Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Saxagliptin / metformin hydrochloride

Proprietary Product Name: Kombiglyze

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

October 2013

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The 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 <http://www.tga.gov.au>.

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 dose combination
Decision:	Approved
Date of decision:	1 May 2013
Active ingredients:	Saxagliptin / metformin hydrochloride
Product name:	Kombiglyze
Sponsor's name and address:	Bristol-Myers Squibb Australia Pty Ltd Level 2, 4 Nexus Court Mulgrave VIC 3170
Dose form:	Film coated tablets
Strengths:	Saxagliptin[1]/metformin hydrochloride 2.5/500 mg, 2.5/850 mg and 2.5/1000 mg
Containers:	Blisters (PA/Al/PVC/Al)
Pack sizes:	Blister packs containing 14 and 56 tablets
Approved therapeutic use:	Kombiglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.
Route of administration:	Oral
Dosage:	Twice daily with meals, so as to yield a total daily dose of 5 mg saxagliptin
ARTG numbers:	AUST R 196044 (2.5/1000 mg), AUST R 196045 (2.5/500 mg), AUST R 196046 (2.5/850 mg)

Product background

This AusPAR describes an application by the sponsor, Bristol-Myers Squibb Australia Pty Ltd, to register a new fixed dose combination (FDC) film coated oral tablets containing immediate release saxagliptin/metformin hydrochloride in three strengths 2.5/500, 2.5/850 and 2.5/1000 mg. The proposed indication for Kombiglyze is

> *as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.*

[1] Saxagliptin is present as saxagliptin hydrochloride which is formed in situ.

Kombiglyze is for twice daily administration to yield a total daily dose of 5 mg saxagliptin,the same as that approved for saxagliptin mono product although the latter is approved for once daily administration. The appropriate FDC strength is selected to achieve the correct metformin dose for an individual patient. For patients inadequately controlled on a maximum tolerated dose of metformin monotherapy, various strength(s) of FDC can be selected to achieve a metformin 1000-2000 mg daily dose range. For patients switching from co administration of saxagliptin and metformin, Kombiglyze is to be initiated at the doses already being taken. For patients taking Kombiglyze as initial combination therapy, the recommendation is for an initial dose of 2.5/500 mg twice daily with subsequent titration to 2.5/850 mg or 2.5/1000 mg as required.

Saxagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor and metformin is a biguanide. Both are approved for the treatment of type 2 diabetes mellitus (T2DM).

Regulatory status

Saxagliptin is currently approved in Australia both as add on and as initial combination therapy. As add on therapy it is approved for use with metformin, a sulfonylurea, or a thiazolidinedione (dual combination). As initial therapy, it is approved for use with metformin (dual therapy). As add on therapy it is also approved for use with basal or premixed insulin with (triple therapy) or without metformin (dual therapy). It has not been investigated in clinical situations where bolus/basal insulin regimens are used.

Table 1 shows the list of countries in which a similar Kombiglyze application has been submitted at the time of the current application.

Table 1: Submission and approval status – Kombiglyze (saxagliptin/metformin).

Country	Submission date	Approval date	Comment
Canada	25 Nov 2010	9 July 2012	KOMBOGLYZE (saxagliptin/metformin hydrochloride) is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with saxagliptin and metformin or who are inadequately controlled on metformin alone (see CLINICAL TRIALS). KOMBOGLYZE is indicated for use in combination with premixed or long/intermediate acting insulin as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are already treated with saxagliptin, metformin and premixed or long/intermediate acting insulin or who are inadequately controlled on metformin and premixed or long/intermediate acting insulin alone (see CLINICAL TRIALS). Presentations: 2.5mg/500mg, 2.5mg/850mg, and 2.5mg/1000mg

Table 1 (continued): Submission and approval status – Kombiglyze (saxagliptin/metformin).

European Union	29 Jul 2010	24 Nov 2011	Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets. *Combination with insulin indication approved: 24 Oct 2012* Komboglyze is also indicated in combination with insulin (ie, triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when insulin and metformin alone do not provide adequate glycaemic control. *Combination with a sulfonylurea indication approved: 18 Feb 2013* Komboglyze is also indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus when the maximally tolerated dose of both metformin and the sulphonylurea does not provide adequate glycaemic control. Presentations: 2.5mg/850mg and 2.5mg/1000mg Note 2.5mg/500mg was not proposed for registration in the EU Centralised Procedure: Rapporteur: The Netherlands Co-rapporteur: Norway
New Zealand	N/A		
Switzerland	23 Aug 2010	29 March 2012	Komboglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients aged 18 years and older with type 2 diabetes mellitus inadequately controlled on their maximally tolerated dose of metformin alone or those already being treated with the combination of saxagliptin and metformin as separate tablets. Proposed Presentations: 2.5mg/500mg, 2.5mg/850mg, and 2.5mg/1000mg
United States	N/A	N/A	Extended-Release Kombiglyze (saxagliptin/metformin fixed dose combination) is currently registered. There are no current plans to register the immediate-release Kombiglyze presentation.

Product Information

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

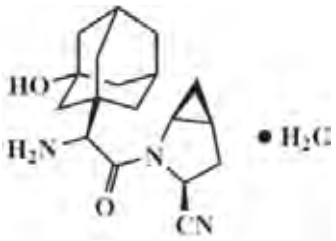
II. Quality findings

Drug substance (active ingredient)

Saxagliptin

The saxagliptin is isolated as the monohydrate (Figure 1). It is manufactured by chemical synthesis and has four chiral centres. Only one polymorph is known. The aqueous solubility of the drug substance is pH dependent and ranges from freely soluble (pH 0.7-6.6), though soluble (pH 6.7-7.7) to sparingly soluble (pH 7.8 and above). According to the Biopharmaceutical Classification System (BCS), saxagliptin is considered highly soluble. However, due to its low permeability (75% is absorbed and the oral systemic bioavailability in only ~ 50% compared to intravenous administration), it is classified as BCS Class 3.

Figure 1: Structure of saxagliptin.

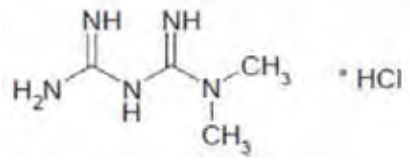


The saxagliptin monohydrate used in the proposed products is manufactured and controlled in the same manner as the saxagliptin monohydrate used in the registered 'Onglyza' tablets.

Metformin hydrochloride

Metformin hydrochloride (Figure 2) is a white/off white powder that is freely soluble in water. It has no chiral centres and no polymorphic forms of the drug substance are known. It is added to the tablets as a pre mix with 0.5% magnesium stearate.

Figure 2: Structure of metformin hydrochloride.



The chemistry and manufacturing control of the metformin hydrochloride and the pre mix are covered by a drug master file and are acceptable.

Drug product

The proposed tablets are produced as unscored, film coated, immediate release products in which the strengths are distinguished by their differing colours, sizes and markings.

Similar to the 'Onglyza' tablets, Kombiglyze tablets contain a core and an active coat containing the saxagliptin. However, in this case the core is not inert but contains metformin hydrochloride.

The specifications of the tablets include tests and limits that adequately control the appearance and assays at release and at expiry for saxagliptin and metformin hydrochloride. The expiry limits for degradants comply with International Conference on Harmonisation (ICH) guidance and associated monographs and, where necessary, tighter release limits have been set to allow for changes on storage. In addition, dissolution studies of saxagliptin and metformin hydrochloride were submitted

Stability data was provided to support a shelf life of 24 months when stored below 25°C. No additional storage conditions are required.

Biopharmaceutics

The pivotal clinical efficacy studies were performed with monotherapy tablets given concomitantly. As such bioequivalence data showing equivalence of the proposed FDC tablets to the monotherapies given concomitantly are required.

The 2.5 mg saxagliptin monotherapy tablet is not registered in Australia (only a 5 mg tablet is registered, and this is taken daily as opposed to twice daily for the FDC tablets). Therefore, data linking the two strengths is required.

The monotherapy metformin tablets used in the clinical and bioavailability studies were not those registered in Australia (US Glucophage was used). A study linking the tablets used and the Australia tablets is required.

Finally, studies determining whether there are any pharmacokinetic interactions between saxagliptin and metformin are required.

- Study CV181081 compared the proposed **2.5/500** FDC tablets to the relevant monotherapy tablets used in the clinical studies given concomitantly. The results showed bioequivalence of both saxagliptin and metformin under both fasting and fed (standard breakfast) conditions.
  - However, although the study did not calculate food effect, the clinical Delegate was asked to note the changes observed with food are not the same as those cited in the PI and it should be considered if the figures in the PI require amending.
- Study CV181092 compared the proposed **2.5/1000** FDC tablets to the relevant monotherapy tablets used in the clinical studies given concomitantly. The results showed bioequivalence of both saxagliptin and metformin under both fasting and fed (standard breakfast) conditions.
  - Similar to Study CV181081, although the study did not calculate food effect, the clinical Delegate was asked to note the changes observed with food are not the same as those cited in the PI and it should be considered if the figures in the PI require amending.
- Study CV181152 compared the 2.5 mg saxagliptin tablets used in the clinical efficacy and bioequivalence studies to a 5 mg saxagliptin tablets that was similar, apart from film coat and printing, to the 5 mg Onglyza tablet registered. This was a multiple dose study with the 2.5 mg tablets given twice daily and the 5 mg tablet given daily. This study was accepted as relevant and the results showed bioequivalence of AUC_{0-24} (area under the plasma concentration-time curve in the first 24 h) for both saxagliptin and 5-hydroxysaxagliptin (the major metabolite of saxagliptin).
- Study CV181120 compared the 500 mg and 1000 mg US Glucophage metformin hydrochloride tablets used in the clinical efficacy and bioequivalence studies to the

500 mg and 1000 mg Diabex metformin hydrochloride tablets marketed in Australia by Alphapharm Pty Ltd under fed conditions. The results showed bioequivalence of both strengths.

- The above studies all used appropriately validated test methods to determine the levels of the analytes in plasma.
- A justification was provided for not performing a bioequivalence study comparing the proposed **2.5/850** FDC to the relevant monotherapy tablets used in the clinical studies given concomitantly. The chemistry and quality aspects of this justification were acceptable with all strengths having similar dissolution profiles at pH 2, 4.5 and 6.8.
- Finally, the company referred to Study CV181017 which was provided in the submission to register the Onglyza 5 mg tablets. This investigated the pharmacokinetic interactions between saxagliptin and metformin and concluded there "is no clinically meaning drug interaction".

Advisory committee considerations

Given there were no biopharmaceutical issues during evaluation, this application was not referred to the Pharmaceutical Sub Committee for consideration.

Quality summary and conclusions

Registration is recommended with respect to chemistry and quality control.

With respect to biopharmaceutics, appropriate studies were provided and the only issue was whether the statements in the PI on the effect of food might require some amendment.

III. Nonclinical findings

Introduction

Bristol-Myers Squibb Australia Pty Ltd has applied to register Kombiglyze, a new FDC of the anti hyperglycaemic agents consisting of saxagliptin and metformin hydrochloride (immediate release), for the treatment of T2DM in adults. Saxagliptin (as Onglyza) is currently approved for use in free combination with metformin for a similar indication. Three strengths of tablets are proposed: 2.5/500, 2.5/850 and 2.5/1000 mg saxagliptin/metformin hydrochloride, with one tablet to be taken twice daily. The maximum daily doses of saxagliptin (5 mg) and metformin hydrochloride (2000 mg) provided by Kombiglyze are currently approved for the individual components. While metformin hydrochloride is currently registered for twice daily dosing, saxagliptin is only registered as a once daily treatment. This is unlikely to alter the toxicology assessment of saxagliptin made previously (see *Toxicology*, below).

The nonclinical submission contained studies investigating the single dose toxicity, repeat dose toxicity and embryofoetal toxicity of the combination. All studies included supportive toxicokinetic data. The pivotal repeat dose toxicity and reproductive toxicity studies were conducted under Good Laboratory Practice (GLP) conditions.

Pharmacology

No nonclinical efficacy studies with the proposed combination had been conducted.

Pharmacokinetics

No obvious pharmacokinetic interaction between saxagliptin and metformin was apparent in studies in dogs or pregnant rabbits. In pregnant rats, the plasma AUC for saxagliptin's active metabolite (BMS-510849 [= 5-hydroxy saxagliptin]; was approximately 2 fold less potent than its parent)and was increased by ~50% with co administration of metformin. The peak plasma levels for saxagliptin and BMS-510849 were reduced (by 70 and 46%, respectively). Metformin kinetics were unaffected and the saxagliptin AUC was not significantly altered in the above species. For humans, the current approved PI document for Onglyza states that co administration of a single dose of saxagliptin (100 mg) and metformin (1000 mg) did not alter the pharmacokinetics of metformin or the AUC for saxagliptin but did reduce the saxagliptin C_{max} (peak plasma drug concentration) by 21%. The Summary of Clinical Pharmacology contained in the original saxagliptin application additionally notes that the pharmacokinetics of BMS-510849 were unaltered with co administration of metformin.

Toxicology

Acute toxicity

A single dose oral toxicity study in dogs revealed gastrointestinal effects manifested by unformed faeces containing mucous and/or blood at higher doses with saxagliptin and metformin alone or in combination (≥5 mg/kg saxagliptin; ≥10 mg/kg metformin). Such faecal effects have been reported previously for each agent, and the effect did not appear to be exacerbated with the combination. No deaths occurred. The study was not conducted according to GLP (but was adequately documented and conducted in an established laboratory), employed a post dose observation period far shorter than recommended (24 h compared with 14 days in the relevant guideline [3BS1a]) and the animals were not subjected to necropsy (recommended for all animals). These deficiencies are compensated for by the pivotal repeat dose toxicity study.

Repeat-dose toxicity

A 3 month repeat dose study with the combination was conducted in dogs. A 2 week pilot study (non GLP and with no necropsy) was also conducted in the species. The duration of the pivotal study and the use of a single species are consistent with the relevant EU guideline.[2] The dog is considered to be an acceptable species based on pharmacokinetic considerations and it had been used for the pivotal non rodent repeat dose toxicity study for saxagliptin conducted previously. While the route (oral administration [PO]) was used the proposed clinical dosing regimen (twice daily) was not. The animals were dosed once daily instead. This is not expected to alter the interpretation of the results as the clinical dosing regimen of 2.5 mg twice daily (BID) saxagliptin was reported to be bioequivalent to 5 mg/day in terms of plasma AUC (Study CV181152), and once daily animal dosing with metformin has been used to support twice daily clinical dosing. The saxagliptin/metformin dose ratios used in the studies in dogs (1:4-1:20) differ markedly from those proposed clinically (1:200-1:400).[3] Given the dominant contribution of metformin to toxicity, and to more closely match the saxagliptin:metformin exposure ratio in humans, some such deviation is warranted, although probably not to such a great extent. Parallel groups receiving only a single agent were included in the studies.

[2] European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products (CHMP/EMEA/CHMP/SWP/258498/2005)", 13 October 2005, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/10/WC500003975.pdf>.
[3] Note also that the metformin doses are in terms of base for animals and the hydrochloride salt for humans.

Relative exposure

Exposure ratios for saxagliptin, its active metabolite and metformin (calculated as animal: human plasma AUC) achieved in the pivotal 3 month study are shown in Table 2. No human AUC values following twice daily dosing with 2.5/1000 mg saxagliptin/metformin hydrochloride FDC tablets appear to have been provided. Data for the individual components administered once daily had been used for the calculations on the basis of bioequivalence (between once daily [QD] and twice daily [BID] dosing at the same daily dose) and the absence of pharmacokinetic interactions between the pair (as reported in the Product Information for Onglyza). High multiples of exposure to saxagliptin and its active metabolite but not metformin were obtained at the maximum doses tested.

Table 2: Relative exposure in the pivotal repeat-dose toxicity study.

Species	Dose (mg/kg/day)		AUC_{0-24h} (ng·h/mL)			Exposure ratio		
	Saxagliptin	Metformin	Saxagliptin	BMS-510849	Metformin	Saxagliptin	BMS-510849	Metformin
Dog (Beagle) 13 weeks [930038455]	5	0	6510	6980	-	80	16	-
	0	20	-	-	32400	-	-	1.6
	1	20	751	1125	33050	9	2.6	1.6
	5	20	5160	6900	29800	64	16	1.5
Human	[2×2.5 mg]	[2×1000 mg][#]	81[a]	438[a]	20451[b]	-	-	-

[#] expressed in terms of metformin hydrochloride (other doses are expressed in terms of saxagliptin or metformin base)

[a] data obtained in Clinical Study CV181002 with administration at 5 mg QD ´ 14 days

[b] Timmins P, et al. (2005) Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin. Pharmacokinet.* 44: 721-729. (While a value of 20544 ng·h/mL is reported for 1000 mg BID administration of the immediate release form, a lower - but essentially equivalent - value for 2000 mg QD administration of the extended release form has been used as a conservative measure.)

Major findings

Treatment related findings in the pivotal study were limited to inhibition of body weight gain (attributed to metformin) and various clinical signs, comprising faecal changes (soft/liquid/red and presence of mucoid material; across all groups), clear eye discharge (attributed to saxagliptin), salivation and sporadic/transient tremors/shivers (attributed to metformin). The combination produced no novel or exacerbated toxicity with one exception. Co administration of 5 mg/kg/day saxagliptin with metformin (20 mg/kg/day) was seen to increase the incidence of tremors/shivers. The finding was not associated with hypoglycaemia and occurred at a low incidence (1-4 observations/dog over 3 months). It was attributed to a behavioural change rather than a neurological effect. At 1 mg/kg/day (relative exposure, 9), co administration of saxagliptin had no effect on the incidence of metformin induced tremors/shivers.

Reproductive toxicity

Embryofoetal development studies were conducted with the combination in rats and rabbits (Table 3). Parallel single agent control groups were not included in an initial rat study, but were in a second study in the species and in the rabbit study. As in the general toxicity studies, the clinical dose ratios were not used. Animal:human exposure ratios are tabulated below. High multiples of the human AUC were achieved for saxagliptin in both species, and for the active metabolite of saxagliptin in rabbits. Exposure multiples for

BMS-510849 and metformin were more modest in rats, and exposure to metformin was roughly equivalent to the anticipated maximum clinical level in rabbits.

Table 3: Relative exposure in embryofoetal development studies.

Species	Dose (mg/kg/day)		AUC_{0-24h} (ng·h/mL)			Exposure ratio		
	Saxagliptin	Metformin	Saxagliptin	BMS-510849	Metformin	Saxagliptin	BMS-510849	Metformin
Rat (SD) Study I [DN08072]	5	200	1630	658	85200	20	1.5	4
	25	200	8860	3510	89300	109	8	4
Rat (SD) Study II [DN09018]	25	0	8300	2410	–	102	6	–
	0	600	–	–	172000	–	–	8
	25	600	8070	3640	197000	100	8	10
Rabbit (NZW) [DN09020]	40	0	17400	69700	–	215	159	–
	0	50	–	–	28600	–	–	1.4
	40	50	20200	76500	22000	249	175	1.1
Human	[2×2.5 mg]	[2×1000 mg][#]	81[a]	438[a]	20451[b]	–	–	–

[#] expressed in terms of metformin hydrochloride (other doses are expressed in terms of saxagliptin or metformin base)

[a] data obtained in Clinical Study CV181002 with administration at 5 mg QD ´ 14 days

[b] Timmins P, et al. (2005) Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clin. Pharmacokinet.* 44: 721-729. (While a value of 20544 ng·h/mL is reported for 1000 mg BID administration of the immediate release form, a lower - but essentially equivalent - value for 2000 mg QD administration of the extended release form has been used as a conservative measure.)

Two foetuses in rats treated at 25/200 mg/kg/day saxagliptin/metformin displayed craniorachischisis in an initial embryofoetal development study. However, the cases were from a single litter. The observed incidence for all animals was within the historical control range for the laboratory and the finding was not confirmed in a subsequent study in rats (involving treatment at 25/600 mg/kg/day saxagliptin/metformin). Other findings in the initial rat study, a low incidences of digital malformations (ectrodactyly and brachydactyly), absent renal papilla(e) in kidneys, and forelimb flexure [again affecting single litters] were also not confirmed in the second study conducted in rats despite greater exposure to saxagliptin and metformin and the use of larger numbers of animals per group. Embryofoetal findings in the second study in rats were limited to an increase in the incidence of wavy ribs with treatment at 25/600 mg/kg/day saxagliptin/metformin (3.3%) and with metformin alone at 600 mg/kg/day (2.0%) which exceeded the historical control range (≤1.4%). This occurred in the context of maternal toxicity (significant suppression of maternal body weight gain).

In rabbits, administration of 40/50 mg/kg/day saxagliptin/metformin was poorly tolerated, resulting in death, moribundity and abortion in 12/30 dams. In contrast, there was only a single death among dams treated with the same dose of metformin alone, and none with saxagliptin alone. Similarly, maternal bodyweight gain was unaffected in the single agent groups but was markedly suppressed with combination treatment (although not in those combination animals that survived to scheduled termination). While metformin induced lactic acidosis may have contributed to the deaths, the increase in toxicity apparent in the combination group was not associated with increased exposure to metformin. No adverse effects on embryofoetal development were noted for saxagliptin or metformin alone, but treatment with the two drugs in combination was associated with a

significant reduction in mean foetal weight (7% lower compared with controls), cases of incompletely ossified pubis and an increased incidence of incomplete ossification of the hyoid.

Pregnancy classification

The sponsor has proposed Category C. This matches the current pregnancy category for metformin (as well as other existing combinations of metformin with a DPP-4 inhibitor; saxagliptin itself is B3) and is considered appropriate.

Paediatric use

Kombiglyze is not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- The nonclinical submission contained studies investigating the single dose toxicity, repeat dose toxicity and embryofoetal toxicity of the combination. No nonclinical efficacy studies with the proposed combination have been conducted.
- Toxicokinetic data obtained in dogs, pregnant rats and pregnant rabbits showed a pharmacokinetic interaction between saxagliptin and metformin in the rat only with an increase in the plasma AUC for the active metabolite (BMS-510849 by ~50%) of saxagliptin and decreases in the C_{max} for saxagliptin and its active metabolite. In humans, the pharmacokinetic interaction between saxagliptin and metformin is reported to be limited to a reduction in the saxagliptin C_{max} (by 21%).
- In the pivotal repeat dose toxicity study, co treatment with saxagliptin and metformin for 90 days in dogs produced no novel or exacerbated toxicity compared to the single agents except for an increase in the incidence of tremors/shivers (observed at 5/20 mg/kg/day saxagliptin/metformin). This finding is considered to reflect a behavioural change in the animals rather than a neurological effect, and not to be associated with hypoglycaemia. The incidence of metformin induced tremors/shivers was unaffected with co administration of saxagliptin at 1 mg/kg/day (yielding 9 times the human AUC).
- Treatment with the combination was associated with an increase in the incidence of wavy ribs in the foetuses of treated rats (the finding occurring in conjunction with significant suppression of maternal body weight gain). In rabbits, the combination was poorly tolerated in comparison with the single agents, causing death, moribundity and abortion; mean foetal weight was reduced and ossification of the pubis and hyoid was impaired. No treatment related teratogenicity was observed in either species.
- There are no nonclinical objections to the registration of Kombiglyze.[4] Amendments to the PI were also recommended.. The Nonclinical Safety Specification of the Risk Management Plan (RMP) should be amended as directed.

[4] Kombiglyze has the following Use in pregnancy statement in the PI: Category C. There are no adequate and well-controlled studies of Kombiglyze XR or its individual components in pregnant women. Because animal reproduction studies are not always predictive of human response, Kombiglyze XR, like other antidiabetic medications, should be used during pregnancy only if clearly needed. Refer to PI (Attachment 1) for further details.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

The dossier is well presented. It is extensive and relies heavily on data which has previously been submitted to TGA to support the use of saxagliptin in combination with metformin, but does include some newly submitted studies to support this dual combination therapy. It does not include any efficacy/safety studies using the FDC product itself. Studies involving administration of the FDC are restricted to those conducted in healthy subjects to establish bioequivalence of the product with its component substances saxagliptin and metformin administered as separate tablets. Pharmacodynamic data are also included to provide justification for the novel twice daily saxagliptin dosing regimen as outlined above. While the application letter and summary documents do not identify any component of the dossier as pivotal, the study providing this pharmacodynamic data (CV181152) is regarded as such by this evaluation as the single obvious change imposed by use of the Kombiglyze FDC is the change in saxagliptin dosing from once to twice daily.

The submission contained the following clinical information:

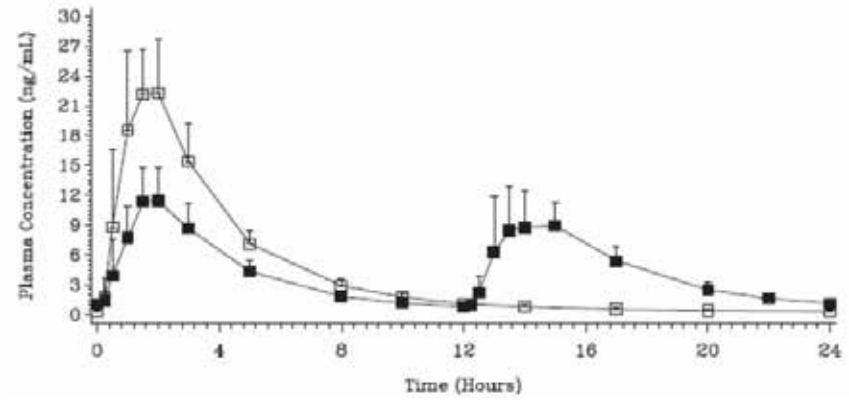
- 6 clinical pharmacology studies, including 5 that provide pharmacokinetic data and 1 that provides pharmacodynamic data;
- 1 efficacy/safety study (CV181057) regarded by this evaluation as pivotal, as it supports the only aspect of saxagliptin/metformin dual combination therapy included in the application which is not yet approved, that of use together with insulin;
- 7 other efficacy/safety studies.

Pharmacokinetics

Evaluator's overall conclusions on pharmacokinetics

The bioequivalence studies show robust evidence of close equivalence between the applicant FDC product and its component substances saxagliptin and metformin administered together as separate tablets. Study CV181120 bridges these findings to products which are registered in Australia. Overall, these findings are strongly supportive of the product as being equivalent to dual combination of saxagliptin and metformin administered separately in a twice daily regimen. Study CV181152 shows that daily exposure to saxagliptin is unaffected by the change from a once daily to twice daily administration regimen but leaves open the question as to whether its pharmacodynamic action, and hence its efficacy, might be altered as a result of the marked change in diurnal distribution of saxagliptin exposure seen with the twice daily regimen (Figure 4).

Figure 4: Time-concentration curves for the two treatments (open squares: once daily treatment; closed squares: twice daily).



The food effect appears to be of no clinical significance, applies to the two component drugs whether administered separately or in combination, and is therefore not critical to the evaluation of the FDC. Likewise, the pharmacokinetic interactions with respect to saxagliptin are noted, are described in the draft PI, but are not specific to the FDC.

Pharmacodynamics

Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic response to the saxagliptin component of the FDC is not altered, in healthy adults, by the change from once daily 5 mg administration in the morning to the 2.5 mg twice daily dosing of the FDC product. No similar study has been conducted in the target population (T2DM patients), but it is not felt likely that findings in relation to timing of these responses would be any different from those in healthy adults. Response as measured by total DPP-4 inhibition and resultant enhancement of GLP-1 secretion over the 24 h dosing interval is unchanged. There is subtle evidence, statistically unconfirmed and not claimed by the sponsor, that DPP-4 inhibition is more reliably maintained over 24 h with the twice daily regimen. This does not appear to be of a degree which would impact significantly on the therapeutic use of the product; if anything, such effect would most likely be beneficial, although there is no specific evidence on this point, as the application does not contain a study which directly compares glycaemic efficacy of the once and twice daily treatment regimens.

Efficacy

The claimed indication for the Kombiglyze FDC is:

> *as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.*

Of the efficacy/safety studies included with the application, none strictly fits the definition of a pivotal study as none was conducted using the applicant product Kombiglyze. The efficacy studies submitted bear upon various aspects of the therapeutic use of saxagliptin and metformin in dual combination therapy as separate formulations. Of these eight studies, together with their long term extensions and International System of Units (SI) compliant versions constituting a total of 14 reports altogether, the one most critical to the application is Study CV 181080, in which a twice daily dose of saxagliptin was employed. This has therefore been included as a pivotal efficacy study for the purpose of this report together with the long term extension of Study CV 181057 which was previously

evaluated in the clinical evaluation report as the pivotal study with reference use of insulin with saxagliptin, with or without metformin.

Evaluator's conclusions on clinical efficacy for the proposed indication

The full proposed indication is

> *"as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate".*

Accordingly, conclusions to be drawn about the efficacy of the saxagliptin/metformin FDC must comply with the primacy of lifestyle measures (diet and exercise) in any treatment algorithm for T2DM.

There are two aspects to be considered. First, and certainly the main brief of this evaluation, is the question of whether Kombiglyze is efficacious as a substitute for saxagliptin and metformin coadministered as separate products whenever their use is appropriate; most obviously this is when the patient is already being effectively treated with both drugs. This latter situation is what meets the definition of a *substitution indication* in the relevant EMA/TGA guideline.[5] A secondary consideration is the range of circumstances when this dual combination therapy, in the form of the FDC Kombiglyze, is appropriate.

The first of these issues is addressed by the pharmacokinetic and pharmacodynamic data summarised in the clinical evaluation report. The bioequivalence studies are sufficient to justify the substitution indication, along with the PD data in Study CV 181152 which shows that the twice-daily dosing of saxagliptin implicit in the use of the product should not affect its efficacy. This is further supported by Study CV 181080, as summarised above, which also used a twice-daily dose of saxagliptin as opposed to the once daily dose approved for saxagliptin given alone. The use of such data for justification of a FDC is compliant with the relevant TGA guideline.[6] It is therefore concluded that *Kombiglyze is an effective substitution product for saxagliptin and metformin in combination when the combined use of these two drugs is indicated*.

The guideline on determining efficacy of FDC[7] draws a distinction between the situation of, on the one hand, substituting the use of the FDC for the separately administered products when the use of the two together, either as add on or initial combination therapy, is justified by clinical evidence; and on the other, substituting the use of the FDC in the situation where the specific patient is already receiving the two drugs, which as mentioned above is the definition of a substitution indication in the guideline. The evidence submitted with this application would support efficacy in either of these situations, and it is therefore felt that the phrasing of the indication as *"…when treatment with both saxagliptin and metformin is appropriate"* is acceptable.

[5] European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf>.
[6] European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf>.
[7] European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on Clinical Development of Fixed Combination Medicinal Products (CHMP/EWP/240/95 Rev. 1)", 19 February 2009, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003686.pdf>.

The second issue, that of when the product should be used within the spectrum of management options available for T2DM, has a number of potential options:

- Add on combination, that is, the use of the FDC when a patient is already taking metformin and the criteria for addition of saxagliptin are met: this is covered by the existing approved indication for saxagliptin (Onglyza).
- The use of the FDC as initial pharmacotherapy when lifestyle measures have failed: again, this is covered by the existing indication for saxagliptin which allows initial combination therapy in appropriate circumstances, the example given being "high initial glycosylated hemoglobin (HbA1c) levels and poor prospects for response to monotherapy". The supportive efficacy/safety studies summarised above give further support for the use of the FDC as initial dual combination therapy as well as for add on combination.
- Use of the product in combination with other oral therapies, for example, sulphonylureas or thiazolidinediones. The sponsor's letter makes it clear that such use ('triple oral therapy') is not part of the application.
- Use of the product in combination with insulin. This is the only area of the application in which there is some uncertainty regarding efficacy. As indicated above, the Advisory Committee on Prescription Medicines (ACPM) has recommended rejection of an application for the use of saxagliptin (Onglyza) in combination with insulin, from which it would follow that use of the FDC with insulin would be contraindicated. However, one of the reasons for ACPM rejecting the application was the absence of clinical data beyond 24 weeks of use in its pivotal Study CV 181057. The current submission for the FDC includes the long term extension report for this study. As outlined above, the 52 week data do indicate maintenance of benefit from saxagliptin versus placebo with no sign of the quantum of benefit diminishing between 24 and 52 weeks. The evidence of efficacy is similar whether or not metformin was also being given. Overall, the conclusion of this evaluation is that there is evidence of benefit from a combination of saxagliptin and metformin given together with insulin, but that the degree of effect is relatively small (0.37% change in HbA1c), and the robustness of the finding is not compelling in view of the possibility that insulin adjustment may have been more intensive in the saxagliptin than the placebo group. It should also be noted that Study CV181057 is the single pivotal study supporting this indication.
- Finally, a point of importance with regard to all of the above options is that the data submitted with this and previous related applications is only supportive of the addition of saxagliptin to existing metformin therapy; and of the addition of saxagliptin, with or without metformin, to existing insulin therapy. There are no studies supporting the addition of metformin, or commencement of the FDC, in patients who fail on saxagliptin monotherapy, although that would be a most unlikely therapeutic proposition. A more plausible scenario, likely to be considered by clinicians, would be that of adding insulin in patients who fail on saxagliptin with or without metformin, or in the context of this application, on the FDC. This use is not supported by the data. The wording of the proposed indication as "…when treatment with both saxagliptin and metformin is appropriate" must take account of this hierarchy of treatment combinations. In practical terms, this means that a patient on the combination of saxagliptin and metformin who develops failure of glycaemic control and is being considered for insulin therapy should cease saxagliptin before insulin is introduced. Should glycaemic failure persist despite insulin, reintroduction of saxagliptin could then be considered on the basis of the submitted evidence.

It is concluded that efficacy of saxagliptin and metformin in the form of Kombiglyze is confirmed in those therapeutic situations for which approved indications already exist. With regard to use with insulin, efficacy of the combination of saxagliptin and metformin

as add on therapy is demonstrated, but the level of evidence for this is marginal in the context of the relevant guideline for basing conclusions regarding efficacy on a single pivotal study.[8]

Safety

Evaluator's overall conclusions on clinical safety

The profile of adverse events related to immunological function including hypersensitivity reactions, minor infections and effects on lymphocyte count, collectively a class effect of DPP-4 inhibitors, remains evident in this submission but there is no evidence of an increase in incidence or severity of these phenomena with longer term administration of saxagliptin, up to 4 years in one study, or of the appearance of any qualitatively different adverse effects. There appear to be no safety issues specific to the combination of saxagliptin with metformin. Hypoglycaemia is not a safety issue of concern for the saxagliptin/metformin combination either on its own or when used in combination with insulin, and is clearly less common with the saxagliptin/metformin combination than with the alternative commonly used dual combination of sulphonylurea and metformin.

List of questions

No questions.

Clinical summary and conclusions

First round benefit-risk assessment

The sponsor's global RMP; an addendum is also included indicating that no risk management activities relating to the FDC are proposed specifically for Australia.

In the following discussion, distinction is drawn between the benefits and risks of dual combination saxagliptin/metformin therapy, and of the fixed combination tablet itself. The former have already been assessed and taken into account in the existing approval of this dual combination therapy except that the issue of use with insulin, at least from the point of view of this evaluation, remains unresolved.

First round assessment of benefits

Dual combination therapy with saxagliptin and metformin has been shown in previous submissions to be beneficial, as assessed by improvements in HbA1c, in the management of T2DM either in the setting of add on therapy or initial combination therapy. Evidence of this benefit is reinforced in the present submission, although remaining restricted to HbA1c improvement as opposed to long term clinical outcomes. Benefit of the combination therapy when used together with insulin is also demonstrated, but both the quantum of benefit obtained and the level of supporting evidence are of lesser degree.

The FDC tablet is proposed, as stated in the letter of application, as a "convenient alternative" to separate administration of saxagliptin and metformin. This is a plausible proposition, but not supported by any evidence of clinical benefit. The suggestion that compliance is improved by use of the FDC is hypothetical rather than proven. It does

[8] European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP): Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)", 31 May 2001, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf>.

involve a twice daily dosing schedule, whereas each component drug taken separately is available as a once daily preparation, although at different times of the day with existing recommendations (saxagliptin in the morning, metformin XR in the evening). The postulated benefit with regard to compliance therefore appears marginal. There might be a financial cost benefit to the consumer in a single preparation, depending on funding and subsidy arrangements.

First round assessment of risks

The risks of dual combination therapy with saxagliptin and metformin in the proposed usage consist of the adverse effect profile of the two drugs added together. As metformin is used as initial pharmacotherapy for virtually all T2DM patients unless contraindicated or not tolerated, its risk profile is not a determining factor in this equation. With regard to saxagliptin, the class effect of adverse effects as described remains a consideration.

No specific risks are seen to apply to the fixed dosage combination tablet.

First round assessment of benefit-risk balance

The benefit-risk balance of dual combination therapy with saxagliptin and metformin, either in the setting of adding saxagliptin to existing metformin therapy, or as initial combination therapy, is favourable.

The benefit-risk balance of dual combination therapy with saxagliptin and metformin given together with insulin is not favourable on current evidence; the possibility that the demonstrated level of benefit could be obtained by intensification of insulin therapy, without exposing the patient to the inherent risks associated with saxagliptin as a DPP-4 inhibitor, has not been excluded.

The benefit-risk balance of the FDC tablet as a form of giving this therapy is neutral to slightly favourable, and the above conclusions can therefore be applied to its use.

First round recommendation regarding authorisation

It is recommended that **the application for all three dosage forms of the saxagliptin and metformin FDC (Kombiglyze) be approved**. This recommendation applies only to the existing approved indications for use of saxagliptin with metformin, and does not extend to use of the product with insulin.

It should be noted that none of the data reviewed by this evaluation included the proposed 2.5 mg saxagliptin/850 mg metformin tablets, or doses of 850 mg metformin. Application for a biowaiver for this strength is included in the biopharmaceutical summary. While assessment of the pharmaceutical data is beyond the expertise of this evaluator, the application appears reasonable and only involves changes in the metformin dosage, which is among the range commonly employed in clinical practice at present. Inclusion of the three strengths improves the capacity for metformin dosage titration using the FDC.

With regard to the question of use with insulin, it should be noted that this evaluation has only considered use of dual combination therapy with saxagliptin and metformin together with insulin. No data regarding use of saxagliptin alone with insulin has been reviewed. It is acknowledged that either of these indications could be reconsidered with further supporting evidence.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Table 4 shows a summary of the Kombiglyze RMP.

Table 4: Summary of Kombiglyze RMP.

Safety concern	Proposed pharmacovigilance activities (routine[b] and additional)	Proposed risk minimisation activities (routine and additional)[a]
Important Identified Risks:		
Lactic acidosis	Routine PV	Product labeling is sufficient to address safety concern. Lactic acidosis is listed in the product labeling.[6] Section 3 Posology and method of administration: Section 5 Warnings and precautions for use: Section 7 Undesirable effects: Section 9 Overdose
Hypersensitivity reactions	Routine PV Epidemiology program for further risk evaluation for hospitalization or ER visits with severe hypersensitivity reactions Hypersensitivity reactions are secondary safety objective in CV outcomes study.	Product labeling is sufficient to address safety concern. Specific hypersensitivity reactions are listed in the product labeling.[3] Section 4 Contraindication: Section 5 Warnings and precautions for use: Section 7 Undesirable effects
Pancreatitis	Routine PV Pancreatitis is a safety objective in a large cardiovascular outcomes trial (CV181088 /D1680C00003) for Onglyza. In addition, a planned adjudication of the reports of pancreatitis in a blinded fashion is currently under the monitoring plan.	Product labeling is sufficient to address safety concern. Pancreatitis is listed in the product labeling[3]. Section 5 Warnings and precautions for use: Section 7 Undesirable effects
Hepatitis	Routine PV	Product labeling is sufficient to address safety concern. Hepatitis is listed in the product labeling.[3] Section 7 Undesirable effects
Infections	Routine PV Severe infections is a secondary safety objective in CV outcomes trial. Epidemiology program for further risk evaluation for hospitalized infections.	Product labeling is sufficient to address safety concern. Specific infections are listed in the product labeling.[4] Section 7 Undesirable effects
Gastrointestinal-related AEs	Routine PV	Product labeling is sufficient to address safety concern. Specific GI-related AEs are listed in the product labeling.[5] Section 7 Undesirable effects
Vitamin B12 deficiency	Routine PV	Product labeling is sufficient to address safety concern. Vitamin B12 deficiency is listed in the product labeling.[1] Section 5 Warnings and precautions for use: Section 7 Undesirable effects
Important Potential Risks:		
Skin lesions (ulcer, erosion, and necrosis)	Routine PV Assessment in cardiovascular outcomes study (CV181088/D1680C00003)	Product labeling is sufficient to address safety concern. Skin lesions are described in the product labeling.[3] Section 5 Warnings and precautions for use Section 11 Non-clinical safety
Lymphopenia	Routine PV Epidemiology program for evaluation of risk factors for lymphopenia Assessment in cardiovascular outcomes study (CV181088/D1680C00003)	Product labeling is sufficient to address safety concern. Effect on lymphocyte counts is described in the product labeling.[6] Section 7 Undesirable effects
Thrombocytopenia	Routine PV Assessment in cardiovascular outcomes study (CV181088/D1680C00003)	None
Hypoglycemia	Routine PV	Product labeling is sufficient to address safety concern.

Table 4 (continued): Summary of Kombiglyze RMP.

Safety concern	Proposed pharmacovigilance activities (routine[b] and additional)	Proposed risk minimisation activities (routine and additional)[a]
		Hypoglycemia is described in the product labeling.[a] Section 7 Undesirable effects
Bone fracture	Routine PV Assessment in cardiovascular outcomes study (CV181088/D1680C00003 [SAVOR])	None
Severe cutaneous adverse reactions	Routine PV Epidemiology program for further risk evaluation for hospitalization or ER visits with severe hypersensitivity and severe skin reactions. Hypersensitivity reaction is a secondary safety objective in CV outcomes study	None
Opportunistic infections	Routine PV	None
Important Missing/Limited Information		
Safety in patient ≥ 75 years of age	Routine PV	Product labeling is sufficient to address safety concern. Specific information for the elderly population is described in the product labeling.[a] Section 3 Posology and method of administration Section 5 Warnings and precautions for use
Safety in paediatric population < 18 years of age	Routine PV A paediatric plan (eg, PIP) has been approved by EMA and FDA and the studies initiated in 2011	Safety not established in this population. Refer to section 1.3.1 describing the ongoing-planned paediatric studies. Specific information for the paediatric population is described in the product labeling[a] Section 3 Posology and method of administration Section 5 Warnings and precautions for use
Safety in pregnancy/breast feeding	Routine PV	Product labeling is sufficient to address safety concern Specific information (warnings and precautions) regarding the use of saxagliptin metformin FDC in pregnancy and nursing women is described in the product labeling.[a] Section 5.13 Pregnancy and lactation
Safety in patients with cardiovascular disease (defined as significant cardiovascular history within 6 months) and patients with compromised cardiac function (CHF NYHA class III and IV)	Routine PV A large cardiovascular outcomes trial (CV181088/D1680C00003) for Onglyza is being conducted to evaluate the effect of saxagliptin on the incidence of CV death, myocardial infarction, or ischaemic stroke in patients with Type 2 diabetes Ongoing CV adjudication in saxagliptin clinical trial program Saxagliptin epidemiology program for further risk evaluation of major adverse cardiovascular events.	Safety not established in this population. Cardiovascular outcomes trial (CV181088/D1680C00003) for Onglyza is ongoing. Product labeling is sufficient to address safety concern Specific information for this population is described in the product labeling Section 4 Contraindication Section 5 Warnings and precautions for use
Safety in immunocompromised patients	Routine PV	None
Malignancy/neoplasm	Routine PV Assessment in cardiovascular outcomes study (CV181088/D1680C00003)	None

a Product label reference is Company Core Data Sheet (CCDS)

b All targeted questionnaires developed for Onglyza also will be used for saxagliptin and metformin HCl FDC

Table 5 summarises the TGA's evaluation of the RMP and the sponsor's responses to the issues raised by the OPR.

Table 5: Reconciliation of issues outlined in the Kombiglyze RMP evaluation report.

Issue	Sponsor's response (verbatim)	Evaluator's comment
Addition of acute kidney injury as a safety concern.	At no time has acute kidney injury been considered a risk or missing information in the Onglyza or Kombiglyze RMP. Although moderate and severe renal impairment was considered important missing/limited information at the time of the original saxagliptin filing in 2008; this was later removed based on the findings from Study D1680C00007 (CV181062). This was a 12 week, multi-centre, randomised, double-blind, placebo controlled study conducted to evaluate the treatment effect of saxagliptin 2.5 mg once daily compared with placebo in 170 patients (85 subjects receiving saxagliptin and 85 subjects receiving placebo) with Type 2 diabetes mellitus (T2DM) and renal impairment (moderate [n=90]; severe [n=41], or end-stage renal disease (ESRD) [n=39]). There were no major, clinically relevant differences between the treatment groups in the incidence and type of adverse events (AEs) within the 3 baseline renal impairment categories and according to insulin use. There was no adverse effect on renal function as determined by estimated glomerular filtration rate (eGFR) or creatinine clearance (CrCl) at Week 12 and Week 52. Concomitant therapy with saxagliptin and metformin was evaluated in Studies CV181014 (saxagliptin added-on to metformin) and CV181039 (initial combination therapy). In both of these studies, there were no consistent or clinically meaningful changes from baseline in blood urea nitrogen (BUN), serum creatinine, or CrCl in any treatment group. In Study CV181014, the incidence of AEs in System Organ Class (SOC) Renal and urinary disorders was 10.9% in the saxagliptin 2.5 mg plus metformin group, 9.4% in the saxagliptin 5 mg plus metformin group, and 8.9% in the placebo plus metformin group; (the overall proportion of subjects with AEs was higher in the saxagliptin 2.5 mg group than in the placebo group). In Study CV181039, the incidence of AEs in SOC Renal and urinary disorders was 4.7% in the saxagliptin 5 mg + metformin group and 4.3% in the metformin group. The pharmacoepidemiology study (CV181157), estimating the incidence and risk of acute kidney injury among new users of Onglyza/Kombiglyze compared to new users of other non DPP4 oral antidiabetic drugs (OADs), was proposed in the initial Onglyza RMP (dated 12 June	Based on the sponsor's response, acute kidney injury does not need to be included as an ongoing safety concern, unless new evidence arises or the Delegate considers it necessary. However, the sponsor needs to make available the results of pharmacoepidemiology study CV181157, so that the need for additional ongoing safety concerns can be re-evaluated.
Issue	**Sponsor's response (verbatim)**	**Evaluator's comment**
	2008) to gather additional safety information post-approval, and was made a postmarketing commitment by the European Medicines Agency (EMA). The study is being conducted to provide reassurance about acute kidney injury among Onglyza/Kombiglyze users in the absence of any safety finding from the clinical development program. This study is currently ongoing and is also providing data to supplement the spontaneous reporting system. There was no evidence of acute kidney injury in any of the saxagliptin nonclinical toxicity studies based on microscopic examination and standard clinical pathology, including urinalysis. Based on the information presented above, the Sponsor concludes that acute kidney injury is not an ongoing safety concern for Kombiglyze.	
Addition of acute liver injury as a safety concern.	The pharmacoepidemiology study estimating the incidence and risk of acute liver failure and acute liver injury among new users of Onglyza/Kombiglyze compared to new users of other non-DPP4 OADs was proposed in the initial Onglyza RMP (dated 12 June 2008) to gather additional safety information post-approval, and was made a postmarketing commitment by EMA and the US Food and Drug Administration (FDA) at the time of approval. At no time has acute liver failure or acute liver injury been considered an identified or potential risk in the Onglyza or Kombiglyze RMP. This study is currently ongoing and being conducted to provide reassurance about acute liver failure/injury among saxagliptin users in the absence of any safety finding in the clinical development program; this study is also providing data to supplement the spontaneous reporting system. In April 2012, the Sponsor received notice from FDA that the postmarketing requirement to conduct a pharmacoepidemiology study on acute liver failure/injury was removed. FDA noted that AE data from FDA's Adverse Event Reporting System (AERS) and other postmarketing data have not shown a liver safety signal with saxagliptin and that the risk of hepatic events can be further assessed through the (currently ongoing) cardiovascular outcomes trial: A Multicentre, Randomised, Double-Blind, Placebo-Controlled Phase IV Trial to Evaluate the Effect of Saxagliptin on the Incidence of Cardiovascular Death, Myocardial Infarction or Ischaemic Stroke in Patients with Type 2 Diabetes (Study D1680C00003: SAVOR).	Based on the sponsor's response, acute liver injury does not need to be included as an ongoing safety concern, unless new evidence arises or the Delegate considers it necessary. However, the sponsor needs to make available the results of pharmacoepidemiology study CV181100, so that the need for additional ongoing safety concerns can be re-evaluated.

Table 5 (continued): Reconciliation of issues outlined in the Kombiglyze RMP evaluation report.

Issue	Sponsor's response (verbatim)	Evaluator's comment
Measures to minimise potential medication errors resulting from tradename mismatches and inadequate labelling	The Sponsor provides assurance that appropriate measures will be undertaken to ensure differentiation of the labelling for the respective presentations.	The sponsor has not commented on the proposed name change to Komboglyze that would align the name for the immediate-release formulation to the name used in other jurisdictions. Furthermore, the sponsor has not outlined which additional measures will be undertaken to minimise potential medication errors from a potential name mismatch or a confusion between immediate-release and extended-release formulation. It is recommended to the Delegate that the tradename be changed to KOMBOGLYZE and/or 'immediate-release' (or a statement to that effect) be printed on the carton and foil. Furthermore, in the s 31 response (section 2.2.5), the sponsor refers to the same FDC marketed in the EU as 'Kombiglyze' whereas the correct name is 'Kamboglyze', indicating how simple it is to confuse the two names.
Changes to proposed Australian PI: statement on skin disorders.	The Sponsor defines the term skin lesion as erosive and/or ulcerative lesions that are consistent with those findings observed in cynomolgus monkeys. The skin toxicity observed in the monkeys (necrotic, ulcerative lesions) has not been associated with saxagliptin exposure in the clinical program. A medical review of the few case reports of skin lesion in the clinical program identified the causes to be secondary to underlying disease (eg, diabetic ulcers, atherosclerotic ischemic ulcers) or related to trauma. Overall, the evaluation of the clinical study data has not revealed any safety	The RMP evaluator requested a statement regarding skin disorders be included in the proposed Australian PI, not only regarding skin lesions. The RMP evaluator agrees that the

Issue	Sponsor's response (verbatim)	Evaluator's comment
	findings that correlate to the skin lesions as defined by the Sponsor. A post hoc analysis of skin lesions potentially related to diabetic foot ulcers was undertaken to provide information on potential effects of saxagliptin on such lesions. The analysis was performed on the controlled Phase 2b/3 short-term plus long-term (ST + LT) population including rescue treatment. The search of the database was done on the verbatim terms level. Search words were- feet, foot, toe, toes, and heel, any of which had to be combined with at least one of the following: wound, ulcer, abscess, furuncle, furunculous, lesion, erosion, necrosis, gangrene, or blister. This approach resulted in the identification of a total of 38/4607 subjects (28/3356 [0.8%] in the saxagliptin groups and 10/1251 [0.8%] in the comparator groups). Of these, 4 were serious adverse events (SAEs) (2 in the saxagliptin groups and 2 in the comparator groups) and 2 resulted in discontinuation of randomised treatment (1 in the saxagliptin groups and 1 in the comparator groups). As classified by the investigator, 6 were in the category of severe/very severe (4 in the saxagliptin groups and 2 in the comparator groups). Taken together, these data do not indicate an increased risk of more frequent or severe diabetic foot ulcers in subjects treated with saxagliptin. To date, there is no evidence of clinical correlation between findings from the monkey toxicology studies and what has been observed in the ongoing clinical program. In addition, there is no evidence of a signal for skin lesions in the post-marketing experience. Therefore, the Sponsor concludes that there are no data to support the inclusion of skin lesions in the Australian PI for Onglyza.	clinical relevance of the skin lesions in the study with cynomolgus monkeys is unknown, but this needs to be communicated in the PI. Furthermore, considering that diabetics are more likely to suffer from skin disorders than non-diabetic populations, a statement regarding post-marketing reports of rash and pruritus in saxagliptin and a general statement regarding routine skin care in diabetics, would not be unreasonable. It is noted that the proposed PI already contains a statement on post-marketing reports of rash, but this should be repeated in the context of diabetic skin care.
Changes to proposed Australian PI: statement on immunocompromised patients.	As part of the assessment of immunological reactivity, infections have been carefully monitored in the saxagliptin development program. Immunocompromised subjects, such as subjects who have undergone organ transplantation or subjects diagnosed with human immunodeficiency virus (HIV), were excluded in the Phase 3 program, partly due to insufficient drug-drug interaction data at the time and partly due to the hypothetical risk of DPP4 inhibition interacting with immunoreactivity. Preclinically, multiple immune endpoints, including T lymphocyte-dependent antibody responses and T- and B-cell proliferation responses, have been evaluated and have not demonstrated adverse changes or impaired function of the immune system. Numerous immunotoxicity assessments demonstrated no adverse effects on immune parameters other than the generalised and non-specific lymphoid	The RMP evaluator agrees that there do not seem to be clinically significant immunosupression events in the studies presented by the sponsor. However, the quoted studies (CV191031 and CV181039) were conducted with healthy volunteers, not immunocompromised patients. The statement requested by the RMP evaluator refers to the fact that

Table 5 (continued): Reconciliation of issues outlined in the Kombiglyze RMP evaluation report.

Issue	Sponsor's response (verbatim)	Evaluator's comment
	hyperplasia and presence of minimal or mild multi-tissue mononuclear cell infiltrates at clinically non-relevant exposures in rats [area under the concentration time curve (AUC) multiple ≥ 36 x the recommended human dose (RHD) of 5 mg) and monkeys (7 x the RHD). These microscopic changes were reversible and no long-term sequelae resulting from lymphoid hyperplasia (ie. lymphoma or auto-immune disease) were observed. Moreover, the general multi-tissue mononuclear cell infiltrates did not result in tissue injury even after chronic dosing (up to 2 years). Collectively, the comprehensive nonclinical immunotoxicity evaluation of saxagliptin adequately characterised its immunotoxic potential and supports that immune health in patients will not be compromised at systemic exposures at the RHD of 5 mg. Study CV181031 was a double-blind, multiple-dose, randomised, parallel group placebo-controlled study to evaluate the effect of single and multiple oral daily doses of 10 and 40 mg of saxagliptin on absolute lymphocyte count when administered to healthy subjects relative to baseline. Changes in absolute lymphocyte counts were not observed following 10 mg saxagliptin daily or interrupted doses. Transient decreases in lymphocyte counts within the normal range were observed following interrupted dosing, but not in once daily 40 mg saxagliptin doses, and no clinical signs or symptoms were observed. Flow cytometry data indicated no particular lymphocyte population was affected following single and multiple oral daily doses of 10 and 40 mg saxagliptin, nor were the decreases likely to be due to a change in proliferation rate or necrosis/apoptosis, and the mechanism for the lymphocyte decreases remains unknown. No flu-like symptoms were reported in this study. Single and multiple daily doses of 10 and 40 mg saxagliptin appeared to be generally safe and well-tolerated. Infection-related AEs were identified as an event of special interest given the role of DPP4, also known as CD26, as a co-stimulatory signalling molecule expressed on the surface of T-cells. An analysis of the 5 pooled placebo-controlled monotherapy and combination studies demonstrated comparable AE frequencies in the SOC Infections and Infestations in the saxagliptin 2.5 mg, saxagliptin 5 mg, and placebo groups (36.4%, 35.9%, and 34.8%, respectively); a higher frequency of AEs was observed in the saxagliptin 10 mg group (40.1%). As preferred terms, sinusitis and gastroenteritis were AEs with some basis for an association with the use of saxagliptin in an integrated safety analysis across the core Phase 3 studies. In treatment-naive subjects, saxagliptin given as monotherapy was associated with a	Immunocompromised patients have not been studied. Making this statement available to clinicians referring to the PI would allow them to make a decision regarding risk and benefit of prescribing the drug for immunocompromised patients.
Issue	**Sponsor's response (verbatim)**	**Evaluator's comment**
	higher reported frequency of infection-related AEs compared with placebo (31.5% and 23.7%). In contrast, the frequency of AEs reported in this SOC for treatment-naive subjects who received saxagliptin monotherapy at 10 mg in Study CV181039 was similar to the frequency in those who received metformin monotherapy (26.6% and 23.5%, respectively). In the add-on combination studies, saxagliptin was associated with a comparable frequency of infection-related AEs in combination with a sulfonylurea (SU) and a marginally higher frequency in combination with either metformin or a thiazolidinedione (TZD). Although AEs in the SOC Infections and Infestations were the most commonly reported AEs across the core Phase 3 studies, relatively few were considered serious, and few led to discontinuation. The frequency of events reported as SAEs or as leading to discontinuation of study drug in this SOC was similar in subjects who received saxagliptin and placebo (approximately 0.5%). Infection-related events that would be considered as opportunistic infections were infrequent in subjects who received saxagliptin in the core Phase 3 clinical program. Further analyses were conducted to evaluate whether an association was apparent between the reductions observed in absolute lymphocyte count and risk for infection. The frequency of infection-related AEs and the type of infections [including those traditionally associated with T-cell dysfunction] reported among saxagliptin-treated subjects with non-isolated declines in lymphocyte count were similar compared with saxagliptin-treated subjects in the overall population. In an analysis of infection-related AEs traditionally associated with T-cell dysfunction (eg, herpes virus, cytomegalovirus, tuberculosis) across the entire Phase 2b/3 clinical program, the frequency of these selected infection-related AEs was comparable between subjects who received saxagliptin and comparator-treatment regimens. Thus, while the clinical significance of the decrease in lymphocyte count relative to placebo is not known, the decreases were not associated with clinically relevant infection-related AEs. Based on the information presented above, the Sponsor concludes that a statement regarding immunocompromised patients is not warranted for the Australian PI.	
Issue	**Sponsor's response (verbatim)**	**Evaluator's comment**
Changes to proposed Australian PI: statement regarding examples where renal function may be impaired.	The Kombiglyze [de] EU SmPC contains the following statement: "Decreased renal function in elderly patients is frequent and asymptomatic. Special caution should be exercised in situations where renal function may become impaired, for example, when initiating antihypertensive or diuretic therapy or when starting treatment with a NSAID." The proposed Australian PI contains the following statement concerning caution in patients in whom development of renal dysfunction is anticipated: > Before initiation of KOMBIGLYZE therapy, and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and KOMBIGLYZE discontinued if evidence of renal impairment is present. Although the SmPC includes specific examples, the Sponsor considers that the statement in the proposed PI broadly indicates that caution should be exercised in all situations where renal function may become impaired.	The sponsor refers to the same FDC marketed in the EU as 'Kombiglyze' whereas the correct name is 'Komboglyze', indicating how simple it is to confuse the two names. The RMP evaluator agrees that a similar statement without specific examples exists in the proposed Australian PI, but the sponsor should include some examples as a reminder for the prescribing clinician.

Suggested wording for conditions of registration

RMP

Implement EU-RMP Version 2 (dated 8 December 2011), and Australian Risk Minimisation Activities (dated 26 March 2012),[9] and any future updates as a condition of registration.

Periodic Safety Update Reports (PSURs)

Post marketing reports are to be provided in line with the current published list of EU reference dates and frequency until the period covered by such reports is not less than three years from the date of this approval letter. The reports are to meet the requirements in accordance with ICH E2C (R2) guideline on Periodic Benefit-Risk Evaluation Reports and Module VII of the EMA Guideline on Good Pharmacovigilance (GPV) Practices relating to PSURs. Submission of the report must be within the 70 days of the data lock point for PSURs covering intervals up to and including 12 months and within 90 days of the data lock point for PSURs covering intervals in excess of 12 months. The submission may be made up of two PSURs each covering six months.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The two active substances are not mixed together within the tablet. Kombiglyze tablets consist of an inner metformin core which is covered by an active coating of saxagliptin. The manufacturing details are considered satisfactory.

- In Australia, the saxagliptin 5 mg tablet is registered. The 2.5 mg saxagliptin tablet used in clinical studies is not registered in here.
- The metformin tablets used in clinical and bioavailability studies were the US registered product.

Appropriate bioequivalence studies linking the study drugs with the Australia registered products were provided and are considered satisfactory.

The company referred to an earlier Study CV 181017 in the submission to register saxagliptin (Onglyza) 5 mg tablets to establish lack of clinically meaningful drug interactions between these two active agents.

This submission of FDC was not referred to the Pharmaceutical Subcommittee. The PCE recommends registration with respect to chemistry and quality control.

Nonclinical

The toxicology dossier included studies single dose toxicity, repeat dose and embryofoetal toxicity studies using the combination.

Data obtained in dogs, pregnant rats and pregnant rabbits showed pharmacokinetic interaction between saxagliptin and metformin in rats – an increase in plasma AUC for the active metabolite of saxagliptin (BMS-510849) and decrease in C_{max}. The evaluators

[9] The Australian Risk Minimisation Activities state that risk minimisation activities for Saxagliptin and Metformin HCl FDC will be conducted in accordance with the Global RMP and that there are no additional risk minimisation activities specific for Australia.

comment that in humans, the pharmacokinetic interaction between saxagliptin and metformin is limited to a reduction in the saxagliptin C_{max}.

In repeat dose toxicity study, co administration of saxagliptin and metformin for 90 days in dogs produced no novel or exacerbated toxicity compared to single agents except for an increase in the incidence of tremors/shivers (observed at 5/20 mg/kg/day saxagliptin/metformin). This finding was considered a behavioural effect rather than a neurological effect or manifestation of hypoglycaemia.

Treatment with the combination was associated with an increase in incidence of wavy ribs in foetuses of treated rats. The finding occurred in conjunction with significant suppression of maternal body weight gain.

In pregnant rabbits, the combination was poorly tolerated in comparison with the single agents causing death, moribund state and abortion. Mean foetal weight was reduced and ossification of the pubis and hyoid was impaired.

No treatment related teratogenicity was observed in either species (rat, rabbit).

The nonclinical evaluators were further contacted in relation to the effect seen in pregnant rabbits and report species related sensitivity to metformin not relevant to human use.

Both saxagliptin and metformin combined use is currently approved. Consequently, there are no nonclinical objections to the registration of Kombiglyze.

Clinical

The clinical dossier consisted of 5 pharmacokinetic, 1 pharmacodynamic, and 8 efficacy studies. The clinical efficacy studies were performed with free combination of mono agents given concomitantly.

Efficacy

The use of metformin/saxagliptin co administration is supported based on previously evaluated studies (Study 181014 as add on therapy and Study 181039 as initial therapy). Both uses are currently approved in Australia. In addition, longer term efficacy data are now available. However, note that these studies do not involve 2.5 mg saxagliptin twice daily dosing.

The dossier also included active controlled studies (Study 181054 comparing metformin/saxagliptin use against metformin/glipizide sulfonylurea [longer term data available; this study is being included in the PI] and Study 181056 comparing metformin/saxagliptin against metformin/sitagliptin in an 18 weeks study).

The Study 181057 investigated saxagliptin use with basal insulin and included 52 weeks. The use with basal insulin (with or without metformin) is now approved in Australia. This is therefore no longer regarded as an issue.

The treatment effect generally observed with respect to the primary outcome (HbA1C) with the use of metformin/saxagliptin combination was modest but sustained and clinically meaningful.

Study 181038 of saxagliptin use in naïve patients with metformin as rescue medication and Study 181066 using sustained release metformin and saxagliptin 5 mg are only marginally relevant to this submission.

This brings to attention Study 181080. This small (n = 160), short (12 weeks), double blind study can be considered pivotal to this submission as this was the only study in which 2.5 mg twice daily saxagliptin dosing was investigated. Metformin was also given twice daily. The 12 week results were as shown in Table 6.

Table 6: 12 week results from study 181080.

Measure: A1C Unit: %	Saxa 2.5 mg (BID) N=74	Placebo N=86
Summary Statistics		
n	74	84
Baseline Mean (SE)	7.92 (0.112)	7.97 (0.090)
Week 12 Mean (SE)	7.36 (0.132)	7.75 (0.117)
Mean Change from Bsl. (SE)	-0.56 (0.094)	-0.23 (0.080)
Adjusted Change From Baseline		
Mean (SE)	-0.56 (0.089)	-0.22 (0.084)
95% Two-Sided CI	(-0.74, -0.38)	(-0.39, -0.05)
Difference vs Placebo (a)		
Mean (SE) (b)	-0.34 (0.122)	
95% Two-Sided CI	(-0.58, -0.10)	
p-value (*)	0.0063	

The results of this study along with the pharmacodynamic Study 181152 support the use of 2.5 mg twice daily dose of saxagliptin as opposed to 5 mg once daily dosing approved for the saxagliptin mono product.

Safety

There appear to be no safety issues specific to the metformin/saxagliptin combination. Please also see the RMP evaluation and comments below.

Risk management plan

The OPR recommends approval subject to adoption of the RMP. The evaluation noted acute renal and liver injury as of ongoing safety concern. Based on evaluation of sponsor's response to the RMP evaluation, the provision of Studies CV181157 and CV181100 as post marketing condition of registration is supported in respect of these identified risks.

The RMP evaluators also recommend that 'immediate release' be printed on the carton and foil to avoid medication errors. This is supported.

The recommendations with respect to PI are also supported.

The 'Dosage and Administration' section should include a statement that the drug should be taken with meals. This is also supported.

Risk-benefit analysis

Delegate considerations

Conclusion

Overall, the data package supports registration of Kombiglyze fixed dose combination tablets in the three strengths (saxagliptin/metformin 2.5/500, 2.5/850 and 2.5/1000 mg) for the indication:

> *"As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate."*

The proposed doing instructions are also supported.

The sponsor is also asked to provide updated PI (using initial PI included at the time of submission as the base document) incorporating all recommendations from various evaluation areas of the TGA or annotated comments where a recommendation is not implemented.

Furthermore, in clinical trials section immediately following the statement that Kombiglyze has not been studied in clinical trials, a description of the Study 181080

should be included noting that the use of 2.5 mg saxagliptin dosing is limited this study and that twice daily and once daily dosing have not been directly compared in an efficacy study.

It is also recommended that results of the bioequivalence studies in tabular format be included in the Pharmacokinetic section of the PI.

The source of metformin pharmacokinetic data in children and adolescents on page 8 of the proposed PI is not clear and is not relevant to this FDC and should be removed.

The sponsor is also requested to include a Consumer Medicine Information (CMI) in its pre ACPM response.

Request for ACPM advice

In addition to the advice on overall adequacy of the data package and advice on any issue on which the ACPM may wish to comment, the ACPM was asked advice with respect to the following:

- The indication as proposed above is consistent with the current approval of saxagliptin mono product and as well as the additional data in the present submission.

  Does the ACPM consider it appropriate that an explicit statement be included that use in a wider spectrum, that is, triple combination (except basal insulin/metformin/saxagliptin) is not intended?

- With respect to use with intermediate or long acting (basal) insulin or premixed insulin, the approval for saxagliptin mono product includes a qualifying statement with the indication that use with short acting insulin (bolus:basal regimen) was not studied. For the FDC this information is included in the clinical trials section within the description of the relevant clinical trial.

  Does the ACPM consider this as sufficient risk control strategy in relation to this aspect of use?

- The use of this FDC involves a change from the existing approved dosage of saxagliptin (Onglyza) 5mg once daily in the morning in dual combination with metformin (in any dosage form) to a regimen of 2.5 mg twice daily in fixed combination with metformin (500, 850 or 1000 mg twice daily). In healthy adults, the pharmacodynamic (study CV181152) response to saxagliptin was not altered by change from once daily 5 mg dosing in the morning to 2.5 mg twice daily dosing of the FDC. This is further supported by a 12 week, placebo controlled, clinical efficacy study (181080). Note the submission did not include a study directly comparing once (5 mg) and twice daily (2.5 mg) treatment regimens. In terms of clinical management, it is expected that lower dose 2.5 mg combination with a range of metformin doses will be found useful.

  The ACPM is requested to provide advice on the clinical rationale and the adequacy of data supporting the use of 2.5 mg twice daily dosing of saxagliptin in fixed combination with metformin as opposed to 5 mg once daily dosing approved for the mono product.

  The sponsor is also asked to inform whether any clinical efficacy studies comparing once and twice daily saxagliptin dosing have been performed. If available, these will need review before decision and finalisation of this submission.

- As discussed in the clinical evaluation report, the data support addition of saxagliptin to existing metformin therapy and saxagliptin (with or without metformin) to existing basal insulin. Initial use of saxagliptin as a single agent is not approved. A clinical scenario may be that of starting insulin in patients who fail on this FDC. This would not be supported by the data in this submission implying that FDC should be ceased before insulin is introduced. In the event of insufficient control on insulin, the FDC may be

reintroduced. This issue of hierarchy of treatment is common to submissions of anti diabetic agents and the general approach is that such instructions be left to the relevant clinical management guidelines.

The ACPM is requested to provide advice regarding instruction for hierarchy of treatment in the PI.

- The RMP evaluators have raised the issue of medication errors and recommended alternative name or addition of immediate release on the product label (carton and foil). The latter recommendation is supported. Note that a submission to register fixed dose combination of immediate release saxagliptin (5 mg) with sustained release metformin (500, 850, 1000 mg) is currently under review.

Response from Sponsor

Introduction

The sponsor acknowledges the recommendation of the clinical evaluator and the Delegate that the submission package supports registration of the Kombiglyze FDC as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate. The sponsor also noted the endorsement of the OPR for a satisfactory RMP submitted with this application. The sponsor sought to take the opportunity to provide additional comments in relation to the Delegate's specific request for ACPM advice.

Appropriate utilisation of the FDC (requests 1 and 2)

The Delegate noted that the proposed indication is consistent with the current approval of the saxagliptin mono product as well as the additional data in the present submission. With respect to the question as to whether it would be appropriate to include an explicit statement that use in a wider spectrum is not intended, the sponsor considers that the proposed Kombiglyze PI provides adequate guidance to the prescriber regarding the suitable use of the FDC of saxagliptin and metformin. The proposed PI summarises data from clinical trials supporting the proposed use consistent with the approved saxagliptin mono product PI while excluding data from clinical trials where the FDC is not suitable for use, such as saxagliptin as add on therapy to a sulfonylurea (SU) or a thiazolidinedione. Furthermore, given the lack of approval for combination use of saxaglipitin as triple therapy with another anti diabetic medication such as a SU, the sponsor believes it unlikely that physicians unfamiliar with saxagliptin and its combined use with metformin would use the FDC in combination with another anti diabetic medication.

The Delegate noted the PI for the saxagliptin mono product includes a qualifying statement with the indication that use with short acting insulin (bolus:basal regimen) was not studied and that this information is included in the Clinical Trials section of the PI for the Kombiglyze FDC. With respect to the Delegate's comment whether this action provides sufficient risk control in relation to this aspect of use, the sponsor proposes that the 'Dosage and Administration' section of the PI for the FDC be amended to contain specific dosing instructions for patients with inadequate glycaemic control obtained with premixed or basal insulin with metformin and also to include the following statement:

> *"Kombiglyze has not been studied in a regimen combining intermediate or long-acting insulin with mealtime bolus doses of short acting insulin (basal:bolus regimens), and its efficacy in this context has not been established."*

The sponsor considers that these revisions to the 'Dosage and Administration' section, along with the addition of the summary of add on combination therapy with insulin (with or without metformin) in the Clinical Trials section of the PI, provide sufficient risk control to ensure the appropriate use of the FDC with insulin (that is, premixed and basal insulin).

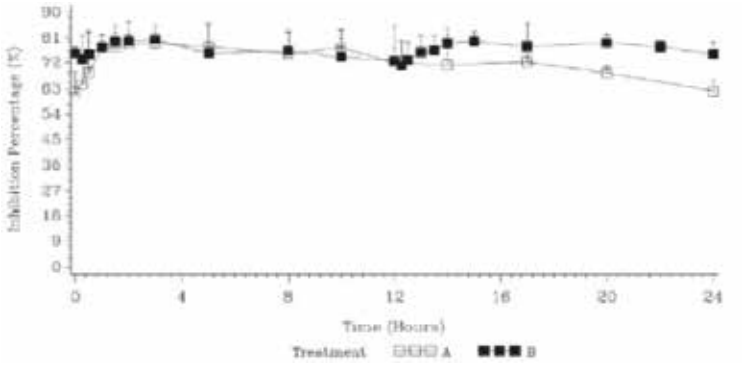
The 'Dosage and Administration' section of the PI will also include dosing instructions for the FDC in all approved indications for concomitant administration of saxagliptin and metformin. Consequently, the sponsor considers that the PI is appropriate and requires no additional statements to prevent use of the FDC in a wider setting than intended. A copy of the amended PI is included as part of the pre ACPM response.

Saxagliptin 2.5 mg BID versus 5 mg QD dosing (request 3)

The Delegate requested that the sponsor identify any clinical efficacy studies comparing the saxagliptin 2.5 mg BID and 5 mg QD dosing regimens. The sponsor confirms that there are no head to head clinical efficacy studies comparing these two dosing regimens but believes Study CV181152 to be an acceptable alternative.

The sponsor undertook the formal bioequivalence Study CV181152 to confirm the comparability of the saxagliptin 2.5 mg BID and 5 mg QD regimens. Pharmacokinetic results confirmed that the daily steady-state exposure (AUC_{0-24}) of saxagliptin after administration of 2.5 mg BID was bioequivalent to that after administration of the 5 mg QD dose. Additionally, pharmacodynamic results showed that inhibition of DPP-4 activity by the 2.5 mg BID saxagliptin dose was equivalent to that of the 5 mg QD saxagliptin dose, resulting in equivalent elevations of post prandial plasma intact glucagon like peptide-1 (iGLP-1) activity for both regimens. The effects of 2.5 mg BID and 5 mg QD on DPP-4 and iGLP-1 activity were comparable. Results for inhibition of DPP-4 activity are reproduced in Figure 5.

Figure 5: Percentage of DPP4 inhibition over time.



BID twice daily; DPP4 dipeptidyl peptidase 4; QD once daily.
Treatment A: 5 mg saxagliptin tablet administered QD for 7 days.
Treatment B: 2.5 mg saxagliptin tablet administered BID for 7 days.
The percentage of DPP4 inhibition was determined over 24 hours after drug administration on the morning of Day 7.

The findings of the TGA's clinical evaluation report support Study CV181152 in demonstrating the equivalence of saxagliptin 5 mg QD + metformin to saxagliptin 2.5 mg BID + metformin, stating

> *"The pharmacodynamic response to the saxagliptin component of the FDC is not altered, in healthy adults, by the change from once daily 5 mg administration in the morning to the 2.5 mg twice daily dosing of the FDC product"*

and that

> *"Response as measured by total DPP-4 inhibition and resultant enhancement of GLP-1 secretion over the 24 hour dosing interval is unchanged".*

Concerning the transferability of the results from healthy adults examined in Study CV181152 to the target patient population, the clinical evaluation report states

> *"Although demonstrated in healthy adults, it is reasonable to extrapolate this comparison of the once and twice daily regimens to the therapeutic situation in T2DM".*

The results from Study CV181152 are supported by the results of Study CV181080, which achieved its primary objective of demonstrating that the 2.5 mg BID regimen of saxagliptin produced a statistically significant reduction in HbA1c compared to placebo. This result was noted by the clinical evaluator who states that

> *"the submission provides adequate evidence (Study 080) that there is an additional effect compared to metformin alone, in terms of reduction of HbA1c".*

While the magnitude of the placebo response was higher than anticipated, the change from baseline in HbA1c in Study CV181080 (-0.56%) was similar to that at Week 12 in other randomised controlled trials with saxagliptin as add-on to metformin (-0.74 in Study CV181014 [dose ranging trial], -0.61 in Study D1680C00001 [head to head versus glipizide trial], and -0.46 in Study D1680C00002 [head to head versus sitagliptin trial]. Furthermore, treatment with saxagliptin 2.5 mg BID was also clinically relevant, as the percentage of individuals achieving an HbA1c <7% in Study CV181080 (39%) was similar to that in Studies CV81014, Study D1680C00001, and Study D1680C00002 (33% to 44%).

The sponsor considers that the results of Study CV181152, supported by the results of Study CV181080, provide evidence that there will be no difference in clinical practice between the efficacy and safety of saxagliptin 2.5 mg BID + metformin compared to saxagliptin 5 mg QD + metformin.

Hierarchy of treatment (request 4)

The Delegate noted the issue of hierarchy of treatment is common to submissions of anti diabetic agents and the general approach is that such instructions be left to the relevant clinical management guidelines. The sponsor believes that there are two aspects that need be considered in relation to the Delegate's request.

PI versus clinical guidelines

The sponsor has concerns that the introduction of specific instructions included in the Kombiglyze PI may cause confusion should the provided information be contrary to clinical guidelines. Clinical management guidelines are developed over time and evolve as experience with a disease state and therapeutic options are evaluated and assessed with the benefit of experience gained outside the context of a clinical trial setting. Any specific instructions regarding the hierarchy of treatment in the Kombiglyze PI could become obsolete and even contrary to best clinical practice. Consequently, the sponsor considers that the information provided in the 'Clinical Trials' and 'Dosage and Administration' sections of the Kombiglyze PI is adequate for ensuring the safe and appropriate use of the FDC in combination with insulin.

Clinical trial design versus clinical practice

The Delegate suggested that the design of the trial conducted using saxagliptin and metformin with insulin does not necessarily support the addition of insulin to the treatment regimen in patients having insufficient control with the FDC alone. However, the design of the trial assessing the use with insulin is in compliance with EU guidance currently adopted by TGA. This guideline[10] states:

[10] European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP): Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus (CPMP/EWP/1080/00)", 30 May 2002, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003262.pdf>.

> *"Regarding **combination with insulin**, efficacy on glycaemic control should be documented vs placebo, ie. insulin alone. Studies should be carried out in patients already treated with insulin for a time sufficient ensure that HbA1c levels are stable before the test drug is added to insulin (ie. at least 2-3 months). The insulin dose will be maintained unchanged as far as possible during the double blind period (unless necessary for safety reasons), and the efficacy will primarily be evaluated on the evolution of HbA1c."*

The guideline further states that

> *"A comparative evaluation versus the combination of insulin plus an oral antidiabetic currently licensed in this indication may be required."*

The sponsor agrees that in a strict interpretation of the study design guidance for the investigation to determine the efficacy and safety of saxagliptin and metformin in combination with insulin, the use of the FDC as add on to insulin is problematic given usual clinical practice/hierarchy of treatment. However, in recognition of the difficulties in conducting trials of other agents in patients requiring insulin, the current (but not TGA adopted) EU guideline[11] proposes a trial design consistent with Study CV181057 conducted by the sponsor and which is considered appropriate for supporting an indication of 'combination with insulin'. In view of the current TGA adopted EU guideline and the approach described in the revised document (although not yet adopted by TGA), the sponsor considers that a general 'in combination' indication is supported by the trial conducted. Consequently, the trial conducted would appear to address the Delegate's concern regarding the hierarchy for utilisation of the FDC with insulin, and therefore specific clinical guidance need not be set out in the PI document.

> *"Combination therapy of glucose lowering agents with insulin may occur in different clinical situations and patient populations. Most frequently, insulin therapy is introduced in patients inadequately controlled on other glucose lowering agents. In this case, some or all of the previous agents may be discontinued and insulin is initiated. Less frequently, patients already receiving insulin may benefit from adding another glucose lowering agent. Reasons for such consideration may be frequent and especially severe hypoglycaemic events preventing the desired level of glycaemic control or insulin induced weight gain in already obese patients. Overall, the most frequently used combination is insulin plus metformin.*
>
> *Even though a study in which insulin is initiated in patients not reaching glycaemic control with the test agent (alone or in combination with another glucose lowering agent, most likely metformin) would reflect the most common clinical scenario, it is not expected to provide relevant data on the effect of the test drug in this setting. However, relevant safety information on the combined use of the test agent and insulin may be gained from such a study and may be reflected in the PI.*
>
> *For appropriate evaluation of both safety and efficacy of the test compound in combination with insulin, the test agent should be added in patients with type 2 diabetes inadequately controlled on a reasonable dose of insulin as single therapy or in combination with another glucose lowering agent, typically metformin or both, if stratified. Treatment groups should be balanced with respect to insulin regimens (for example, basal only versus basal bolus regimen). In order to support a general claim "combination therapy with insulin", the study population should represent a wide range of BMI and include a substantial percentage of patients with long diabetes*

[11] European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)", 14 May 2012, Web, accessed 10 September 2013 <www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129256.pdf>.

duration (for example ≥ 10 year) and elderly patients to adequately reflect the whole target population."

The sponsor considers that the information provided in the 'Clinical Trials' and 'Dosage and Administration' sections of the Kombiglyze PI is adequate for ensuring the safe and appropriate use of the FDC in combination with insulin.

Amendments to carton labels (request 5)

The Delegate noted that RMP evaluators raised the issue of medication errors and recommended an alternative name or the addition of 'immediate release' on the product label. The sponsor considers that the potential for medication errors is minimal; therefore, the addition of a proposed trade name or 'immediate release' to the product label (carton and foil) is not necessary. The RMP evaluator also raised concerns of potential confusion with the product proposed for registration in Australia with products registered in other jurisdictions (Komboglyze in Europe and Canada, Kombiglyze XR in the US). The sponsor considers the probability of any such errors to be extremely low, and the trade name proposed is suitable for use when considered in the context of the trade names of other products registered for use in Australia.

The sponsor also considers the request for the inclusion of 'immediate release' on the carton to be inconsistent with the TGA requirements outlined in Therapeutic Goods Order No. 69 "General requirements for labels for medicines" (TGO 69) (April 2009) and the "Best practice guideline on prescription medicine labelling" (January 2011). The TGO 69 requirement for the labelling of products is to include the 'name of the dosage form' as a word or words denoting the usual name of the dosage form, in this instance 'tablets' as per the Australian Approved Names List. Differentiation of dosage forms is usually reserved for tablets that exhibit certain characteristic such as dispersible, enteric coated, modified release formulations using the appropriate term from the Australian Approved Names List. However, there is no Australian approved term for 'immediate release' tablets other than tablets.

The sponsor acknowledges that an application is currently under review by TGA for a modified release formulation of saxagliptin and metformin with the currently proposed trade name of Kombiglyze XR. Given that the Kombiglyze XR application is under review, the sponsor believes that the proposal to include 'immediate release' on the label has the potential to cause confusion in the absence of a modified release formulation, as per the usual practice of TGA to differentiate by use of a term such as 'modified release' as described above.

Conclusion

The sponsor notes the recommendations of the Clinical Evaluator and Delegate that the submission supports registration of the proposed FDC of saxagliptin and metformin, and considers that the proposed Indication and PI provide appropriate guidance to ensure the safe and appropriate use of Kombiglyze.

Advisory Committee considerations

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered these products to have an overall positive benefit-risk profile for the indication as proposed:

As an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.

The proposed dosing instructions are also supported.

Proposed amendments to the PI/CMI

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI and specifically advised on the inclusion of the following:

- a statement in the 'Precautions' and 'Contraindications' section of the PI clarify the renal function contraindication which is not in line with Australian Prescriber advice, standard clinical practice, or international guidelines.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of:

- **Kombiglyze 2.5/1000** saxagliptin (as hydrochloride)/metformin hydrochloride 2.5 mg/1000 mg immediate-release film-coated tablet blister
- **Kombiglyze 2.5/500** saxagliptin (as hydrochloride)/metformin hydrochloride 2.5 mg/500 mg immediate-release film-coated tablet blister
- **Kombiglyze 2.5/850** saxagliptin (as hydrochloride)/metformin hydrochloride 2.5 mg/850 mg immediate-release film-coated tablet blister

indicated for:

> *Kombiglyze is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both saxagliptin and metformin is appropriate.*

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the Kombiglyze (saxagliptin/metformin) 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg tablets RMP, identified as EU-RMP Version 2 (dated 8 December 2011) and Australian Risk Management Activities (dated 26 March 2012), and any subsequent revisions as agreed with the TGA and its OPR.

Attachment 1. Product Information

The Product Information approved at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

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