of hypoglycemia of greater severity (which are defined as: requiring third party assistance, hospitalization for hypoglycemia, or resulting in coma) will be considered as unlisted and will be expedited according to local regulations.	Listing as an adverse event in CDS and local labels (CDS section 4.8, Undesirable effects)
Gastrointestinal hemorrhage	Routine pharmacovigilance activities	None
Neuropsychiatric events	Routine pharmacovigilance activities	None
Acute pancreatitis	Routine pharmacovigilance activities	None
Breast cancer	Routine pharmacovigilance activities	None
Edema-related events	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist in studies LAF237A23137 and LAF237A23138.	None
Important missing information		
Gender incidence/ frequency differences	Routine pharmacovigilance activities Gender stratification of data in PSUR	None

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
Patients ≥75 years of age	Routine pharmacovigilance activities Specific age stratification of data in study reports and PSUR	The CDS and local labels will state that there is limited information on patients >75 years of age. (CDS Section 4.2 Posology and method of administration) The Pharmacokinetics of vildagliptin in healthy elderly subjects (≥70 years) in described in the CDS and local labels. (CDS Section 5.2 Pharmacokinetic properties)
Patients with moderate or severe renal impairment	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/checklist Post marketing clinical studies in renally impaired patients, LAF237A23137 and LAF237A23138	CDS section 4.2 states that vildagliptin and metformin is contraindicated in patients with creatinine clearance below 60 ml/min. In the elderly, the [CDS] advises regular checks of renal function and that vildagliptin and metformin has not been studied in patients over 75 years of age.
Patients with severe hepatic impairment	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/checklist	CDS states that vildagliptin and metformin should not be used in patients with hepatic impairment including those with increased baseline liver enzyme levels (alanine aminotransferase [ALT] or aspartate aminotransferase [AST[) > 2.5 times the upper limit of normal [ULN] (CDS section 4.2). Also it is contraindicated in patients with hepatic impairment [Annex 2],
Patients with compromised cardiac function	Routine pharmacovigilance activities Targeted follow-up using a questionnaire/ checklist. European post-marketing long-term observational study	SPC sates: Cardiac failure: Experience with vildagliptin therapy in patients with congestive heart failure of New York Heart Association (NYHA) functional class I-II is limited and therefore vildagliptin should be used cautiously in these patients. There is no experience of vildagliptin use in clinical trials in patients with NYHA functional class III-IV and therefore use is not recommended in these patients. (EU SmPC section 4.4). Metformin is contraindicated in patients with heart failure, therefore LMF is contraindicated in this patient population (Annex 2) CDS: Vildagliptin/metformin is contraindicated in patients with congestive heart failure requiring pharmacologic treatment (see section

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimization activities
		4.4 Special warnings and precautions for use).
Pregnancy	Routine pharmacovigilance activities	The CDS and local labels state that vildagliptin should not be used during pregnancy unless the benefit to the mother outweighs the potential risk to the fetus. (CDS Section 4.6 Pregnancy and lactation)

In regard to identified safety concerns, the sponsor proposed routine pharmacovigilance activities consistent with the activities outlined in the TGA-adopted EU guidance document on planning pharmacovigilance activities as well as the additional pharmacovigilance activities outlined in Table 10.[6,7]

Routine risk minimisation activities will include warnings or notification of undesirable effects in the Australian product information (PI) for the identified safety concerns: transaminase elevations, angioedema, lactic acidosis, skin lesions, drug-induced liver injury (DILI), hypoglycaemia, oedema-related events, patients ≥ 75 years of age, patients with moderate or severe renal impairment, patients with severe hepatic impairment, patients with compromised cardiac function and pregnancy. [8] No additional risk minimisation activities have been planned.

Overall, the OMSM reviewer considered that the submitted RMP was acceptable. Nevertheless the sponsor should consider making some provision to pro-actively gain information on the safety profile of vildagliptin/metformin in each of the following patient groups:

- Paediatric patients
- Pregnant and lactating women

This may take the form of a patient register, the details of which should be submitted to the TGA for assessment.

In addition little detail has been provided regarding the questionnaires/checklists to be employed as part of additional pharmacovigilance activities, therefore the sponsor should provide copies of the questionnaire/checklist for each specified safety concern to the TGA.

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[6] EMEA. ICH Topic E2E, Pharmacovigilance planning, June 2005. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03).

[7] Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

[8] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Furthermore no assessment of the protocols for the European post-marketing long-term observational study to assess various safety outcomes in association with vildagliptin (Galvus) and the fixed dose combination of vildagliptin with metformin (Eucreas) or for the proposed population-based post-marketing epidemiologic study could be made until the sponsor provides these documents as requested. In regard to the latter study the planned reporting dates are highly questionable and should be revised accordingly.

The OMSM reviewer also made comment with respect to the draft Australian PI but a consideration of these matters is beyond the scope of this AusPAR.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

Registration was recommended with respect to chemistry, quality control and biopharmaceutics.

Nonclinical

The nonclinical evaluator noted that no new, specific fixed combination studies to model efficacy were submitted. A limited number of studies involving vildagliptin or metformin alone or the combination with metformin were submitted: pharmacokinetic studies examining interactions between vildagliptin and metformin (in rats and dogs), repeat-dose toxicity studies with the combination (in rats and dogs) and embryofetal toxicity studies with the combination (in rats and rabbits).

The Delegate noted that the evaluator observed that, "Metformin itself was shown to be able to inhibit DPP-IV, but this was very weak and not clinically relevant (that is, only 20% inhibition was observed at 1000 µM, a concentration >50-times greater than the clinical C_{max} for the drug at the maximum recommended human dose)." Nonetheless, a previous submission suggested that metformin is not negative control in humans.

Clinical

The attention of the clinical evaluator focused upon the newly submitted data.

Pharmacokinetic/bioavailability Data

Five biopharmaceutical studies of similar, acceptable design were submitted. One (Study LMF237A2304) was to choose which of two formulations to develop, three (Studies LMF237A2303, LMF237A2307 and LMF237A2301) were to evaluate bioequivalence of the component drugs given separately in the corresponding strength of metformin or as each of the three combined-dose tablets (vildagliptin/metformin 50/500, 50/850 or 50/1000 mg), and one (Study LMF237A2101) examined the effect of food on bioavailability of the components of a vildagliptin/metformin 50/1000 mg tablet.

Study LMF 2303 was of the same design as Study LAF 2301 but it employed a dose of 50/500 mg vildagliptin/metformin. Bioequivalence was shown for both active components.

Study LMF 2307 was similar to the above but employed a dose of 50/850 mg vildagliptin/metformin. Bioequivalence was shown for both active components.

Study LMF2101 is the food study that was mentioned above (Table 5). The evaluator noted a later and longer time to maximal serum concentrations of metformin in the presence of food.

There was, in addition, a randomised crossover comparison of the multiple dose pharmacokinetics of vildagliptin (100 mg) and of metformin (1000 mg), each given either

alone or as a combined tablet (not currently applied for in this dose combination), in patients with Type 2 diabetes mellitus who required metformin. The proposed "for marketing" formulation of the combined tablet was not used. The evaluator concluded that the absorption of vildagliptin was slowed and C_{max} decreased, but the mean AUC was not significantly reduced in repeat dosing with metformin. The extent of absorption of metformin was slightly increased.

Phase 3 Studies

Study CLMF237A2302 was a large study (n=1,179 patients of whom 995 completed the study) that compared four methods of commencing and escalating the intensity of 24 weeks treatment with metformin and/or vildagliptin, of drug-naïve patients with diabetes mellitus type 2 and HbA1c of 7.5-11%.

The results of the study support a dose response for metformin in the fixed combination arms (Table 6).

The evaluator remarked: "In the ITT population, HbA1c declined from baseline with all four treatments (-1.61%, -1.82%, -1.09% and -1.36% for low dose combination, high dose combination, vildagliptin and metformin respectively)." "This result is consistent with the premise that the efficacy of the two drugs is not impaired by administration as a combined formulation."

Study 2204 assessed the effect on HbA1c of adding vildagliptin 50 mg once daily for 12 weeks, after a 4-week placebo run-in, to metformin, in patients with T2DM. Patients continued unchanged on a previously stable metformin dose of 1500 – 3000 mg daily for at least 3 months and, after randomisation, received either placebo or vildagliptin 50 mg once daily or vildagliptin 100 mg once daily. The 100 mg daily arm was "prematurely terminated". It was a randomised, double blind, multicentric, European study with three parallel groups (n = 51 on placebo, 56 on vildagliptin 50 mg, 25 on vildagliptin 100 mg). There was statistical superiority of vildagliptin 50 mg over placebo (mean difference of -0.65%). No margin of clinically significant superiority was evidently set. No rescue medication was provided. There was a blinded 40 week extension study that continued 29 patients on placebo and 42 patients on vildagliptin 50mg die.

Efficacy was maintained in the vildagliptin group and deterioration occurred with placebo as shown in Table 11.

Table 11: Study 2204EO1 – ANOVA results for change in HbA1c from baseline to endpoint

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to placebo (SE)	95% CI	p-value
Met+LAF 50mg	42	7.62 (0.09)	-0.50 (0.14)	-1.10 (0.22)	(-1.53, -0.67)	<0.0001*
Met+Placebo	29	7.78 (0.11)	0.60 (0.17)			

* Indicates statistical significance at the 5% level.
SE = standard error; CI= confidence interval
n is the number of patients with observations at both baseline and endpoint.

Study 2303 was a US and European study that assessed the effect on HbA1c of adding placebo, vildagliptin 50 mg once daily or twice daily for 24 weeks, to metformin, in patients with T2DM. Patients continued unchanged on a previously stable metformin dose of at least 1500 mg daily for at least 3 months and, after randomisation, received metformin 2000 mg

daily unless a lower dose was required due to intolerance. One thousand patients were screened and 544 randomised to compensate for an analytical laboratory problem that affected other US studies. It was a randomised, double blind, multicentric study with three parallel groups (n = 182 on placebo, 177 on vildagliptin 50 mg, 185 on vildagliptin 50 mg bd). There was statistical superiority of vildagliptin 50 mg qd over placebo (mean difference of -0.73%) and of vildagliptin 50 mg bd over placebo (mean difference of -1.10%). No margin of clinically significant superiority was evidently set. No rescue medication was provided. The placebo group deteriorated during the study (Table 12).

Table 12: Study 2303 - ANCOVA results for change in HbA1c (%) from baseline to endpoint

Treatment	n	Baseline mean (SE)	Adjusted mean change (SE)	Mean difference to Placebo+Met (SE)	95% CI	p-value
Primary ITT population						
Vilda 50 mg qd + Met	143	8.38 (0.08)	-0.51 (0.10)	-0.73 (0.14)	(-1.00, -0.47)	< 0.001*
Vilda 50 mg bid + Met	143	8.38 (0.09)	-0.88 (0.10)	-1.10 (0.14)	(-1.37, -0.84)	< 0.001*
Placebo + Met	130	8.30 (0.08)	0.23 (0.10)			
Per Protocol population						
Vilda 50 mg qd + Met	126	8.36 (0.08)	-0.57 (0.11)	-0.74 (0.15)	(-1.03, -0.45)	< 0.001*
Vilda 50 mg bid + Met	125	8.37 (0.09)	-0.93 (0.11)	-1.10 (0.15)	(-1.39, -0.81)	< 0.001*
Placebo + Met	114	8.30 (0.08)	0.17 (0.11)			
Sensitivity ITT population^						
Vilda 50 mg qd + Met	174			-0.65 (0.12)	(-0.88, -0.42)	< 0.001*
Vilda 50 mg				0.12)	(-1.24, -0.78)	< 0.001*
Placebo + Met	171					

Source: PTT 9.1-1a, PTT 9.1-2a and PTT 9.1-3a

Baseline is measurement from an NGSP Level 1 certified laboratory on sample obtained on day of randomization, or an earlier visit (scheduled or unscheduled) which was closest to Visit 2, if Day 1 measurement is missing.

Endpoint is final available post-randomization assessment up to last regular scheduled visit.

n is number of patients with observations at both baseline and endpoint.

Adjusted means, SE, CIs and p values from ANCOVA model containing terms for treatment, baseline and pooled centers.

* Indicates statistical significance at 5% level according to the Hochberg step-up procedure.

^ Sensitivity ITT population includes patients with no valid baseline HbA_{1c} values as well as patients incorrectly randomized due to BARC-US assay issues. The analysis as described in Section 6 is a weighted average of the treatment differences at the study endpoint in patients with and without baseline and, therefore, no overall estimates of baseline or the change from baseline is available.

Study LAF237A2303E1 was a 28 week extension to study 2303, the multicentre, double-blind, randomized parallel group study that compared the effect of 24 weeks of treatment with vildagliptin 50 mg qd or bd to placebo as add-on therapy in patients with T2DM inadequately controlled with metformin monotherapy. It sought to address the long-term safety of vildagliptin in combination with metformin during 52 weeks of treatment and also assess the long-term efficacy of vildagliptin plus metformin. In the extension study, 141 patients were randomized to vildagliptin 50 mg qd and 143 to vildagliptin 50 mg bd, while 133 who had been on placebo were switched to vildagliptin 50 mg qd.

This efficacy from Weeks 24-52 may be appreciated in Table 13 and figure below, which the Delegate interpreted to show loss of effect from Weeks 24 to endpoint in patients pre-treated with vildagliptin (the sign is positive, not negative).

Table 13: Study 2303E1 – Change in HbA1c (%) from Week 24 to extension study endpoint

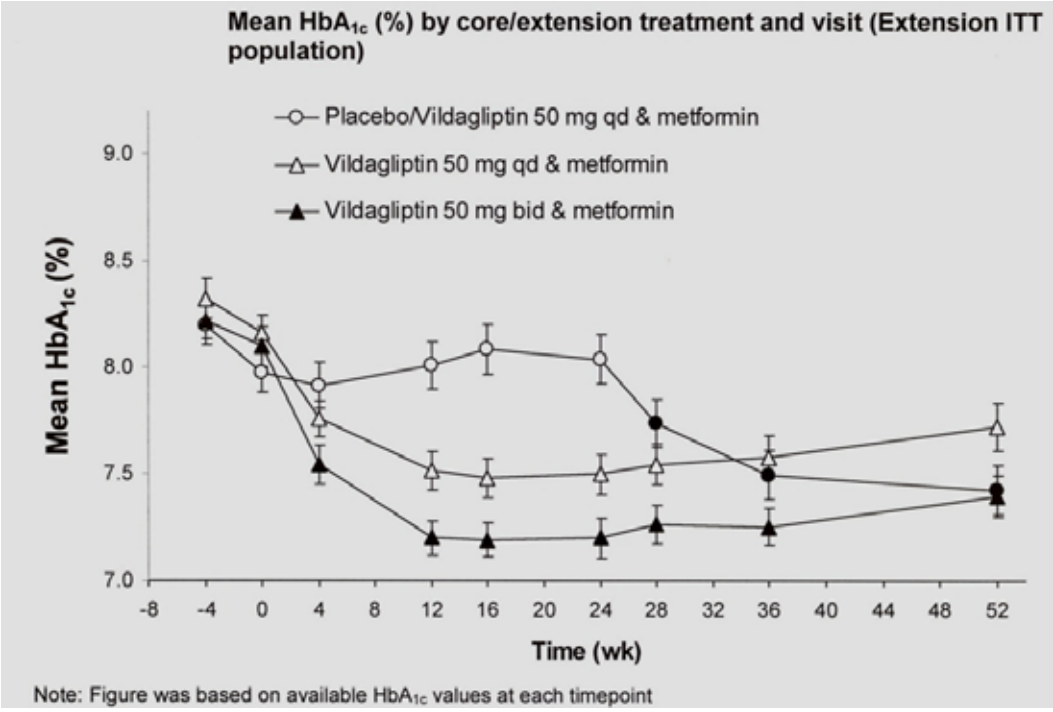
Treatment	n	Week 24 mean (SE)	Unadjusted mean change from Week 24 (SE)	95% CI for change from Week 24#	P-value for change from Week 24#
Extension ITT population					
Vilda 50 mg qd + Met (core + extension)	137	7.49 (0.09)	0.35 (0.07)	(0.22, 0.49)	<0.001*
Vilda 50 mg bid + Met (core + extension)	139	7.21 (0.09)	0.35 (0.06)	(0.23, 0.48)	<0.001*
Placebo + Met/Vilda 50 mg qd + Met)	131	8.01 (0.12)	-0.35 (0.07)	(-0.49, -0.20)	<0.001*
Extension PP population					
Vilda 50 mg qd + Met (core + extension)	110	7.43 (0.09)	0.37 (0.08)	(0.21, 0.53)	<0.001*
Vilda 50 mg bid + Met (core + extension)	111	7.22 (0.08)	0.32 (0.07)	(0.17, 0.46)	<0.001*
Placebo + Met/Vilda 50 mg qd + Met)	96	7.79 (0.10)	-0.36 (0.09)	(-0.53,-0.19)	<0.001*

Endpoint is the final available post-Week 24 assessment up to the last regular scheduled visit.

n is the number of patients with observations at both Week 24 and endpoint.

95% CI and p-value based on one-sample t-distribution.

* indicates statistical significance at 5% level.



Note: Figure was based on available HbA_{1c} values at each timepoint

Safety

In regard to safety, the evaluator remarked that, in the new study: "The overall incidence of adverse events in the four groups was 55.9 %, 57.5 %, 51.5% and 59.9% for low dose combined, high dose combined, vildagliptin and metformin monotherapy groups respectively. There were more gastrointestinal AEs with treatments containing metformin but no other consistent difference across groups…" The mean duration of exposure was approximately 22 weeks for all 4 groups. No particular safety concerns were identified.

Recommendations of Clinical Evaluator:

The evaluator appeared to be dissatisfied with the lack of a defined population that would use fixed combination tablets and recommended that, "the three combined tablets of vildagliptin/metformin containing 50/500 mg, 50/850 mg and 50/1000 mg be approved for use to improve glycaemic control in conjunction with diet and exercise, of patients with type 2 diabetes mellitus who are already treated with metformin and vildagliptin or who are not adequately controlled on metformin alone".

Risk Management Plan

The European RMP was acceptable but several matters required attention (for example, updates to the PI, protocols for some proposed studies, further information on use in paediatric and pregnant/lactating women).

Risk-Benefit Analysis

Delegate Considerations

The Delegate noted that fixed combination products can offer certain potential advantages:

- there might be comparable or better efficacy (with the fixed combination products) than when one component is given at a higher dose but with a better safety profile;
- that the efficacy is above the one achievable by a single substance but with an acceptable safety profile;
- there might be better "patient compliance"; or,
- there might be a defined population that requires this fixed combination, for example poorly controlled type II diabetics who are likely need the maximal dose of metformin.

None of these advantages has yet been demonstrated.

Fixed combination products can offer certain potential disadvantages:

- There is the potential for confusion between strengths. The PI and Consumer Medicine Information (CMI) should make it clear that a single strength should be prescribed and be in the possession of the patient at any one time. Patients need to understand that it is the dose of metformin that is being titrated and that must be considered.
- There is the potential for confusion about the separate actives. Tablets containing the separate active ingredients should be discarded (for example, handed back to the dispensing pharmacist) to avoid accidentally exceeding the daily limit of metformin (2000 mg per day).
- This particular combination has low but not zero risks of hypoglycaemia when patients are transferred from metformin monotherapy with no particular advice to start at a lower total daily dose of metformin.

These disadvantages (risks) will have to be managed. The Delegate requested the advice of the Advisory Committee on Prescription Medicines (ACPM) on these particular risks.

There were no pharmaceutical chemistry or nonclinical reasons to withhold approval. The bioavailability issues seem to be adequately addressed by the studies submitted, by the pharmaceutical chemistry aspects of the justification for not conducting a study against Australian-sourced metformin and by Study CLMF237A2302. The proposed indication was acceptable in the light of the previously submitted studies.

The Delegate proposed that the submission should be approved for the indication:

as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus 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.

Sponsor Response

In its pre-ACPM response, the sponsor discussed the advantages and disadvantages of fixed dose combinations as discussed by the Delegate.

Potential advantages of the fixed dose combination

The combined use of metformin and vildagliptin results in an improved glucose-lowering effect by combining different mechanisms of action. A likely clinical benefit of Galvumet is also the expected improvement of compliance and simplification of therapy. The combination of two classes of anti-hyperglycaemic agents in one single tablet can improve compliance with treatment, and thus eventually glycaemic control.

Improving compliance

Poor compliance with medication has been extensively reported in a chronic disease like diabetes mellitus type 2 (Kardas 2005).[9] With the increased need for combined oral therapy, compliance becomes an issue, as both the frequency of dosing and the number of tablets affects the adherence to therapy (Paes, Bakker and Soe-Agnie 1997).[10] Compliance was shown to fall in patients taking a combination of metformin and sulfonylurea to less than half of that in patients using monotherapy (Dailey 2003).[11]

A long prospective study in 11,896 type 2 diabetic patients treated by their general practitioner with one or two oral antidiabetic agents, that evaluated compliance based on self reported standard questionnaire, has suggested the relevance of reducing the daily dosing frequency of oral antidiabetic agents in order to improve compliance and metabolic control (Guillausseau 2003).[12] HbA1c levels were associated with compliance with treatment, with a 1.4% mean difference between group with optimal and group with worst compliance. Other determinants of compliance assessed in this study included age, diabetes duration, educational level and severity of complications. The results showed that optimal compliance (no omission) was reported in only 46% of cases. It was also demonstrated that HbA1c levels were positively correlated with daily dosing frequency of oral antidiabetic agents, age and low educational level. Interestingly no correlation was found with diabetes duration.

It was also generally admitted by practitioners that issues such as the cost of treatment associated with polypharmacy has a negative impact on compliance (Neutel 2003).[13] It was believed that fixed combinations can help increase adherence to treatment by limiting the expenses accrued by patients to a single a co-payment per prescription.

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[9] Kardas P. The DIACOM study (effect of DosIng frequency of oral Antidiabetic agents on the COMpliance and biochemical control of type 2 diabetes). Diabetes Obesity Metab 2005; 7: 722-728.

[10] Paes AH, Bakker A, Soe-Agnie CJ. Impact of dosage frequency on patient compliance. Diabetes Care 1997; 20: 1512-1517.

[11] Dailey GE. Glyburide/metformin tablets: a new therapeutic option for the management of Type 2 diabetes. Exp Opinion Pharmacother 2003; 4: 1417-1430.

[12] Guillausseau PJ. Influence of oral antidiabetic drugs compliance on metabolic control in type 2 diabetes. A survey in general practice. Diabetes Metab 2003; 29: 79-81.

[13] Neutel JM, Smith DHG. Improving patient compliance: a major goal in the management of hypertension. J Clin Hypertension 2003; 5: 127-132.

Thus fixed combinations such as Galvumet can play an important role in ensuring patients' compliance with their oral antidiabetic treatment and therefore improve metabolic control. It was believed that an improved tolerability has also a positive effect on compliance.

Improving safety and efficacy

Metformin is an established first line treatment for diabetes mellitus type 2, acting primarily to enhance hepatic and peripheral insulin sensitivity. However despite its excellent efficacy, low frequency of hypoglycaemia and the lack of weight gain, gastrointestinal intolerance in the form of nausea, diarrhoea and abdominal pain prevents its use in about 10% of patients (Krentz et al., 2005).[14] Additionally, the rare but serious risk of lactic acidosis which results from the accumulation of metformin is more likely to occur in patients treated with high doses of metformin. These risks mandate slow upward titration when starting therapy, and often prevent the use of higher, more efficacious doses of metformin.

Given the multiple pathophysiological lesions in T2DM, combination therapy is a logical approach to its management. By combining agents with different mechanisms of action (such as metformin and vildagliptin), the aim is not only to enhance efficacy and augment the therapeutic response, but also to achieve equal or better blood glucose control at a lower total daily dose of metformin.

This observation could form the basis of an argument supporting initiating newly diagnosed T2DM patients on a low fixed combination and titrating up to the highest tolerated dose of Galvumet rather than titrating up metformin monotherapy to the highest tolerated dose first. Furthermore, initial combination therapy with vildagliptin and metformin as fixed dose combination was shown to be significantly more efficacious than each individual monotherapy without losing the favourable characteristics of the monotherapies regarding weight and hypoglycaemia. Although these data are not being considered for a first line indication, they provide important supportive evidence of the positive benefit/risk of Galvumet.

It should be noted that evidence shows that the lowest dose of Galvumet demonstrated superior efficacy compared to the highest approved dose of metformin in a 24-week multicenter, randomised, double-blind, active controlled initial combination therapy study with the fixed dose combination of vildagliptin plus metformin in drug naïve patients with diabetes mellitus type 2 with HbA1c levels comprised between 7.5 and 11.0% (Study 2302).

Managing the potential risks of the fixed dose combination

The Delegate has identified certain theoretical disadvantages (risks) of fixed combination products and has sought the Committee's advice and views on effective ways to manage these particular risks. It was also noted that the Delegate favours the inclusion of precautionary statements in the Product Information (PI) and the Consumer Medicine Information (CMI) as a means to minimise these potential risks emerging from the patient's confusion within the Galvumet product range or between Galvumet and the monotherapy tablets.

Mitigating the risk of confusion between strengths

The Delegate noted: "There is the potential for confusion between the strengths. The PI and the CMI should make it clear that a single strength should be prescribed and be in the possession of the patient at any one time. Patients need to understand that it is the dose of metformin that is being titrated and that must be considered."

[14] Krentz AJ, Bailey CJ. Oral antidiabetic agents: current role in type 2 diabetes mellitus. Drugs 2005; 65: 385-411.

The sponsor indicated that it has taken significant steps to mitigate the risk of confusion between the strengths by ensuring that they can be distinguished unambiguously from each other and comply with the practices described in the TGA's "Best practice guideline on prescription medicine labelling" and mandatory requirements of Therapeutic Goods Orders for the labelling of medicines.

Specifically, each strength will supplied in a distinct colour coded carton to differentiate the strengths from one another (respectively yellow, orange and red for Galvumet 50/500, Galvumet 50/850 and Galvumet 50/1000). The strengths of both active ingredients will also appear alongside the brand name and throughout the labelling as well as in the PI and CMI.

In addition, the Dosage and Administration of the proposed PI contain explicit instructions on the recommended dose of Galvumet based on the patient's current dose of metformin which make it amply clear that it is the dose of metformin that is being titrated.

The sponsor reviewed the CMI of the currently approved fixed combinations containing metformin. To the best of its knowledge, no other fixed combination containing metformin includes statements addressing the theoretical risk of confusion about separate active ingredients. The sponsor recognised the importance of patient education to avoid accidentally exceeding the daily limit of metformin (2000 mg per day) and the key role healthcare professionals can play in patient education in Australia. A statement advising patients to discard any other medicine containing metformin that their doctor might have prescribed to them in the past and that they may still have in their possession is therefore proposed for inclusion in the Galvumet CMI. It was noteworthy that this statement also covers the risk for confusion within the Galvumet product range.

Additional information on the rare but serious risk of lactic acidosis has also been included in the Galvumet CMI. The wording proposed is not dissimilar to the wording found in the Janumet (sitagliptin/metformin) CMI. The effectiveness of these proposed CMI statements will be tested independently with consumers directly as part of the sponsor's routine pre-launch activities.

Mitigating the risk of hypoglycaemia

The Delegate noted: "This particular combination has low but not zero risk of hypoglycaemia when patients are transferred from metformin monotherapy with no particular advice to start at a lower total daily dose of metformin."

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). It is noteworthy that no severe hypoglycaemic events were reported in the vildagliptin arms.

In current clinical practice, most patients would already be on a free combination of metformin and Galvus before switch to a fixed combination at the same dose level. For the others, it is likely that the dose of metformin would be titrated up to the maximum tolerated dose before a second agent is added. It should be noted that in most cases the addition of a second agent is unlikely to be accompanied by a reduction of the total daily dose of metformin. Study 2303 was designed to mimic the latter scenario. Patients were randomised once they reached the maximum tolerated dose of metformin (that is, 92% of patients in each treatment arm received at least 2000 mg of metformin daily). Vildagliptin 50 mg qd or vildagliptin 50 mg bd or placebo were then added to their metformin treatment at randomisation. Results showed no statistical difference in the number of hypoglycaemic events between the treatment groups.

The risk of hypoglycaemia when patients are transferred from metformin monotherapy to Galvumet should not be dissimilar to the risk of adding vildagliptin to metformin. It should therefore not be assumed that adding vildagliptin to the maximum tolerated dose of metformin increases the probability of hypoglycaemic events.

Concluding remarks

The sponsor welcomed the Delegate's proposal to approve the use of vildagliptin/metformin fixed combination as an adjunct to diet and exercise to improve glycaemic control in patients with diabetes mellitus type 2 whose diabetes is not adequately controlled on metformin alone or who are already treated with the combination of vildagliptin and metformin, as separate tablets.

It has been demonstrated that the advantages of fixed dose combinations in the treatment of diabetes mellitus type 2 can extend beyond improving compliance. Additionally, no new safety concerns have been identified as a result of the review of this application. The safety and efficacy profile of Galvumet is by no means less than the combined safety and efficacy profiles of Galvus (vildagliptin) and metformin taken concomitantly at the same dose level.

Moreover, the apparent disadvantages of the Galvumet combinations are not in any way different to those of other metformin fixed combinations already registered and marketed in Australia. It was therefore the sponsor's view that there should be no objection to the approval of Galvumet (vildagliptin/metformin) fixed combination tablets in Australia.

Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

As an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus 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.

In making this recommendation, the ACPM agreed with the evaluation by the Delegate that the submission provided sufficient information to support a positive risk benefit profile for this fixed dose combination. The ACPM further agreed with the Delegate's proposed changes to the Product Information (PI) and Consumer Medicines Information (CMI).

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Galvumet 50/500/Sobrea 50/500 (containing 50 mg vildagliptin/500 mg metformin hydrochloride), Galvumet 50/850/ Sobrea 50/850 (containing 50 mg vildagliptin/850 mg metformin hydrochloride) and Galvumet 50/1000/ Sobrea 50/1000 (containing 50 mg vildagliptin/1000 mg metformin hydrochloride), indicated for:

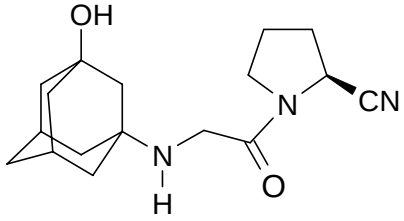
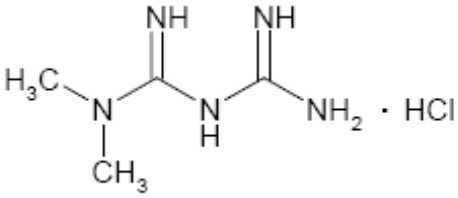
[TRADENAME] is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes whose diabetes is not adequately controlled on metformin hydrochloride alone or who are already treated with the combination of vildagliptin and metformin hydrochloride, as separate tablets. Treatment of type 2 diabetes should not be initiated with this fixed-dose combination.

Among the conditions of registration was that all negotiated Risk Management Plan (RMP) procedures are to be complied with to the satisfaction of TGA.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

GALVUMET®
(*vildagliptin/metformin hydrochloride*)

Active ingredients:	**Vildagliptin**	**Metformin hydrochloride**
Chemical names:	(S)-1-[2-(3-Hydroxy-adamantan-1-ylamino)acetyl]-pyrrolidine-2(S)-carbonitrile	Imidodicarbinimidic, N,N-dimethyl-, monohydrochloride
Molecular formula:	$C_{17}H_{25}N_3O_2$	$C_4H_{11}N_5.HCl$
Molecular weight:	303.40	165.6
Structural formula:		
CAS number:	274901-16-5	1115-70-4

DESCRIPTION

Vildagliptin is a white to slightly yellowish or slightly greyish crystalline powder with a melting point/range of approximately 150°C. It is freely soluble in water.

Metformin is a white crystalline powder which is almost odourless and hygroscopic. It is freely soluble in water, slightly soluble in ethanol (96%), and practically insoluble in chloroform and in ether.

GALVUMET tablets are available in 3 strengths:

50 mg vildagliptin and 500 mg metformin hydrochloride

50 mg vildagliptin and 850 mg metformin hydrochloride

50 mg vildagliptin and 1,000 mg metformin hydrochloride

Each tablet contains the following excipients - iron oxide red CI77491, iron oxide yellow CI77492, hypromellose, hydroxypropylcellulose, magnesium stearate, polyethylene glycol, and talc.

PHARMACOLOGY

Pharmacodynamics

GALVUMET combines two antihyperglycemic agents with different mechanisms of action to improve glycaemic control in patients with type 2 diabetes (T2D): vildagliptin, a member of the DPP-4 (dipeptidyl-peptidase-4) inhibitor class and metformin hydrochloride, a member of the biguanide class.

Vildagliptin

Vildagliptin, a member of the islet enhancer class, is a high affinity dipeptidyl-peptidase-4 (DPP-4) inhibitor that improves glycaemic control.

The administration of vildagliptin results in rapid and near-complete inhibition of DPP-4 activity. In patients with type 2 diabetes, administration of vildagliptin led to inhibition of DPP-4 enzyme activity for a 24-hour period. Vildagliptin inhibition of DPP-4 results in increased fasting and postprandial endogenous levels of the incretin hormones GLP-1 (glucagon-like peptide 1) and GIP (glucose-dependent insulinotropic polypeptide).

By increasing the endogenous levels of these incretin hormones, vildagliptin enhances the sensitivity of beta cells to glucose, resulting in improved glucose-dependent insulin secretion. Treatment with 50 to 100 mg daily in patients with T2D significantly improved markers of beta cell function. The degree of improvement in beta-cell function is dependent on the initial degree of impairment; in non-diabetic (normal glycaemic) individuals, vildagliptin does not stimulate insulin secretion or reduce glucose levels.

By increasing endogenous GLP-1 levels, vildagliptin enhances the sensitivity of alpha cells to glucose, resulting in more glucose-appropriate glucagon secretion. The reduction in inappropriate glucagon during meals in turn attenuates insulin resistance.

The enhanced increase in the insulin/glucagon ratio during hyperglycaemia (due to increased incretin hormone levels) results in a decrease in fasting and postprandial hepatic glucose production, leading to reduced glycaemia.

The known effect of increased GLP-1 levels to delay gastric emptying is not observed with vildagliptin treatment. In addition, a reduction in postprandial lipaemia that is not associated with vildagliptin's incretin mediated effect to improve islet function has been observed.

Metformin Hydrochloride

Metformin hydrochloride improves glucose tolerance in patients with T2D, lowering both basal and postprandial plasma glucose. Metformin hydrochloride decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin hydrochloride does not produce hypoglycaemia in either patients with T2D or normal subjects (except in special circumstances), and does not cause hyperinsulinaemia. With metformin

hydrochloride therapy, insulin secretion remains unchanged while fasting insulin levels and day-long plasma insulin response may actually decrease.

Metformin hydrochloride stimulates intracellular glycogen synthesis by acting on glycogen synthase and increases the transport capacity of specific types of membrane glucose transporters (GLUT-1 and GLUT-4).

In humans, independently of its action on glycaemia, metformin hydrochloride has favourable effects on lipid metabolism. This has been shown at therapeutic doses in controlled, medium-term or long-term clinical studies: metformin hydrochloride reduces total cholesterol, LDLc and triglyceride levels.

Pharmacokinetics

Linearity

Vildagliptin
Vildagliptin is rapidly absorbed with an absolute oral bioavailability of 85%. Peak plasma concentrations for vildagliptin and the area under the plasma concentration versus time curve increased in an approximately dose-proportional manner over the therapeutic dose range.

Metformin Hydrochloride
Studies using single oral doses of metformin tablets indicate a lack of dose proportionality, due to increased absorption of metformin with increasing doses.

Absorption

In the bioequivalence studies of GALVUMET at three dose strengths (50 mg/500 mg, 50 mg/850 mg and 50 mg/1,000 mg), versus free combination of vildagliptin and metformin hydrochloride tablets at the corresponding doses, the area under the curve (AUC) and maximum concentration (C_{max}) of both the vildagliptin component and the metformin hydrochloride component of the GALVUMET tablets were demonstrated to be bioequivalent to that of free combination tablets.

Food does not affect the extent and rate of absorption of vildagliptin from GALVUMET. The C_{max} and AUC of the metformin hydrochloride component from GALVUMET were decreased by 26% and 7% respectively when given with food. The absorption of metformin hydrochloride was also delayed as reflected by the T_{max} (2.0 to 4.0 hrs) when given with food. These changes in C_{max} and AUC are consistent but lower than those observed when metformin hydrochloride when given alone under fed conditions. The effects of food on the pharmacokinetics of both the vildagliptin component and metformin hydrochloride component of GALVUMET were similar to the pharmacokinetics of vildagliptin and metformin hydrochloride when given alone with food.

Vildagliptin

Following oral administration in the fasting state, vildagliptin is rapidly absorbed with peak plasma concentrations observed at 1.75 hours. Co-administration with food slightly decreases the rate of absorption of vildagliptin, as characterized by a 19% decrease in peak concentrations, and a delay in the time to peak plasma concentration to 2.5 hours. There is no change in the extent of absorption, and food does not alter the overall exposure (AUC).

Metformin Hydrochloride

The absolute bioavailability of a 500 mg metformin hydrochloride tablet given under fasting conditions is approximate 50 to 60%. Studies using single oral doses of metformin hydrochloride tablets 500 mg to 1,500 mg, and 850 mg to 2,550 mg, indicate that there is a lack of dose proportionality with increasing doses, which is due to decreased absorption rather than an alteration in elimination. Food decreases the extent of and slightly delays the absorption of metformin hydrochloride, as shown by approximately a 40% lower mean peak plasma concentration (C_{max}), a 25% lower area under the plasma concentration versus time curve, and a 35 minute prolongation of time to peak plasma concentration (T_{max}) following administration of a single 850 mg tablet of metformin hydrochloride with food, compared to the same tablet strength administered fasting. The clinical relevance of these decreases is unknown.

Distribution

Vildagliptin

The plasma protein binding of vildagliptin is low (9.3%), and vildagliptin distributes equally between plasma and red blood cells. The mean volume of distribution of vildagliptin at steady state after intravenous administration (V_{ss}) is 71 L, suggesting extravascular distribution.

Metformin Hydrochloride

The apparent volume of distribution (V/F) of metformin hydrochloride following single oral doses of 850 mg averaged 654 ± 358 L. Metformin hydrochloride is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin hydrochloride partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of metformin hydrochloride, steady state plasma concentrations of metformin hydrochloride are reached within 24 to 48 hours and are generally < 1 microgram/mL. During controlled clinical trials of metformin hydrochloride, maximum metformin hydrochloride plasma levels did not exceed 5 micrograms/mL, even at maximum doses.

Metabolism

Vildagliptin

Metabolism is the major elimination pathway for vildagliptin in humans, accounting for 69% of the dose. The major metabolite, LAY151, is pharmacologically inactive and is the hydrolysis product of the cyano moiety, accounting for 57% of the dose, followed by the amide hydrolysis product (4% of the dose). DPP-4 contributes partially to the hydrolysis of vildagliptin as shown in an in-vivo study using DPP-4 deficient rats. Vildagliptin is not metabolized by cytochrome P450 enzymes to any quantifiable extent. In-vitro studies demonstrated that vildagliptin does not inhibit or induce cytochrome P450 enzymes.

Metformin Hydrochloride

Metformin is excreted unchanged in the urine and does not undergo hepatic metabolism. In patients with significantly decreased renal function, the plasma half-life of metformin is prolonged and renal clearance is decreased.

Elimination

Vildagliptin

Following oral administration of [^{14}C]-vildagliptin, approximately 85% of the dose is excreted into the urine and 15% of the dose is recovered in the faeces. Renal excretion of the unchanged vildagliptin accounts for 23% of the dose after oral administration. After an intravenous administration to healthy subjects, the total plasma and renal clearances of vildagliptin are 41 L/hour and 13 L/hour, respectively. The mean elimination half-life after intravenous administration is approximately 2 hours. The elimination half-life after oral administration is approximately 3 hours and is independent of dose.

Metformin Hydrochloride

Intravenous single-dose studies in normal subjects demonstrate that metformin hydrochloride is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) or biliary excretion. Renal clearance is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Elderly

Vildagliptin
In otherwise healthy elderly subjects (≥ 70 years), the overall exposure to vildagliptin (100 mg once daily) was increased by 32% with an 18% increase in peak plasma concentration compared to younger healthy subjects (18 to 40 years). These changes are not considered to be clinically relevant. DPP-4 inhibition by vildagliptin is not affected by age in the age groups studied.

Metformin Hydrochloride
Limited data from controlled pharmacokinetic studies of metformin hydrochloride in healthy elderly subjects suggest that total plasma clearance of metformin hydrochloride is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin hydrochloride pharmacokinetics with aging is primarily accounted for by a change in renal function.

GALVUMET treatment should not be initiated in patients ≥ 80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced.

Paediatric
No pharmacokinetic data are available in children.

Gender

Vildagliptin
No differences in the pharmacokinetics of vildagliptin were observed between male and female subjects with a diverse range of age and body mass index (BMI). DPP-4 inhibition by vildagliptin was unaffected by gender.

Metformin Hydrochloride
Metformin hydrochloride pharmacokinetic parameters did not differ significantly between normal subjects and patients with T2D when analysed according to gender (males=19, females-16). Similarly, in controlled clinical studies in patients with T2D, the antihyperglycaemic effect of metformin hydrochloride was comparable in males and females.

Obesity

Vildagliptin
BMI does not show any impact on the pharmacokinetic parameters of vildagliptin. DPP-4 inhibition by vildagliptin was unaffected by BMI.

Hepatic Impairment

Vildagliptin
The effect of impaired hepatic function on the pharmacokinetics of vildagliptin was studied in subjects with mild, moderate, and severe hepatic impairment based on the Child-Pugh scores (ranging from 6 for mild to 12 for severe) in comparison to subjects with normal hepatic

function. The exposure to vildagliptin (100 mg) after a single dose in subjects with mild and moderate hepatic impairment was decreased (20% and 8%, respectively), while the exposure to vildagliptin for subjects with severe impairment was increased by 22%. The maximum change (increase or decrease) in the exposure to vildagliptin is ~30%, which is not considered to be clinically relevant. There was no correlation between the severity of hepatic function impairment and changes in exposure to vildagliptin.

The use of vildagliptin is not recommended in patients with hepatic impairment including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.

Metformin hydrochloride

No pharmacokinetic studies of metformin hydrochloride have been conducted in subjects with hepatic insufficiency.

Renal Impairment

Vildagliptin

In subjects with mild, moderate, and severe renal impairment, and patients with end stage renal disease (ESRD) on haemodialysis, systemic exposure to vildagliptin was increased (C_{max} 8% to 66%; AUC 32% to 134%) compared to subjects with normal renal function. Exposure to the inactive metabolite (LAY151) increased with increasing severity of renal impairment (AUC 1.6- to 6.7-fold). Changes in exposure to vildagliptin did not correlate with severity of renal impairment, whereas changes in exposure to the inactive metabolite did correlate. Elimination half-life of vildagliptin was not affected by renal impairment. Based on the evaluation of safety, tolerability, and effectiveness of vildagliptin in patients enrolled in clinical trials whose GFR values were < 60 mL/min, no dosage adjustment is required in patients with mild renal impairment. The use of vildagliptin is not recommended in patients with moderate or severe renal impairment or in patients with ESRD on haemodialysis (see PRECAUTIONS Renal Impairment).

Metformin Hydrochloride

In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin hydrochloride is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance.

Race

Vildagliptin

There is no evidence that ethnicity affects the pharmacokinetics of vildagliptin.

Metformin Hydrochloride

No studies of metformin hydrochloride pharmacokinetic parameters according to race have been performed. In controlled clinical studies of metformin hydrochloride in patients with T2D, the antihyperglycemic effect was comparable in white (n=249), black (n=51) and Hispanic (n=24) patients.

CLINICAL TRIALS

Vildagliptin

More than 15,000 patients with T2D participated in double-blind, placebo- or active-controlled clinical trials of more than 2 years treatment duration. In these studies, vildagliptin was administered to more than 9,000 patients at daily doses of 50 mg once daily, 50 mg twice daily, or 100 mg once daily. More than 5,000 male and more than 4,000 female patients received vildagliptin 50 mg once daily or 100 mg daily. More than 1,900 patients receiving vildagliptin 50 mg once daily or 100 mg daily were ≥ 65 years of age. In these trials, vildagliptin was administered as monotherapy in drug-naïve patients with T2D or in combination in patients not adequately controlled by other antidiabetic medicinal products.

Overall, vildagliptin improved glycaemic control when given as monotherapy or when used in combination with metformin hydrochloride, as measured by clinically relevant reductions in HbA_{1c} and fasting plasma glucose from baseline at study endpoint. When given as monotherapy or in combination with metformin hydrochloride in studies of up to 52 weeks duration, these improvements in glucose homeostasis were durable.

Metformin

The prospective randomised (UKPDS) study has established the long-term benefit of intensive blood glucose control in type 2 diabetes. Analysis of the results for overweight patients treated with metformin hydrochloride after failure of diet alone showed:

a significant reduction of the absolute risk of any diabetes-related complication in the metformin hydrochloride group (29.8 events/1,000 patient-years) versus diet alone (43.3 events/1,000 patient-years), $p = 0.0023$, and versus the combined sulphonylurea and insulin monotherapy groups (40.1 events/1,000 patient-years), $p = 0.0034$;

a significant reduction of the absolute risk of diabetes-related mortality: metformin hydrochloride 7.5 events/1,000 patient-years, diet alone 12.7 events/1,000 patient-years, $p = 0.017$;

a significant reduction of the absolute risk of overall mortality: metformin hydrochloride 13.5 events/1,000 patient-years versus diet alone 20.6 events/1,000 patient-years ($p = 0.011$), and versus the combined sulphonylurea and insulin monotherapy groups 18.9 events/1,000 patient-years ($p = 0.021$); and

a significant reduction in the absolute risk of myocardial infarction: metformin hydrochloride 11 events/1,000 patient-years, diet alone 18 events/1,000 patient-years ($p = 0.01$).

Vildagliptin combination therapy with metformin

The efficacy and safety of the separate components have previously been established and the efficacy and safety of the co-administration of the separate components have been evaluated in clinical studies. These clinical studies established an added benefit of vildagliptin in patients with inadequately controlled T2D while on metformin hydrochloride therapy. GALVUMET tablets were shown to be bioequivalent to the individual components.

In a double-blind, placebo-controlled trial (Study 2303; n=544) in patients with T2D whose hyperglycaemia was inadequately controlled on a maximal dose of metformin hydrochloride alone, the addition of vildagliptin (50 mg once daily or 100 mg in divided doses) for 24 weeks led to statistically significant reductions in HbA_{1c} and increased the proportion of patients achieving at least a 0.7% reduction in HbA_{1c}, when compared to patients who were continued on metformin hydrochloride alone. Group mean baseline HbA_{1c} (%) ranged from 8.3% (placebo plus metformin hydrochloride) to 8.4% (in both vildagliptin plus metformin hydrochloride groups). Vildagliptin combined with metformin hydrochloride resulted in additional statistically significant mean reductions in HbA_{1c} compared to placebo (between group differences of -0.7% to -1.1% for vildagliptin 50 mg and 100 mg, respectively). The proportion of patients who achieved a clinically meaningful and robust decrease in HbA_{1c} (defined as a decrease $\geq$ 0.7 % from baseline) was statistically significantly higher in both vildagliptin plus metformin hydrochloride groups (46% and 60%, respectively) versus the metformin hydrochloride plus placebo group (20%). Patients on the combination of vildagliptin plus metformin hydrochloride did not experience a meaningful change in body weight compared to baseline. After 24 weeks, there was a decrease from baseline for both systolic and diastolic blood pressure in the vildagliptin treatment groups combined with metformin hydrochloride. Mean changes from baseline were -2.0/-0.8 mmHg, -3.5/-2.2 mmHg, and -0.8/-0.1 mmHg, in patients receiving metformin hydrochloride combined with vildagliptin 50 mg once daily, vildagliptin 50 mg twice daily or placebo, respectively. The incidence of gastrointestinal side effects ranged from 10% to 15% in the vildagliptin plus metformin hydrochloride groups as compared to 18% in the metformin hydrochloride plus placebo group.

The effect of vildagliptin in combination with metformin hydrochloride was evaluated in another, double-blind, placebo-controlled clinical trial (Study 2204E1) of 52 weeks total duration (12-week core study plus a 40-week extension) involving 132 patients with T2D on stable doses of metformin hydrochloride (1,500 mg to 3,000 mg daily). The addition of vildagliptin (50 mg once daily) to metformin hydrochloride resulted in an additional statistically significant reduction in mean HbA_{1c} (-0.6%) from baseline compared to placebo plus metformin hydrochloride (+0.1%) at the end of the 12-week study interval (mean baseline HbA_{1c} of 7.7% and 7.9%, respectively). Of these patients, 71 continued add-on treatment with vildagliptin or placebo for an additional 40 weeks (placebo-controlled, double-blind extension) and 58 of these patients completed the full 52-week treatment. At 52 weeks, mean change from baseline in HbA_{1c} was statistically significantly greater and sustained with vildagliptin (50 mg) plus metformin hydrochloride versus patients continued on metformin hydrochloride alone (between group difference of -1.1%) indicating a durable effect on glycaemic control. In contrast, glycaemic control in the metformin hydrochloride plus placebo group deteriorated over the course of the study.

In a double-blind, active-controlled 24 week trial (Study 2354; n=576), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to pioglitazone (30 mg once daily) in patients with type 2 diabetes inadequately controlled with metformin alone. Mean reductions from baseline HbA_{1c} of 8.4% were -0.9% with vildagliptin added to metformin and -1.0% with pioglitazone added to metformin. The decrease in HbA_{1c} from baseline > 9.0% was greater (-1.5%) in both treatment groups. Patients receiving pioglitazone in

addition to metformin experienced an increase in weight of 1.9 kg while those receiving vildagliptin in addition to metformin experienced an increase in weight of 0.3 kg. In a 28 week extension, HbA_{1c} reductions were similar between treatment groups and the body weight difference further increased.

In a long term, double-blind, active-controlled trial of more than 2 years (Study 2308; n=3118), vildagliptin (100 mg/day; 50 mg in the morning and 50 mg in the evening) was compared to glimepiride (up to 6 mg/day) in patients with type 2 diabetes treated with metformin. After 1-year, mean reductions in HbA_{1c} were -0.4% with vildagliptin added to metformin and -0.5% with glimepiride added to metformin. Body weight change with vildagliptin was -0.2 kg vs + 1.6 kg with glimepiride. The incidence of hypoglycaemia was significantly lower in the vildagliptin group (1.7%) than in the glimepiride group (16.2%). At the study endpoint (2 years), the HbA_{1c} was similar to baseline values in both treatment groups and the body weight changes and hypoglycaemia differences were maintained.

In a 24-week trial (LMF237A2302) the efficacy of the fixed dose combination of vildagliptin and metformin (gradually titrated to a dose of 50 mg/500 mg twice daily or 50 mg/1,000 mg twice daily) as initial therapy in drug-naïve patients was evaluated. The mean HbA1c reductions were significantly greater with vildagliptin plus metformin combination therapy compared to either monotherapy. Vildagliptin/metformin 50 mg/1,000 mg twice daily reduced HbA1c by -1.82% and vildagliptin/metformin 50 mg/500 mg twice daily by -1.61% from a mean baseline HbA1c of 8.6%. The decrease in HbA1c observed in patients with a baseline ≥10.0% was greater. Body weight decreased in all groups, with a mean reduction of -1.2 kg for both vildagliptin plus metformin combinations. The incidence of hypoglycemia was similar across treatment groups (0% with vildagliptin plus metformin combinations and 0.7% with each monotherapy).

INDICATIONS

GALVUMET is indicated as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes 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 of type 2 diabetes should not be initiated with this fixed-dose combination.

CONTRAINDICATIONS

Hypersensitivity
GALVUMET is contraindicated in patients with known hypersensitivity to vildagliptin or metformin hydrochloride or to any of the excipients (see DESCRIPTION).

Renal Disease
GALVUMET is contraindicated in patients with renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL (>135 micromol/L) in males and ≥ 1.4 mg/dL (> 110 micromol/L) in females or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicaemia (see DOSAGE and ADMINISTRATION and PRECAUTIONS).

Congestive Heart Failure
GALVUMET is contraindicated in patients with congestive heart failure requiring pharmacologic treatment (see PRECAUTIONS).

Diabetic Ketoacidosis
GALVUMET is contraindicated in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

Radiologic Studies
GALVUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see PRECAUTIONS).

PRECAUTIONS

General
GALVUMET is not a substitute for insulin in insulin-requiring patients. GALVUMET should not be used in patients with T1D or for the treatment of diabetic ketoacidosis.

Renal Impairment
GALVUMET should not be used in patients with renal failure or renal dysfunction, e.g. serum creatinine levels ≥ 1.5 mg/dL (> 135 micromol/L) in males and ≥ 1.4 mg/dL (> 110 micromol/L) in females (see CONTRAINDICATIONS).

Monitoring of Renal Function
Metformin hydrochloride is known to be substantially excreted by the kidney and the risk of metformin hydrochloride accumulation and lactic acidosis increases with the degree of renal function impairment. Patients with serum creatinine levels above the upper limit of normal for their age should not receive GALVUMET. Since advancing age is associated with reduced renal function, GALVUMET should be carefully titrated in the elderly to establish the minimum dose for adequate glycaemic effect, and renal function should be monitored regularly. Also, special caution should be exercised where renal function may become impaired, for example when initiating antihypertensive or diuretic therapy or when starting treatment with an NSAID. Renal function should be assessed and verified as normal before the initiation of GALVUMET, then at least once a year in patients with normal renal function and at least two to four times a year in patients with serum creatinine levels at the upper limit of normal. Additionally, patients

in whom renal dysfunction is anticipated should have their renal function assessed more frequently. GALVUMET should be discontinued if evidence of renal impairment is present.

Concomitant Medications that May Affect Renal Function or Metformin Hydrochloride Disposition

Concomitant medications that may affect renal function, result in significant haemodynamic change or interfere with the disposition of metformin hydrochloride, such as cationic drugs that are eliminated by renal tubular secretion should be used with caution (see PRECAUTIONS – Interactions with other drugs).

Hepatic Impairment

Vildagliptin, and hence GALVUMET is not recommended in patients with clinical or laboratory evidence of hepatic impairment, including patients with a pre-treatment ALT or AST >2.5X the upper limit of normal.

Since impaired hepatic function has been associated with some cases of lactic acidosis (a risk associated with metformin hydrochloride), GALVUMET should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Liver Enzyme Monitoring

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. LFTs should be performed prior to the initiation of treatment with GALVUMET. GALVUMET is not recommended in patients with a pre-treatment ALT or AST >2.5X the upper limit of normal. LFTs should be monitored during GALVUMET treatment at three-month intervals during the first year and periodically thereafter. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. Should an increase in AST or ALT of 3 X upper limit of normal or greater persist, withdrawal of therapy with GALVUMET is recommended. Patients who develop jaundice or other signs suggestive of liver dysfunction should discontinue GALVUMET and contact their physician immediately. Following withdrawal of treatment with GALVUMET and LFT normalisation, GALVUMET should not be reinitiated. GALVUMET is not recommended in patients with hepatic impairment.

Lactic Acidosis

Lactic acidosis is a very rare but serious metabolic complication that can occur due to metformin accumulation. Reported cases of lactic acidosis in patients on metformin have occurred primarily in diabetic patients with significant renal failure. The incidence of lactic acidosis can and should be reduced by also assessing other associated risk factors, such as poorly controlled diabetes, ketosis, prolonged fasting, excessive alcohol intake, hepatic insufficiency and any conditions associated with hypoxia (see CONTRAINDICATIONS).

Lactic acidosis is characterised by acidotic dyspnoea, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/L and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, treatment with the medicinal product should be discontinued and the patient hospitalised immediately (see OVERDOSAGE).

Use in Children

The safety and effectiveness of GALVUMET in paediatric patients have not been established. Therefore, GALVUMET is not recommended for use in children below 18 years of age.

The Elderly (≥ 65 Years)

As metformin is excreted via the kidney, and elderly patients have a tendency to decreased renal function, elderly patients taking GALVUMET should have their renal function monitored regularly. GALVUMET should only be used in elderly patients with normal renal function (see CONTRAINDICATIONS).

Effects on fertility

No studies have been conducted with vildagliptin and metformin in combination to evaluate potential effects on fertility. Fertility studies have been performed with vildagliptin in rats at doses producing exposures equivalent to up to 160 times the human dose and have revealed no evidence of impaired male or female fertility or early embryonic development due to vildagliptin. Fertility of male or female rats was also unaffected by metformin administration at doses up to 600 mg/kg/day, or approximately 3-times the maximum recommended daily human dose on a body surface area basis.

Use in Pregnancy (Category C)

Embryofetal development (teratology) studies have been conducted in rats and rabbits with the combination of vildagliptin and metformin hydrochloride in a 1:10 ratio There was no evidence of teratogenicity at oral doses yielding plasma exposure levels up to *ca* 14-20 times (rats) or 1.3-2 times (rabbits) that anticipated in patients at the maximum recommended clinical dose. An increase in the incidence of incomplete ossification in rats and an increase in early resorptions in rabbits were observed at these doses.

However, there are no adequate and well-controlled studies in pregnant women, and animal studies are not always predictive of the human response. Therefore GALVUMET should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.

Because current information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital anomalies as well as increased neonatal morbidity and mortality, most experts recommend that insulin monotherapy be used during pregnancy to maintain blood glucose levels as close to normal as possible.

Use in Lactation

No studies have been conducted with the combined components of GALVUMET. As it is not known whether vildagliptin and/or metformin hydrochloride is excreted in human milk GALVUMET should not be administered to breast-feeding women.

Carcinogenicity

No carcinogenicity studies have been conducted with the combined components of GALVUMET.

Long-term oral studies with vildagliptin in rats and mice showed evidence of haemangiosarcomas at high exposures. Tumour incidence was increased at exposure levels 46-235 times (mice) and 150 times (rats) human exposure at the maximum clinical dose, based on AUC. No significant increase in incidence was observed at 15 (males) to 80 (females) times human exposure in mice. No effect levels of *ca* 80 to 160 times the human exposure were established in rats. Mammary tumour incidence was increased in female mice at approximately 185 times the maximum anticipated human exposures to vildagliptin, but was not increased at *ca* 80 times. The tumours are thought to result from species-specific hormonal disturbances. Based on the available data vildagliptin is not anticipated to present a carcinogenic risk at clinically relevant exposures.

Long-term carcinogenicity studies with metformin were performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 and 1,500 mg/kg/day respectively. These doses are approximately three to four times the recommended human daily dose on a body surface area basis. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. However, an increased incidence of benign stromal uterine polyps was seen in female rats treated with 900 mg/kg/day.

Genotoxicity

Vildagliptin was not mutagenic in a bacterial reverse mutation assay and a human lymphocyte chromosomal aberration assay. Some clastogenic potential was exhibited in an in vitro micronucleus test in V79 Chinese hamster cells after long exposure to high, cytotoxic concentrations. However, no clastogenicity was observed in either mouse or rat micronucleus tests in vivo at up to ca 400 times the maximum human exposure, based on AUC. Furthermore, an in vivo mouse liver comet assay using the same dose was also negative. The weight of evidence indicates vildagliptin is unlikely to be genotoxic in humans at clinically relevant doses.

Metformin was not mutagenic in the bacterial reverse mutation assay, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes), or *in vivo* micronuclei formation test (mouse bone marrow).

Effects on skin

In a 13-week toxicology study in cynomolgus monkeys, skin lesions have been recorded at all oral doses administered (5 to 160 mg/kg/day). These were consistently located on the extremities (hands, feet, ears and tail) and included flaking skin, peeling skin, scabs, tail sores and blisters. At 5 mg/kg/day (approximately equivalent to human AUC exposure at the 100 mg dose), lesions were reversible despite continued treatment. Necrotic lesions of the tail were observed at ≥ 80 mg/kg/day (18 times human AUC exposure at the maximum recommended clinical dose). Skin lesions were not reversible in monkeys treated at 160 mg/kg/day (35 times human AUC exposure) during a 4-week recovery period. Skin lesions have not been observed in other animal species and no excess of skin lesions with vildagliptin treatment relative to comparator treatments have been observed in the clinical trial programme.

Interactions with Other Drugs

No clinically relevant pharmacokinetic interaction was observed when vildagliptin (100 mg once daily) was co-administered with metformin hydrochloride (1,000 mg once daily). Drug interactions for each component of GALVUMET have been extensively studied. However, the concomitant use of the active substances in patients in clinical studies and in widespread clinical use has not resulted in any unexpected interactions.

The following statements reflect the information available on the individual active substances (vildagliptin and metformin).

Vildagliptin

Vildagliptin has a low potential for drug interactions. Since vildagliptin is not a cytochrome P (CYP) 450 enzyme substrate nor does it inhibit nor induce CYP 450 enzymes, it is not likely to interact with co-medications that are substrates, inhibitors or inducers of these enzymes.

Furthermore, vildagliptin does not affect metabolic clearance of co-medications metabolised by CYP 1A2, CYP 2C8, CYP 2C9, CYP 2C19, CYP 2D6, CYP 2E1, and CYP 3A4/5. Drug-drug interaction studies were conducted with commonly co-prescribed medications for patients with T2DM or medications with a narrow therapeutic window. As a result of these studies no clinically relevant interactions with other oral antidiabetics (glibenclamide, pioglitazone, metformin hydrochloride), amlodipine, digoxin, ramipril, simvastatin, valsartan or warfarin were observed after co-administration with vildagliptin.

Metformin Hydrochloride

Furosemide

Furosemide increased C_{max} and blood AUC of metformin with no change in renal clearance of metformin. Metformin decreased C_{max}, blood AUC of furosemide, with no change in renal clearance of furosemide.

Nifedipine
Nifedipine increased absorption, C_{max} and AUC of metformin, and increased excretion of metformin in urine. Metformin had minimal effects on nifedipine.

Glyburide
Glyburide produced no changes in metformin PK/PD parameters. Decreases in C_{max}, blood AUC of glyburide were observed, but were highly variable. Therefore the clinical significance of this finding was unclear.

Cationic drugs
Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Thus, with cimetidine increases in metformin plasma/blood concentration and AUC were observed to be 60% and 40% respectively. Metformin had no effect on cimetidine PK. Although such interactions remain theoretical (except for cimetidine), careful monitoring of patients and doses of metformin and such medications are recommended.

Other
Certain drugs tend to produce hyperglycaemia and may lead to loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. Close monitoring of glycaemic control and metformin dose adjustments are recommended when such drugs are administered or withdrawn for these patients.

There is an increased risk of lactic acidosis in acute alcohol intoxication (particularly in the case of fasting, malnutrition or hepatic insufficiency) due to the metformin active substance of GALVUMET. Consumption of alcohol and medicinal products containing alcohol should be avoided (see PRECAUTIONS).

Administration of Intravascular Iodinated Contrast Materials
GALVUMET should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function and increase the risk of lactic acidosis. In patients undergoing such studies, GALVUMET should be temporarily discontinued at the time of or prior to the procedure, withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic States
Cardiovascular collapse (shock), acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxaemia have been associated with lactic acidosis and may also cause pre-renal azotmeia. If such events occur in patients receiving GALVUMET therapy, the medication should be promptly discontinued.

Surgical Procedures
Use of GALVUMET should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake
Alcohol is known to potentiate the effect of metformin hydrochloride on lactate metabolism. Patients should be warned against excessive alcohol intake while receiving GALVUMET.

Vitamin B_{12} Levels
The metformin component of GALVUMET has been associated with a decrease in serum vitamin B_{12} levels without clinical manifestations, in approximately 7% of patients. Such decrease is very rarely associated with anaemia and appears to be rapidly reversible with discontinuation of metformin hydrochloride and/or vitamin B_{12} supplementation. Measurement of haematological parameters on at least an annual basis is advised for patients receiving GALVUMET and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (e.g., those with inadequate vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal vitamin B_{12} levels. In these patients, routine serum vitamin B_{12} measurements at minimally two-to-three-year intervals may be useful.

Change in Clinical Status of Patients with Previously Controlled T2DM
A patient with T2DM previously well-controlled on GALVUMET who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should promptly be evaluated for ketoacidosis and/or lactic acidosis. If acidosis of either form occurs, GALVUMET must be stopped immediately and appropriate measures initiated.

Hypoglycaemia
Hypoglycaemia does not usually occur in patients receiving GALVUMET alone, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or ethanol use. Elderly, debilitated or malnourished patients and those with adrenal or pituitary insufficiency or alcohol intoxication are susceptible to hypoglycaemic effects. Hypoglycaemia may be difficult to recognize in the elderly and in people taking beta-adrenergic blocking drugs.

Loss of Control of Blood Glucose
When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, surgery, etc., a temporary loss of glycaemic control may occur. At such times, it may be necessary to withhold GALVUMET and temporarily administer insulin. GALVUMET may be reinstituted after the acute episode is resolved.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. Patients who are prone to dizziness should therefore avoid driving vehicles or using machines.

ADVERSE REACTIONS

There have been no therapeutic clinical trials conducted with GALVUMET. However, bioequivalence of GALVUMET with co-administered vildagliptin and metformin has been demonstrated (see PHARMACOLOGY - Pharmacokinetics). The data presented here relate to the co-administration of vildagliptin and metformin, where vildagliptin has been added to metformin. There have been no studies of metformin added to vildagliptin.

Rare cases of angioedema have been reported on vildagliptin at a similar rate to controls. A greater proportion of cases were reported when vildagliptin was administered in combination with an angiotensin converting enzyme inhibitor (ACE-Inhibitor). The majority of events were mild in severity and resolved with ongoing vildagliptin treatment.

Rare cases of hepatic dysfunction (including hepatitis) have been reported with vildagliptin. In these cases, the patients were generally asymptomatic without clinical sequelae and liver function tests (LFTs) returned to normal after discontinuation of treatment. In data from controlled monotherapy and add-on therapy trials up to 24 weeks in duration, the incidence of ALT or AST elevations ≥ 3x ULN (classified as present on at least 2 consecutive measurements or at the final on-treatment visit) was 0.2%, 0.3% and 0.2% for vildagliptin 50 mg daily, vildagliptin 50 mg twice daily and all comparators, respectively. These elevations in transaminases were generally asymptomatic, non-progressive in nature and not associated with cholestasis or jaundice.

In clinical trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group, and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg bid + metformin or the placebo + metformin treatment groups.

In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo and metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms.

Vildagliptin is weight neutral when administered in combination with metformin.

Gastrointestinal adverse reactions including diarrhoea and nausea are known to occur very commonly during the introduction of metformin hydrochloride. In the vildagliptin monotherapy clinical program (n = 2,264) where vildagliptin was administered 50 mg once daily, 50 mg twice daily, or 100 mg once daily, the rate of diarrhoea was 1.2%, 3.5% and 0.8 % respectively and the rate of nausea was 1.7%, 3.7% and 1.7% respectively as compared to 2.9% for both in the

placebo group (n = 347) and 26.2% and 10.3%, respectively, in the metformin hydrochloride group (n = 252).

Overall, gastrointestinal symptoms were reported in 13.2% (50 mg once daily or twice daily) of patients treated with the combination of vildagliptin and metformin hydrochloride compared to 18.1% of patients treated with metformin hydrochloride alone.

Adverse reactions reported in patients who received vildagliptin in double-blind studies as add-on to metformin and as monotherapy, are listed in **Table 1** for each indication, by system organ class and absolute frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100, < 1/10); uncommon (≥ 1/1,000, < 1/100); rare (≥ 1/10,000, < 1/1,000); very rare (< 1/10,000), including isolated reports. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: Other adverse reactions reported in patients who received vildagliptin 50 mg oncedaily (n=233) or 50 mg twice daily (n=183) as add-on therapy to metformin compared to placebo plus metformin in double-blind studies

Nervous system disorders	
Common	Tremor, dizziness, headache

Long term clinical trials of up to more than 2 years did not show any additional safety signal or unforeseen risks when vildagliptin was added on to metformin.

Vildagliptin

Adverse reactions for vildagliptin component from monotherapy double blind studies are presented in Table 2.

Table 2: Adverse reactions reported in patients who received vildagliptin 50 mg once daily (n=409) or 50 mg twice daily (n=1,373) as monotherapy in double-blind studies

Nervous system disorders	
Common	Dizziness
Uncommon	Headache
Gastrointestinal disorders	
Uncommon	Constipation
General disorders and administration site conditions	
Uncommon	Oedema peripheral

None of the adverse reactions reported for the vildagliptin monotherapy were observed at clinically significant higher rates when vildagliptin was administered concomitantly with metformin.

The overall incidence of withdrawals from monotherapy trials due to adverse reactions was no greater for patients treated with vildagliptin at a dose of 50 mg once daily (0.2%) or vildagliptin at a dose of 50 mg twice daily (0.1%) than for placebo (0.6%) or comparators (0.5%).
In monotherapy studies, hypoglycaemia was uncommon reported in 0.5% (2 of 409) of patients treated with vildagliptin 50 mg once daily and 0.3% (4 of 1,373) of patients treated with vildagliptin 50 mg twice daily compared to 0.2% (2 of 1,082) of patients in the groups treated with an active comparator or placebo, with no serious or severe events reported. Vildagliptin is weight neutral when administered as monotherapy.
Long term clinical trials of up to 2 years did not show any additional safety signals or unforeseen risks with vildagliptin monotherapy.

Post-marketing Experience with vildagliptin

During post-marketing experience the following additional adverse drug reaction has been reported (frequency not known): urticaria, pancreatitis.

Metformin Hydrochloride
Known adverse reactions for metformin are summarized in Table 3.

Table 3: Known adverse reactions for metformin

Metabolism and nutrition disorders		
	Very rare	Decrease of vitamin B12 absorption*, lactic acidosis
Nervous system disorders		
	Common	Metallic taste
Gastrointestinal disorders		
	Very common	Nausea, vomiting, diarrhoea, abdominal pain, loss of appetite
Hepatobiliary disorders		
	Very rare	Liver function test abnormalities, hepatitis**
Skin and subcutaneous tissue disorders		
	Very rare	Skin reactions such as erythema, pruritus, urticaria

*A decrease of vitamin B12 absorption with decrease of serum levels has been very rarely observed in patients treated long-term with metformin and appears generally to be without clinical significance. Consideration of such aetiology is recommended if a patient presents with megaloblastic anaemia.

**Isolated cases of liver function test abnormalities or hepatitis resolving upon metformin discontinuation have been reported.

Gastrointestinal undesirable effects occur most frequently during initiation of therapy and resolve spontaneously in most cases. To prevent them, it is recommended that metformin be taken in 2 daily doses during or after meals. A slow increase in the dose may also improve gastrointestinal tolerability.

DOSAGE AND ADMINISTRATION

Life threatening lactic acidosis can occur due to accumulation of metformin. The main risk factor is renal impairment, other risk factors include old age associated with reduced renal function and high doses of metformin above 2 g per day.

To minimise the risk of lactic acidosis, only one strength of GALVUMET should be prescribed and used at any one time. Patients should also be advised to discard their previous metformin medication when initiated on GALVUMET.

Adults

The use of antihyperglycaemic therapy in the management of T2D should be individualized on the basis of effectiveness and tolerability. The recommended starting dose of GALVUMET should be based on the patient's current regimen of vildagliptin and/or metformin hydrochloride. GALVUMET should be given with meals to reduce the gastrointestinal side effects associated with metformin hydrochloride. When using GALVUMET the maximum daily dose of vildagliptin (100 mg) should not be exceeded.

Starting dose for patients inadequately controlled on metformin hydrochloride monotherapy:
Based on the patient's current dose of metformin hydrochloride, GALVUMET may be initiated at either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength twice daily.

Starting dose for patients switching from combination therapy of vildagliptin plus metformin hydrochloride as separate tablets:
GALVUMET may be initiated with either the 50 mg/500 mg, 50 mg/850 mg or 50 mg/1,000 mg tablet strength based on the dose of vildagliptin or metformin already being taken.

OVERDOSAGE

Accidental overdose resulting from the continuance of previously prescribed products may occur. To avoid accidental overdose, patients should be advised to discard their previous metformin medication when prescribed with GALVUMET.

Symptoms and treatment

Vildagliptin

In healthy subjects (seven to fourteen subjects per treatment group), vildagliptin was administered in once-daily doses of 25, 50, 100, 200, 400, and 600 mg for up to 10 consecutive days. Doses up to 200 mg were well tolerated. At 400 mg, there were three cases of muscle pain, and individual cases of mild and transient paraesthesia, fever, oedema and transient increase in lipase levels (2x ULN). At 600 mg, one subject experienced oedema of the feet and hands, and an excessive increase in creatine phosphokinase (CPK) levels, accompanied by elevations of aspartate aminotransferase (AST), C-reactive protein, and myoglobin. Three

additional subjects in this dose group presented with oedema of both feet, accompanied by paraesthesia in two cases. All symptoms and laboratory abnormalities resolved after study drug discontinuation.

Vildagliptin is not dialyzable, however the major hydrolysis metabolite (LAY151) can be removed by haemodialysis.

Metformin Hydrochloride
Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycaemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin hydrochloride overdose cases. Metformin hydrochloride is dialyzable with a clearance of up to 170 mL/min under good haemodynamic conditions. Therefore, haemodialysis may be useful for removal of accumulated drug from patients in whom metformin hydrochloride overdosage is suspected.
In the event of overdosage, appropriate supportive treatment should be initiated according to patient's clinical signs and symptoms.

PRESENTATION AND STORAGE CONDITIONS

Presentation

GALVUMET is available in three strengths:
50 mg/500 mg: light yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "LLO" on the other side.
50 mg/850 mg: yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "SEH" on the other side.
50 mg/1,000 mg: dark yellow, ovaloid bevelled edge, film-coated tablet imprinted with "NVR" on one side and "FLO" on the other side.

GALVUMET is available in blister packs containing 10, 30, 60, 120, 180 or 360 tablets.
Some pack sizes may not be marketed.

Storage
Do not store above 30°C, store in the original package.

NAME AND ADDRESS OF THE SPONSOR

Novartis Pharmaceuticals Australia Pty Limited
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® = Registered Trademark

POISON SCHEDULE OF THE MEDICINE

Schedule 4: Prescription Only Medicine

DATE OF APPROVAL

Approved by the Therapeutic Goods Administration: 8 December 2010

For Internal use Only
(gam111110i.doc) based on the CDS dated 12/03/09, Corrigendum 27/03/09 additional pack sizes, TGA Nonclinical Evaluation Report, TGA Clinical Evaluation Report dated 4/06/2010, S31 PCE-2 dated 30/06/2010, PSC recommendations and our Pre-ACPM response dated 8 September 2010 and TGA e-mail dated 12 October 2010 and 5 November 2010.

Therapeutic Goods Administration

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