Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Linagliptin / Metformin HCl

Proprietary Product Name: Trajentamet

Sponsor: Boehringer Ingelheim Pty Ltd

September 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

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT)
ANCOVA	Analysis of covariance
ANOVA	analysis of variance
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate transaminase (SGOT)
AUEC	Area under the glucose concentration curve
BI1356	Linagliptin
BID	Administered twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)
BP	Blood pressure
CD1750	The major metabolite of linagliptin
CI	Confidence interval
CK	Creatinine kinase
Cl	Chloride

Abbreviation	Meaning
Cmax	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRP	C-reactive protein
CYP	Cytochrome P 450
DPP-4	Dipeptidyl-Peptidase IV
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GI	Gastrointestinal
GIP	Gastric inhibitory polypeptide
GLDH	Glutamate Dehydrogenase
Glim	Glimepiride
GLP-1	Glucagon-like peptide 1
gMean	geometric mean
HbA1c	Glycosylated haemoglobin A1c
HOMA	Homeostasis model assessment
HR	Heart rate
ICH	International Committee on Harmonisation
INR	International normalised ratio
IRB	Institutional Review Board
ISR	Insulin secretion rate
IVRS/IWRS	Interactive voice/web response system

Abbreviation	Meaning
LDH	Lactic dehydrogenase
Lina	Linagliptin
LLN	Lower limit of normal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
Met	Metformin
MI	Myocardial infarction
MTT	Meal tolerance test
N	Number
NONS	Non-switched set
OAD	Oral antidiabetic agent
OC	Observed cases
OLS	Open-label arm of study
OR	Odds ratio
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	per oral
PPG	Post -prandial glucose
PPS	Per protocol set
RS	Randomised set
SAE	Serious adverse event
SAF-Cx	Safety grouping from the linagliptin/metformin FDC dossier
SAF-M1	Updated safety grouping from the original linagliptin monotherapy dossier
SAF-x	Safety grouping from the original linagliptin monotherapy dossier
SC	Subcutaneous

Abbreviation	Meaning
SU	Sulphonylurea
SWS	Switched Set
T2DM	T2DM
TIA	Transient ischaemic attack
TS	Treated Set
t1/2	Terminal half-life of the analyte in plasma
Tmax	Time from dosing to the maximum concentration of the analyte in plasma
Tmin	Time from dosing to the minimum concentration of the analyte in plasma
ULN	Upper limit of normal
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New Fixed Combination
Decision:	Approved
Date of decision:	14 May 2013
Active ingredients:	Linagliptin/Metformin HCl
Product names:	Trajentamet[1]
Sponsor's name and address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Rd, North Ryde, NSW 2113
Dose form:	Film coated tablets
Strengths:	Linagliptin/metformin hydrochloride 2.5/500 mg, 2.5/850 mg and 2.5/1000 mg
Containers:	Blisters (PVC/PCTFE-Aclar/Al) and bottles (HDPE)[2]
Pack sizes:	Blister packs containing 10, 14, 28, 30, 56, 60, 84, 90, 98, 100 and 120 tablets. HDPE bottles containing 14, 60 and 180 tablets.
Approved therapeutic use:	*Trajentamet is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or those already being treated and well controlled with the free combination of linagliptin and metformin.* *Trajentamet is indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.*
Route of administration:	Oral (PO)
Dosage:	Twice daily with meals
ARTG Numbers:	AUST R 195088, 195100, 195101, 195106, 195107and 195090.

[1] In the sponsor's pre-Advisory Committee on Prescription Medicines (ACPM) response dated 18 March 2013, the sponsor sought only to adopt the trade name: Trajentamet® as the primary trade name from the original submission and withdraw the tradenames: Trajenta Duo®; Jentaduo®; Jentadueto®; Trametfo® and Thundrion®.
[2] PVC=Polyvinyl chloride; PCTFE= A fluoropolymer is a fluorocarbon based polymer with multiple strong carbon–fluorine bonds. It is characterized by a high resistance; Al=aluminium; HDPE=High-density polyethylene.

Product background

Linagliptin is a selective orally administered DPP-4 inhibitor that acts to lower blood glucose by extending the half-life of glucagon-like peptide 1 (GLP-1). GLP-1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion, and is associated with slowing of gastric emptying. It is approved for combination use with metformin in Australia.

Metformin hydrochloride is a well established biguanide and hypoglycaemic agent and is registered as 500 mg, 850 mg and1000 mg tablets by a number of Australian sponsors, including the innovator company Alphapharm Pty Ltd. The Australian innovator brand name is 'Glucophage' for the 500 and 850 mg tablets and 'Diabex' for the 1000 mg strength.

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd to register a fixed-dose combination tablet containing the two antihyperglycaemic agents; linagliptin and metformin.

The proposed indications for the fixed dose combination of linagliptin and metformin are:

> *Trajentamet is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or in those already being treated and well controlled with the free combination of linagliptin and metformin.*
>
> *Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

Linagliptin (as Trajenta) is currently approved for use in free combination with metformin for a similar indication and in a triple free combination with a sulfonylurea.

Three strengths are proposed for Trajentamet. The maximum proposed daily dose of Trajentamet is 5 mg of linagliptin and 2000 mg of metformin hydrochloride. These daily doses are currently approved for the individual components. While metformin hydrochloride is currently registered for twice daily dosing, linagliptin is only registered as a once daily treatment. This is unlikely to alter the toxicity assessment of linagliptin made previously (see *III. Nonclinical Findings*; *Toxicity* below).

Other drugs (sitagliptin, vildagliptin, saxagliptin) in the same class are approved for use as dual and triple therapy with specified other oral antidiabetic agents. Fixed dose combinations with metformin are registered in Australia for sitagliptin and vildagliptin.

Regulatory status

Linagliptin (tablets 5 mg as Trajenta®) was approved by the TGA on 21 October 2011 for use at a dose of 5 mg once daily (QD) in

> *Adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylureas or metformin plus sulphonylureas.*

The international regulatory status of this product is summarised below.

Table 1. International regulatory status.

Country	Submission Date Status	Approved Indication
European Union (EU) Centralised Procedure	1 July 2010 Approved 20 July 2012	*Jentadueto is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin.* *Jentadueto is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea*
USA	19 January 2011 Approved 30 January 2012	*Jentadueto® is a dipeptidyl peptidase-4 (DPP-4) inhibitor and biguanide combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate*
Switzerland	30 August 2011 Approved 05 October 2012	*Jentadueto is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients with type II Diabetes mellitus inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin.* *Jentadueto is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

Product Information

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

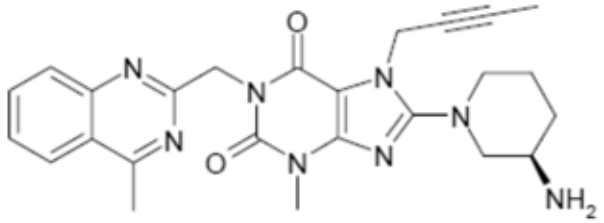
II. Quality findings

Drug substances (active ingredients)

Linagliptin

Linagliptin is made by chemical synthesis. It has one chiral centre and is presented as a single (R) enantiomer (See Figure 1). Linagliptin solubility is high. The drug substance is milled. There is limited particle size control. Particle size does not significantly affect tablet dissolution. Impurity controls are acceptable.

Figure 1. Linagliptin structure

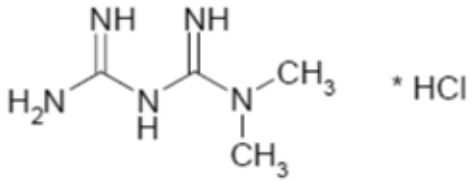


Metformin hydrochloride

Metformin hydrochloride (structure shown below) is a white to off-white powder that is freely soluble in water. It has no chiral centres and no polymorphic forms of the drug substance are known.

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

Figure 2. Metformin HCl structure



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. They are manufactured using conventional fluid bed granulation, compression and film-coating processes.

The different strengths are not direct scales but the excipients used in their manufacture are all substances that are commonly used in pharmaceutical formulations. Arginine is included in the formulation as a stabiliser.

The specifications include tests and limits that adequately control: appearance; loss on drying and arginine assay. In addition, for each of the active ingredients limits are included for assay (including uniformity), degradation products and dissolution.

Upon storage at 30ºC, an increase was observed in the loss on drying and this was associated with a decrease in the dissolution rate of both drug substances. The changes were more marked for product stored in blisters than in HDPE bottles (with desiccant). For the 2.5/500 mg tablets

(worst case) increases in loss on drying were associated with a drop in dissolution (of both drug substances) of about 10%.

Bioequivalence data (Study 1288.6/U11-1379) were provided which demonstrated that the decrease in dissolution does not influence the product's bioavailability and the expiry dissolution limits for the product are considered sufficient.

The proposed shelf life is 24 months when stored below 30°C, with the added instruction that the product should be protected from moisture. Adequate stability data have been provided to support the proposed shelf-life.

Biopharmaceutics

The following bioavailability and bioequivalence data are considered relevant.

- A study (1288.4/U10-2236) to investigate the relative bioavailability of a 2.5 mg linagliptin and 1000 mg metformin hydrochloride fixed dose tablet administered with and without food. The study revealed that food had no significant effect on the peak plasma concentration (C_{max}) or the area under the plasma concentration time curve (AUC) of linagliptin but reduced the C_{max} of metformin by about 20% (no food-effect was observed for metformin AUC).
- Three crossover studies (1288.1/U10-2278, 1288.2/U10-2276 and 1288.3/U10-2303) designed to assess whether the proposed fixed dose formulations of 2.5 mg/500 mg 2.5 mg /850 mg and 2.5 mg/1000 mg linagliptin/metformin tablets are bioequivalent to free combinations of 2.5 mg linagliptin and 500 mg, 850 mg and 1000 mg metformin hydrochloride comparator products.
- In each case, bioequivalence twixt the fixed dose combination and the single tablets was demonstrated.
- A crossover study (1218.45/U08-2132) conducted to investigate the pharmacokinetics and pharmacodynamics of multiple 5 mg doses of linagliptin tablets given once daily compared to multiple 2.5 mg doses given twice daily. The duration for each of the two treatment periods was 7 days. Bioequivalence twixt the 2 x 2.5 mg and 5 mg doses was demonstrated.
- A study (1288.6/U11-1379) conducted to investigate the relative bioavailability of fast and slow dissolving batches of the proposed 2.5 mg/1000 mg linagliptin/metformin tablets. The fast and slow dissolving batches were shown to be bioequivalent, in support of the expiry dissolution limits.

It should also be noted that the metformin products used in the comparative bioequivalence studies were not from Australia rather they were Glucophage tablets from Germany. Data were provided to shown that the EU Glucophage product is equivalent to the Australian innovator formulations (500 mg and 850 mg Glucophage and 1000 mg Diabex tablets). In line with Appendix 15 (Section 7) of the Australian regulatory Guidelines for Prescription Medicines (ARGPM)[3], the Australian innovator was shown to be qualitatively and quantitatively similar to the overseas reference product. In addition, a bioequivalence study was conducted (1218.47/U09-2346) which showed that in the case of metformin hydrochloride minor formulation differences did not influence bioavailability.

Quality summary and conclusions

This application was not considered by the Pharmaceutical Sub-Committee.

[3] <http://www.tga.gov.au/pdf/pm-argpm-ap15.pdf>

All matters raised with the company have now been satisfactorily addressed.

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

III. Nonclinical findings

Introduction

The nonclinical submission contained new studies assessing the pharmacokinetic and toxicological interactions of linagliptin and metformin in rats, while a previously evaluated study (Study U09-1799-01) assessed the pharmacological interaction of these two agents. All studies were of high quality and were conducted, where appropriate, under Good Laboratory Practice (GLP) conditions. The package of nonclinical studies was in accordance with recommendations in the EU guideline on the non-clinical development of fixed combinations of medicinal products.[4] No major deficiencies were identified in the nonclinical dataset.

Pharmacology

Primary pharmacology

Linagliptin is a DPP-4 inhibitor that is suggested to improve the glycaemic control in patients with type 2 diabetes by enhancing the levels of the active forms of GLP-1 and GIP, which stimulate glucose-dependent insulin secretion. Metformin is a well established antihyperglycaemic agent that lowers both basal and postprandial plasma glucose. The combination of linagliptin with metformin is suggested to have a greater glucose lowering effect than monotherapy with either component at corresponding doses.

In a previously submitted study in diabetic mice, significantly greater glucose tolerance was seen in animals treated with linagliptin and metformin in combination compared with monotherapy with either component (37% reduction in $AUC_{glucose}$ compared to 13–19% reduction with monotherapy). The efficacious dose (1/200 mg/kg/day PO [linagliptin/metformin]) was similar to the intended clinical dose of linagliptin and below or only marginally higher (58–117%) than the various proposed clinical doses of metformin (on a body surface area basis), thus supporting the proposed clinical use.

Pharmacokinetics

In the previous assessment of linagliptin, it was concluded that:

- Linagliptin is unlikely to affect the pharmacokinetics of co-administered drugs (such as metformin) via interactions with CYP450 enzymes or transporters.
- While linagliptin is a substrate for CYP3A4, this is not a major clearance mechanism and therefore inhibitors of this isozyme are unlikely to affect linagliptin exposure.
- Linagliptin is a substrate for P-glycoprotein, so co-administration of an inhibitor or inducer of this transporter may affect linagliptin exposure.

A newly submitted *in vitro* study demonstrated metformin hydrochloride (at ≤100 µM; ~7 times the clinical C_{max} at the maximum recommended human dose) had no significant inhibitory

[4] EMEA/CHMP/SWP/258498/2005; <http://www.tga.gov.au/pdf/euguide/swp25849805final.pdf>

activity against CYP1A1/1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4 or 4A11. These findings further lend support that CYP450 mediated pharmacokinetic drug interactions between linagliptin and metformin are unlikely. A published paper indicated metformin was not a substrate for P-glycoprotein. Therefore, pharmacokinetic drug interactions involving this transporter are unlikely.

Altogether, the *in vitro* data predict a low probability of pharmacokinetic drug interactions between metformin and linagliptin. Consistent with this, no effect on the plasma kinetics of either compound was observed when administered in combination to rats. It is stated in the existing Trajenta product information document that no clinically meaningful changes in the pharmacokinetics of linagliptin or metformin were observed in healthy human volunteers, confirming the predictions based on nonclinical data.

Toxicology

Repeat-dose toxicity studies with the linagliptin/metformin combination of up to 3 months duration were conducted in rats. The duration of the pivotal study and the use of a single species are consistent with the EU guideline on the nonclinical development of fixed combinations of medicinal products.[5] Rats are considered an appropriate species to assess the toxicity of linagliptin (based on pharmacodynamic responsiveness and pharmacokinetic parameters [established in the previous submission]) and have been used previously in studies to assess the toxicity of metformin in combination with another DPP-4 inhibitor (vildagliptin [Galvumet AusPAR[5]]). While the clinical route (PO) was used in all studies, the proposed clinical dosing regimen (twice daily (BID)) was not used; animals were dosed once daily with metformin and linagliptin. This is not expected to alter the interpretation of the results as the clinical dosage regimen of 2.5 mg BID linagliptin was reported to be bioequivalent to 5 mg/day in terms of plasma AUC and once daily animal dosing with metformin has been used to support twice daily clinical dosing. Parallel single-agent control groups were included in the pivotal study to aid in the interpretation of toxicity findings.

The dose ratios of linagliptin/metformin tested in rats (1:200 or 1:400) were selected to match the range of ratios to be used clinically. However, the clinical ratio is with respect to metformin hydrochloride, while in animals it is with respect to metformin base.

No human AUC values following twice daily dosing with 2.5/1000 mg [linagliptin/metformin hydrochloride] fixed-dose combination tablets appear to have been provided in the clinical submission. On the basis of bioequivalence for linagliptin at 5 mg QD compared to 2.5 mg BID and the absence of pharmacokinetic interactions between the pair of drugs (as reported in the Product Information for Trajenta), data for the individual components (158 nM.h for linagliptin Study 1218.2] and 159 μM.h for metformin) have been used in animal: human exposure comparisons (Table 2). Maximum exposures achieved in the pivotal study were 4 and 23 times the clinical exposures to linagliptin and metformin, respectively. The maximum tolerated dose of metformin was exceeded in the submitted studies with premature deaths attributed to metformin. Relative exposure to metformin was significantly greater compared to linagliptin. Given this and the dominant contribution of metformin to toxicity, suitable adjustment of the linagliptin: metformin dose ratios used in rats to achieve more clinically relevant linagliptin: metformin exposure levels would have been desirable.

[5] <http://www.tga.gov.au/pdf/auspar/auspar-galvumet.pdf>

Table 2. Relative exposure in repeat-dose toxicity studies

Species	Study No. & duration	Dose (mg/kg/day)		AUC_{0-24h}		Exposure ratio	
		Linagliptin	Metformin	Linagliptin (nM·h)	Metformin (µM·h)	Linagliptin	Metformin
Rat (Wistar Han)	2 weeks (U09-2246-01)	0	100	–	178	–	1.1
		0	200	–	374	–	2.4
		0	1000	–	2795	–	18
	2 weeks (U09-1632-01)	2.5	500	459	1795	3	11
		5	1000	562	3625	4	23
	2 weeks (U09-2243-01)	0.5	100	139	236	0.9	1.5
		1	200	303	458	2	3
	13 weeks (U10-1492-01) [pivotal]	0.5	100	158	224	1.0	1.4
		2	400	303	1180	2	7
		4	800	327	3615	2	23
		2	800	236	3710	1.5	23
		4	0	361	–	2.3	–
		0	800	–	3595	–	23
Human		[2 × 2.5 mg]	[2 × 780 mg][a]	158	159	–	–

[a] corresponding to 2 × 1000 mg metformin hydrochloride

No drug-related effects were observed in rats that received 4 mg/kg/day PO linagliptin alone for 3 months. Toxicities observed in metformin-treated rats (at ≥400 mg/kg/day PO) were generally similar to those reported previously, with the target organs being the heart (hypertrophy, cytoplasmic vacuolation), mandibular, parotid and sublingual salivary glands (ductular epithelial hypertrophy), kidney (basophilic tubules, hyaline droplets, epithelial pigment storage) and adrenal gland (cortical hypertrophy, cytoplasmic vacuolation). All of these effects appeared to be reversible.

When linagliptin was provided in combination with metformin, the only new histopathological changes observed were slight atrophy of the uterus and minimal to slight mucous hypersecretion of the vaginal epithelium. The NOEL for these changes was 2/400 mg/kg/day [linagliptin/metformin] (at least twice the clinical exposure). These changes are consistent with mild oestrus cycle/hormonal disruption, possibly occurring secondary to effects on body weight or otherwise representing non-specific toxicity, and are not expected to be of clinical concern. Greater suppression of body weight gain was seen with the combination of linagliptin and metformin than either agent alone, and this was considered to be an additive pharmacodynamic effect.

The NOAEL for the linagliptin/metformin combination in the pivotal study was 0.5/100 mg/kg/day PO, resulting in exposures approximately equivalent to that expected clinically for each agent at the maximum recommended human dose.

Reproductive toxicity

An embryofetal development study was conducted in rats with the linagliptin/metformin combination. Parallel single-agent control groups were included in this study. An embryofetal development toxicity study in rats with metformin was also submitted, while previously evaluated embryofetal toxicity studies with linagliptin were used as a reference. As with the repeat-dose toxicity studies, dose ratios of 1:200 and 1:400 linagliptin/metformin were used. The maximum exposures achieved were up to 4- and 30 times higher than that expected clinically for linagliptin and metformin, respectively (Table 3).

Table 3. Relative exposure in embryofetal toxicity studies in rats

Species	Study	Dose (mg/kg/day)		AUC_{0-24h}		Exposure ratio	
		Linagliptin	Metformin	Linagliptin (nM·h)	Metformin (µM·h)	Linagliptin	Metformin
Rat (Wistar Han)	U10-2386-01	0	200	–	638	–	4
		0	500	–	1730	–	11
		0	1000	–	3690	–	23
	U10-2448-01	1	200	238	528	1.5	3
		2.5	500	347	1510	2	9
		5	1000	618	4810	4	30
		2.5	1000	347	3830	2	24
		5	0	470	–	3	–
		0	1000	–	3670	–	23
Human		[2×2.5 mg]	[2×780 mg][a]	158	159	–	–

[a] corresponding to 2 × 1000 mg metformin hydrochloride

An increased incidence of fetal damage (delayed ossification, anophthalmia, polydactylia and skeletal malformations of bones of the rib, sternebra and scapula) was seen in litters from dams treated with ≥500 mg/kg/day PO metformin. The combination of linagliptin with metformin did not induce any new fetal findings and did not appear to significantly increase the incidence of fetal damage. Therefore, the adverse fetal effects seen in the combination study are attributable solely to metformin, and these may be associated with alterations in maternal blood glucose levels. The No Observable Adverse Effect Level (NOAEL) for embryofetal toxicity was 1/200 mg/kg/day PO [linagliptin/metformin], resulting in exposures 1.5 and 3 times higher than that expected clinically for linagliptin and metformin, respectively, at the maximum recommended human dose.

Pregnancy classification

The sponsor has proposed Category B3[6], which is the current pregnancy category for linagliptin. Given the adverse fetal effects observed with the linagliptin/metformin combination in rats, Category C[7] would be more appropriate. This is the current pregnancy category for metformin.

Impurities

One linagliptin related degradant was specified at a level above the applicable International Conference on Harmonization (ICH) qualification threshold in the drug product. The proposed expiry limit has been adequately qualified by submitted toxicology data. However, the proposed limit should be based foremost on available batch and stability data.

Paediatric use

Trajentamet was not proposed for paediatric use and no specific studies in juvenile animals were submitted.

Nonclinical summary and conclusions

- In diabetic mice, linagliptin and metformin in combination had a greater glucose lowering effect than monotherapy. The efficacious dose was similar to the intended clinical dose of linagliptin and comparable or lower than the proposed clinical doses of metformin (on a body surface area basis), supporting the proposed clinical use.
- *In vitro* data predict a low probability of pharmacokinetic drug interactions between metformin and linagliptin. No pharmacokinetic interactions were observed in rats with co-administration.
- Repeat-dose toxicity studies of up to 3 months duration and an embryofetal toxicity study in rats revealed no novel or exacerbated toxicity of clinical relevance with the linagliptin/metformin combination. The majority of the toxicities were attributable to metformin.
- There are no objections on nonclinical grounds to the registration of Trajentamet. The proposed indication includes concomitant use with a sulfonylurea (that is, triple therapy). No nonclinical data were provided that addressed potential pharmacological, pharmacokinetic or toxicological interactions of linagliptin/metformin with a sulfonylurea. This triple free combination is already approved in Australia, and it was considered to be acceptable for support for triple therapy to rely solely on clinical data.
- Amendments to the draft Product Information were recommended but these are beyond the scope of this AusPAR.

[6] Category B3
Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

[7] Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted 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

Clinical rationale

More than 50% of Australians are overweight or obese and at least 4% of the population are known to have T2DM. The prevalence is much higher in the indigenous population. Three diabetics in five have cardiovascular disease, in particular coronary artery disease, and microvascular complications resulting in nephropathy, neuropathy and retinopathy. However, long-term intervention studies such as the UK PDS in T2DMs[8] and the DCCT in type 1 diabetes[9] have shown that outcomes such as retinopathy and nephropathy occur less frequently in patients with optimal glycaemic control.

Diabetes is the result of a complex metabolic dysfunction involving insulin resistance, impaired insulin secretion and increased glucose production. Linagliptin and other Dipeptidyl-Peptidase IV (DPP-4) inhibitors[10] lower blood glucose by extending the circulating half-life of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Both hormones increase insulin production and secretion and lower plasma glucose after a meal by enhancing glucose-stimulated insulin release, and by limiting glucagon secretion which slows gastric emptying and increases satiety. However, the risk of hypoglycaemia is low because GLP-1 and GIP activity cease when plasma glucose levels approach the lower limit of normal. GLP-1 also reduces hepatic glucose output by reducing glucagon secretion from islet alpha-cells. Furthermore, in animal models islet beta-cell function is conserved although this has not been confirmed in man.

Metformin is a biguanide which has been in clinical use for 50 years.[11] It lowers basal and postprandial glucose but it does not stimulate insulin secretion. It is thought to act by inhibiting hepatic gluconeogenesis and glycogenolysis, increasing glucose uptake in muscle and delaying intestinal glucose absorption. It reduces glycosylated HbA1c but it does not cause weight gain or hypoglycaemia. It also reduces total cholesterol, low-density lipoprotein (LDL) and triglycerides independently of glucose control.

Diabetes is progressive and patients who initially respond to one OAD often require combination therapy with two or three Oral antidiabetic agent (OAD) and/or insulin. The combination of linagliptin and metformin reduces fasting plasma glucose (FPG) and HbA1c more than either component alone. A fixed dose combination (FDC) decreases the daily number of medications and may be expected to improve compliance in patients treated with oral antidiabetic agents.[12] It is proposed that the FDC be used alone or in combination with a sulphonylurea if required.

[8] UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352, 837-853
[9] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14), 977-986
[10] Elrishi MA, et al. The dipeptidyl-peptidase-4 (DPP-4) inhibitors: a new class of oral therapy for patients with T2DM. Pract Diabetes Int 2007; 24 (9), 474-482
[11] Davidson MB, Peters AL. An overview of metformin in the treatment of T2DM. Am J Med 1997; 102(1), 99-110
[12] Melikian C, et al. Adherence to oral antidiabetic therapy in a managed care organisation: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002; 24(3), 460-467

Scope of the clinical dossier

The submission contained the following clinical information:

- Seven clinical pharmacology studies, including 7 that provided pharmacokinetic data and 1 that provided pharmacodynamic data. No population pharmacokinetic analyses.
- One dose ranging study (1218.6), a pivotal Phase III efficacy and safety study (1218-46) and 4 supporting studies.

Paediatric data

The submission did not include paediatric data.

Good clinical practice (GCP)

All studies were conducted in accordance with International Conference on Harmonization (ICH) GCP.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 4 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

Table 4. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose - Multi-dose	 ND ND	 - -
	Bioequivalence† - Single dose	Study 1288.1 Study 1288.2 Study 1288.3 Study 1288.6	Bioequivalence of a 2.5 mg linagliptin/1000 mg Metformin FDC tablet compared with single tablets of Linagliptin 2.5 mg and metformin 1000 mg Bioequivalence of a 2.5 mg linagliptin/500 mg metformin FDC tablet compared to free combination of linagliptin 2.5 mg and metformin 500 mg tablets. Bioequivalence of a 2.5 mg linagliptin/850 mg metformin FDC tablet compared to co-administration of free linagliptin 2.5 mg and metformin 850 mg tablets. Relative bioavailability of two different batches of a 2.5 mg linagliptin/1000 mg metformin FDC tablets

PK topic	Subtopic	Study ID	*
		Study 1218.57	Bioequivalence of BMS Glucophage® tablets and Merck Glucophage® tablets in the strengths of 1000 mg and 500 mg.
	Food effect	Study 1288.4	Investigate the effect of food on the relative bioavailability of a 2.5 mg linagliptin+1000 mg metformin FDC tablet.
PK in special populations	Target population § -Single dose - Multi-dose	ND ND	- -
	Hepatic impairment	ND	-
	Renal impairment	ND	-
	Neonates/infants/children/adolescents	ND	-
	Elderly	ND	-
	Afro-American	Study 1218.55	Investigate the PK of 5 mg Linagliptin administered orally in patients with T2DM of African American origin.
Genetic/gender-related PK	Males vs. females	ND	-
PK interactions	ND	ND	-
Population PK analyses	Healthy subjects	ND	-
	Target population	ND	-
	Other	ND	-

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ND No new data was provided by the sponsor.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacokinetics

All three dosage strengths of the FDC formulation (2.5 mg linagliptin/1000 mg Metformin FDC tablet, 2.5 mg linagliptin/500 mg metformin FDC and 2.5 mg linagliptin/850 mg metformin FDC tablets) were bioequivalent with the relevant doses of free tablets of linagliptin and metformin, which were produced by BI Pharma and Merck, respectively. Across all three studies, the 90% CIs for linagliptin AUC and C_{max} ranged from 97 to 110 and 94 to 102, respectively, whereas, for metformin AUC and C_{max} the 90% CIs ranged from 96 to 107 and 94 to 109, respectively. In addition, the US (BMS) and European (Merck) formulations of the free metformin tablets were bioequivalent.

A high fat, high caloric meal had little effect on Linagliptin AUC and C_{max} and the AUC of Metformin, whereas, it prolonged metformin T_{max} by about 2 h and lowered the Metformin C_{max} by about 18.1%.

In Afro-American subjects with T2DM the T_{max} following 5 mg oral linagliptin was 1.5 h and at steady state the $AUC_{\tau,ss}$ was 194 nmol.h/L and $C_{max,ss}$ was 16.4 nmol/L.

In 8 Caucasian men, aged 42 to 64 years, with Type 2 diabetes (Study 1218.2) the corresponding values were 1.5 hours, 74.7 ng.h/ml (158 nmol.h/L) and 5.24 ng/mL (11.1 nmol/L), respectively, possibly indicating that the AUC_{ss} and $C_{max,ss}$ were approximately 23% and 48% higher, respectively, in Afro-American subjects compared to Caucasians.

The accumulation factors at steady state in these subjects were 1.40 and 1.49 for linagliptin AUC and C_{max}, respectively; however, no studies have examined the BE of the free and FDC tablet combinations at steady-state.

No studies have examined the drug-drug interactions between the proposed FDC tablets with other drugs.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 5 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 5. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	ND	ND	-
Secondary Pharmacology	ND	ND	-
Gender other genetic and Age-Related Differences in PD Response	Effect of race	Study 1218.55	To investigate the PD linagliptin in patients with T2DM of African American origin.
PD Interactions	ND	ND	-
Population PD and PK-PD analyses	Healthy subjects	ND	-
	Target population	ND	-

* Indicates the primary aim of the study.§ Subjects who would be eligible to receive the drug if approved for the proposed indication.‡ And adolescents if applicable. ND No new data provided by the sponsor.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

Evaluator's overall conclusions on pharmacodynamics

Only one new study (as summarised below) examined the PD of the proposed FDC formulation.

In Afro-American subjects with Type II diabetes mellitus inhibition of plasma DPP-4 activity correlated with linagliptin plasma concentrations.

In these subjects at steady-state, the E_{24} and E_{ss} of plasma DPP-4 inhibition was 75% and 85%, respectively. By comparison in Caucasian subjects (Study 1218.2), these values were 71% and 85%, respectively, possibly indicating that the increased exposure in Afro-American subjects, seen in the PK study, does not translate to a change in inhibition of plasma DPP-4 activity.

No information is provided comparing the PD of the free tablets and FDC combination following single-doses or at steady-state in healthy subjects or in subjects with Type 2 diabetes.

Efficacy

Dosage selection for the pivotal studies

Dose ranging Study 1218.6

The endpoints of HbA1c, FPG, PK and DPP-4 inhibition together showed that the linagliptin 5 mg and 10 mg doses were approximately equivalent and both were superior to the 1 mg dose, all doses given once daily (QD).

Studies providing efficacy data

Studies providing efficacy data have been listed above under *Scope of the clinical dossier*.

Evaluator's conclusions on the clinical efficacy of the combination of linagliptin and metformin for the treatment of type 2 diabetes

The three proposed linagliptin/metformin FDC formulations are 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg given twice daily. The 2.5 mg/850 mg combination is intended to permit optimal titration of the metformin dose when the highest dose is not indicated or not tolerated. The intermediate dose was not tested in the pivotal efficacy study but it is justifiable to interpolate from the lowest and highest dose data.

The pivotal study was placebo-controlled and compared the highest and lowest dose free combinations, linagliptin 2.5 mg BID and metformin 500 mg or 1000 mg BID, and the respective monotherapies, linagliptin 5 mg QD (which is therapeutically equivalent to 2.5 mg BID as shown in Study 1218.62) or metformin 500 mg or 1000 mg BID. The pivotal study was extended into the long-term extension Study 1218.52 in which the treatments were the same (with the exception of placebo). Another uncontrolled long-term Study 1218.40 compared the efficacy of the linagliptin and metformin combination (with and without SU) in patients extending treatment from supporting studies. The main efficacy variable in all studies was changes in HbA1c from baseline over time and the key secondary variables included FPG and target HbA1c <7.0%. To allow meaningful comparisons, randomisation in the key studies was stratified by the quality of diabetic control at baseline (HbA1c above or below 8.5%) and the number of OADs being used at the time of enrolment. Studies that investigated the efficacy of the linagliptin and metformin combination lasted from 12 to 104 weeks but exposure was similar in the respective treatment groups in each study. With the exception of the open-label extension study, the pivotal and supportive studies were randomised, double-dummy, double-blind and placebo and/or active-controlled. The studies were well balanced for baseline characteristics including age, gender, race, disease characteristics and baseline HbA1c, and they were representative of the target diabetic patient population.

In the pivotal study, both free combinations of twice daily linagliptin 2.5 mg and metformin 500 mg and 1000 mg were superior to the individual metformin components (500 mg and 1000 mg BID) and to linagliptin 5 mg QD. The mean treatment differences in HbA1c from baseline to Week 24 were -0.51% (95% CI -0.73, -0.30, p<0.0001) for Lina 2.5 + Met 1000 compared with Met 1000 alone, and -1.14% (95% CI -1.36, -0.92, p<0.0001) for Lina 2.5 + Met 1000 compared to Lina 5 mg alone. The Lina 2.5 + Met 500 combination was also superior to the individual components (p<0.0001 for both comparisons), and overall there was a benefit in favour of Lina 2.5 + Met 1000 compared with Lina 2.5 + Met 500, and Met 1000 monotherapy. In the extension studies, the benefit in favour of the linagliptin/metformin combination treatments was either sustained or marginally increased for up to 102 weeks of continuous therapy. Patients who had received linagliptin + metformin + SU had a decrease in mean HbA1c of -0.72% from baseline to Week 24 and this was also sustained for up to 102 weeks.

There were statistically significant and clinically meaningful reductions in FPG with the linagliptin/metformin treatment groups in all trials from baseline until the end of the observation periods. This was associated with reduced use of rescue medication and more patients achieved HbA1c levels <7.0%. These and other efficacy endpoints were notably consistent with mean changes in HbA1c ranging from -0.51% to -0.64% in the various studies. Changes in HbA1c ≥0.5% are clinically meaningful and lead to improved disease outcomes in patients with any baseline level of HbA1c. Overall, there is a clear efficacy benefit in favour of the linagliptin/metformin combination compared with either component alone.

Safety

Studies providing evaluable safety data

The studies tabulated below provided evaluable safety data with groupings based on the study treatments, comparators, background treatment and study duration (note the SAF-C nomenclature) (Table 6).

Table 6. Studies providing safety data in this submission. Groupings of studies for the evaluation of safety.

Safety grouping	Study characteristics and objectives	Studies	Phase	Planned treatment duration	Treatments	Number of patients, N Randomised (total)	Treated
SAF-C1	Double-blind, placebo-controlled study with metformin background; comparing safety of linagliptin plus metformin versus metformin alone	1218.17	III	24 weeks	Lina: 5 mg qd Met: background	701	Lina+Met: 523 Met:177 total 700
SAF-C2	Double-blind, active-controlled study with metformin background; comparing safety of linagliptin plus metformin versus glimepiride plus metformin	1218.20	III	104 weeks	Lina: 5 mg qd Glim: 1 to 4 mg qd Met: background	1552	Lina+Met: 776 Glim+Met: 775 total 1551
SAF-C3	Double-blind, placebo-controlled study with metformin background (different metformin doses); comparing safety of linagliptin plus metformin versus metformin alone	1218.62	II	12 weeks	Lina: 2.5 mg bid[9] Lina: 5 mg qd[9] Met: background	491	Lina2.5+Met:223 Lina5+Met: 224 Met: 44 total 491
SAF-C4	Double-blind, placebo-controlled study; comparing different doses of linagliptin and metformin combination therapies with respective monotherapies	1218.46[3]	III	24 weeks	Pbo Lina: 5 mg qd Met: 500 mg bid Met: 1000 mg bid Lina 2.5 mg + Met 500 mg, bid Lina 2.5 mg + Met 1000 mg, bid	791	Pbo: 72 Lina5: 142 Met500: 144 Met1000: 147 Lina2.5+Met500: 143 Lina2.5+Met1000:143 total 791
SAF-C5[10]	Double-blind, placebo-controlled studies with metformin background; comparing safety of linagliptin plus metformin (free or fixed combination) with metformin alone	1218.6[2] 1218.17 1218.46[3] 1218.62	II III III II	≤24 weeks	Lina: 5, 10 mg qd; Met:background see SAF-C1 see SAF-C4 see SAF-C3	333 701 791 491	Lina5:66,Lina10:66,Met:71 see SAF-C1 see SAF-C4 see SAF-C3 total 1971
SAF-C6	Studies to assess long-term safety of linagliptin and metformin combination therapy	1218.46[4] 1218.52[5]	III III	≤78 weeks[3]	Met: 1000 mg bid Lina 2.5 mg + Met 500 mg, bid Lina 2.5 mg + Met 1000 mg, bid	567[8]	Met1000: 147[5] Lina2.5+Met500: 143[5] Lina2.5+Met1000: 143[5] total 433[5]

Safety grouping	Study characteristics and objectives	Studies	Phase	Treatment duration	Treatments	Number of patients, N Randomised (total)	Treated
SAF-C7	Double-blind, placebo-controlled study with metformin and SU background; comparing safety of linagliptin plus metformin and SU versus metformin and SU alone	1218.18	III	24 weeks	Lina: 5 mg qd Met: background SU: background	1058	Met+SU: 263 Lina+Met+SU: 792 total 1055
SAF-C8	All studies with linagliptin plus metformin (metformin as background or given as free combination with linagliptin) to assess safety in a large patient population	1218.6[2] 1218.17 1218.18 1218.20 1218.40[4] 1218.46 1218.52 1218.62	II III III III III III III II	≤104 weeks	see SAF-C5 see SAF-C1 see SAF-C7 see SAF-C2 Lina: 5 mg qd; Met,SU:background see SAF-C4, incl. open-label arm[6] see SAF C6 see SAF-C3	333 701 1058 1552 --[4] 791 + 66 567[8] 491	Lina+Met:132 Lina+Met: 523 Lina+Met: 792 Lina+Met: 776 Lina+Met: --[4] Lina+Met: 352 Lina+Met: 286[8] Lina+Met: 447 total 3529
SAF-C9	Studies in healthy subjects[7]	1288.1 1288.2 1288.3 1288.4 1218.4 1218.47	I I I I I I	<2 weeks	Lina 2.5 mg + Met 1000 mg Lina 2.5 mg + Met 500 mg Lina 2.5 mg + Met 850 mg Lina 2.5 mg / Met 1000 mg Lina 10 mg qd + Met 850 mg tid Lina 2.5 mg + Met 1000 mg	96 95 96 32 16 20	FDC: 96, free: 95 FDC: 94, free: 95 FDC: 96, free: 96 32 16 FDC: 20, free: 20 total 354

Patient exposure

In placebo-controlled studies, 1183 patients received placebo and 2566 patients received linagliptin 5 mg. Study duration ranged from 12 days to 24 weeks. Mean exposure was 133.9 days in placebo patients and 148.2 days for patients treated with linagliptin 5 mg. The duration of exposure in the linagliptin 5 mg group was 1041.4 patient years. In long-term follow-up studies of linagliptin monotherapy, 336 patients received linagliptin 5 mg and 523 patients received linagliptin 5 mg + metformin as background therapy for up to 102 weeks. The mean exposure was 617 days in patients receiving linagliptin and 623 days for patients receiving linagliptin + metformin. The duration of exposure was 567.9 patient years in patients receiving linagliptin and 891.5 patient years in patients receiving linagliptin + metformin.

In the placebo-controlled trial 1218.17 (SAF-C1, see tabulated studies above), 177 patients received metformin and 523 patients received linagliptin + metformin for a planned duration of 24 weeks. Mean exposure was comparable between groups (165 days met and 167 days Lina + Met). In the active-controlled Study 1218.20 (SAF-C2), 776 patients received linagliptin + metformin and 775 patients received linagliptin + glimepiride (Glim) for a planned duration of 104 weeks. Mean exposure was 627 days for Lina + Met patients and 625 days for Glim + Met patients. In the placebo-controlled trial with different linagliptin dosing regimens (1218.62, SAF-C3), 44 patients received metformin and 447 patients received linagliptin + metformin for a planned duration of 12 weeks. Mean exposure was comparable between groups (84 days Met and 83 days Lina + Met). In the pivotal efficacy study of free combination linagliptin + metformin (1218.46, SAF-C4), 72 patients received placebo, 142 patients received linagliptin 5 mg, 291 patients received metformin monotherapy, and 286 patients received linagliptin + metformin combination therapy for a planned duration of 24 weeks. The mean exposure was comparable across the treatment groups (144 days placebo, 158 days Lina, 159 days Met and 161 days Lina + Met).

In the pooled metformin-controlled studies (SAF-C5), 583 patients received metformin and 1388 patients received linagliptin + metformin and the planned study durations ranged from 12 to 24 weeks. The mean exposure was 146 days in the Met group and 130 days in the Lina + Met group. In the SAF-C6 long-term safety group, 147 patients received metformin 1000 mg, 143 patients received linagliptin 2.5 mg + metformin 500, and 143 patients received linagliptin 2.5 mg + metformin 1000 mg with a planned study duration of at least 24 weeks. The planned duration of the extension Study 1218.52 was 54 weeks but at the time of the interim analysis about 50% had an exposure of 24 weeks or more. Mean exposure was comparable across the groups (327 days Met 1000, 333 days Lina 2.5 + Met 500 and 335 days Lina 2.5 + Met 1000). In SAF-C7, the 263 patients received Met + SU and 792 patients received Lina + Met + SU. The mean exposure in both treatment groups was 170 days. In SAF-C8 (all Phase II and III trials), 3529 patients received linagliptin + metformin with planned study durations ranging from 12 to 54 weeks. The mean exposure was 545 days. In SAF-C9, 354 healthy subjects were treated with linagliptin + metformin. The studies ranged from one to nine days and the mean exposure was two days.

Postmarketing experience

This is a new drug application and no postmarketing data are available for the FDC. Linagliptin monotherapy has been approved in Australia only recently and no postmarketing data have been submitted in this application. Metformin has been in widespread use for 50 years and extensive post-marketing data are available.

Safety issues with the potential for major regulatory impact

Liver toxicity

No signals suggestive of liver toxicity were identified. In SAF-C8, there were 129 (3.7%) hepatic events in 3529 patients in the Lina + Met group.

Haematological toxicity

No signals suggestive of haematological toxicity were identified.

Serious skin reactions

No severe cutaneous adverse reactions were identified in any study.

Cardiovascular safety

Cardiovascular safety was assessed in a meta-analysis of eight trials in a total of 5239 diabetic patients. The primary endpoint was the adjudicated composite of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke and angina requiring hospitalisation. Median drug exposures in the linagliptin, placebo and active comparator groups were 175, 367 and 619 days respectively. A total of 11 primary events were observed in the linagliptin group and 23 events in the total comparator group with incidence rates per 1000 years of 5.3 for linagliptin and 16.8 for the comparators. A Kaplan-Meier plot illustrating the timescale of the events is shown in Figure 3. There was a highly significant risk reduction in favour of linagliptin compared with the total comparator group (Figure 4). When all placebo-controlled trials versus linagliptin were plotted, there were trends in favour of linagliptin but the differences in cardiovascular risk were not statistically significant (Figure 5).

Figure 3. Kaplan-Meier plot for time to primary endpoint (linagliptin versus total comparator.

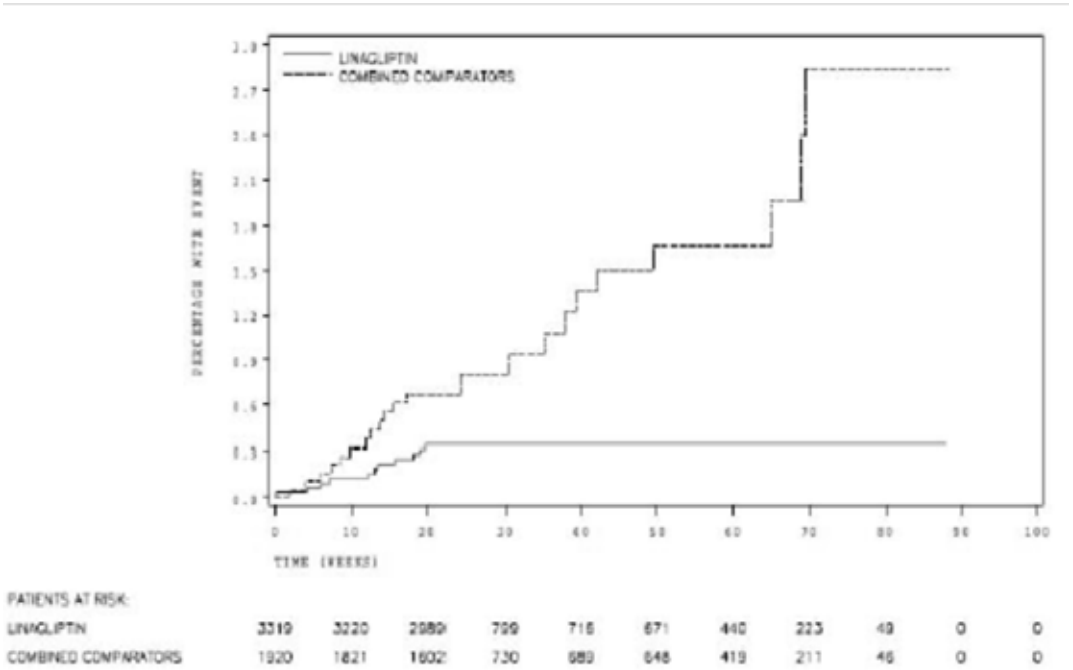


Figure 4. Forest plot of risk of primary end point for linagliptin versus total comparator. a) risk with 95% CI and b) risk with 98% CI

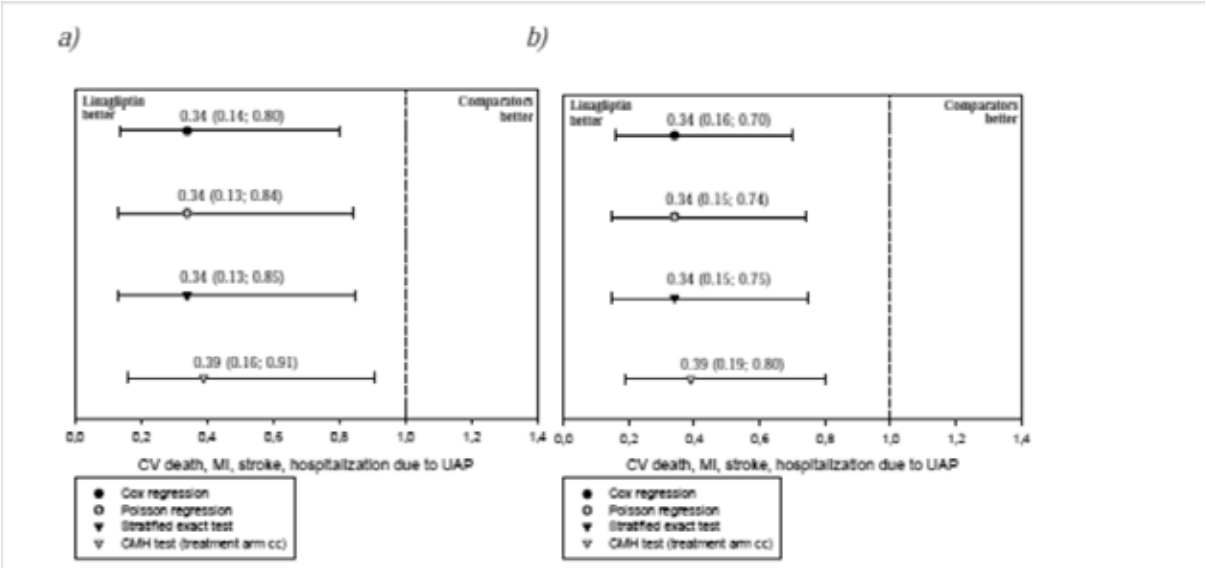
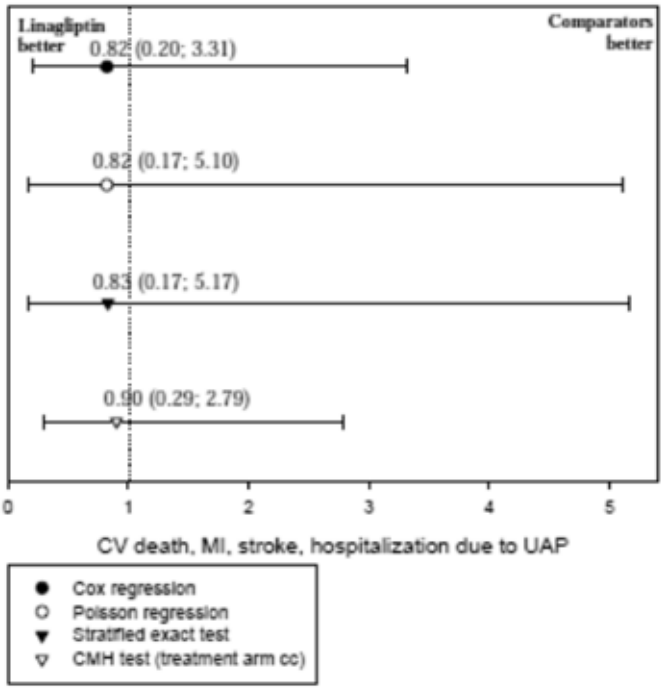


Figure 5. Forest plot of risk of primary end point for all placebo-controlled trials versus linagliptin



Evaluator's overall conclusions on clinical safety

The safety of the combination of linagliptin and metformin was assessed in 3529 patients with type 2 diabetes. Long-term exposure was high with 2694 patients receiving treatment for at least 24 weeks, 2081 patients for at least 52 weeks and 1756 patients for more than 78 weeks. The adverse event profile of the linagliptin/metformin combination was assessed in placebo-controlled studies, in studies against active comparators, in long-term extension studies and in sub-group analyses. In studies of the free combination (SAF-C4), adverse event rates were comparable between treatment groups (52.8% placebo, 54.9% linagliptin, 49.5% metformin and 50.7% linagliptin/metformin). Severe AEs (1.4% placebo and 1.4% linagliptin, 2.1%

metformin and 2.1% linagliptin/metformin) and AEs of special interest (2.8% placebo, 4.2% linagliptin, 2.4% metformin, and 1.7% linagliptin/metformin) were also comparable between groups. AEs leading to discontinuation were infrequent, comparable in each group but numerically highest in the placebo group.

In all Phase II and III studies (SAF-C8), SAEs occurred in approximately 10% of patients and were comparable between treatment groups. The incidence by preferred term was less than 1% and there were no trends towards a particular organ system. Serious cardiac disorders were reported in 2% of patients, mainly angina in 0.5% and myocardial infarction in 0.3%. However, a meta-analysis of events per 1000 years showed no increased risk in patients receiving the linagliptin/metformin combination. Events of special interest, including stroke, acute and chronic pancreatitis, serious skin eruptions, renal failure and hypersensitivity reactions, were no more common in patients receiving the combination treatment. There were 14 deaths during the treatment periods in all studies and 4 deaths in post-treatment follow-up periods. Nine deaths occurred in patients receiving linagliptin/metformin and five deaths in patients receiving metformin monotherapy or in combination with glimepiride. None of the deaths was considered drug related and the incidence per 1000 patient years was similar in the combination group compared with metformin monotherapy.

Overall the incidence of significant laboratory abnormalities was low and comparable in each treatment group. There was no trend towards increasing renal impairment during long-term treatment. There was no evidence of liver toxicity and the incidence of significant hepatic events was low in all treatment groups. Analyses in sub-groups showed no effects on safety based on age, gender, race, BMI, ethnicity, hepatic function and degree of renal impairment (although metformin is contra-indicated in patients with hepatic and severe renal failure).

There was an increased incidence of GI disturbance such as nausea, vomiting and diarrhoea in the metformin groups. In the linagliptin groups, there was an increased incidence of nasopharyngitis and cough compared with placebo and a low but increased incidence of pancreatitis. The incidence of these adverse drug reactions was in keeping with the known safety profiles of linagliptin and metformin and there was no evidence to suggest an increased incidence of AEs when used in combination.

The incidence of hypoglycaemia was generally low and similar (<3%) in patients treated with linagliptin and placebo. It was identified as an AE only in patients treated with linagliptin/metformin and SU. In general, the symptomatic hypoglycaemic events were not severe and did not require external intervention.

List of questions

Pharmacokinetics

The accumulation factors for linagliptin AUC and C_{max} were 1.40 and 1.49, respectively, (in Afro-American subjects) with T2DM at steady state. Please confirm that no data were submitted in the dossier regarding the bioequivalence of the free tablets and proposed FDCs formulations at steady-state.

Please confirm that no new information is submitted regarding the drug-drug interaction between the proposed FDC tablets and other drugs.

First round clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefits of the linagliptin/metformin FDC in the proposed usage are:

- Increased convenience and compliance (the only potential benefit compared with the free combination).
- Flexible metformin dosage
- A sustained improvement in glycaemic control
- Reduced use of rescue medication
- Good tolerability (including special groups)
- Lipid and weight neutral
- Hypoglycaemic events comparable to placebo
- Reduced dependence on SU (hypoglycaemia and weight gain)
- Potential to delay need for insulin by prolonging OAD therapy (not tested and an arguable benefit)
- Potential for better long-term disease outcomes (e.g. retinopathy, nephropathy) associated with HbA1c reduction

First round assessment of risks

The risks of the linagliptin/metformin FDC in the proposed usage are:

- Adverse events related to linagliptin (for example, nasopharyngitis, cough)
- Adverse events related to metformin (for example, GI side effects and lactic acidosis)
- Adverse events related to sulphonylureas (for example, hypoglycaemia, weight gain)
- Thoughtless prescribing without due attention to metformin precautions and contra-indications

First round assessment of benefit-risk balance

The benefit-risk balance of the linagliptin/metformin FDC given for the proposed usage was considered to be favourable.

First round recommendation regarding authorisation

Authorisation is recommended for the linagliptin/metformin FDC for the proposed indications:

a) *'as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or those already being treated and well controlled with the free combination of linagliptin and metformin*'.

b) '*in combination with a sulphonylurea (that is, triple combination therapy)as an adjunct to diet and exercise in patients inadequately controlled on their maximum tolerated dose of metformin and a sulphonylurea'*.

Second round evaluation of clinical data submitted in response to questions

Sponsor's response to *pharmacokinetics* question listed above (Section 10).

Boehringer Ingelheim confirmed that there were no bioequivalence studies done under steady state conditions with the FDC formulation. The sponsor had not received the clinical evaluation report at this stage and therefore did not have any context as to why this question has been asked, that is, data on the pharmacokinetics characteristics of linagliptin in Afro-American subjects and whether the bioequivalence data on the FDC formulation was performed at steady state.

The sponsor provided the following comments: The linagliptin/metformin FDC is an immediate release tablet that is recommended to be taken as two tablets twice daily. Linagliptin is also an immediate release tablet, but is recommended to be taken as one tablet daily.

The bioequivalence studies conducted with the free tablets and the proposed FDC formulations (Studies 1288.1, 12882 and 1288.3) were single dose studies as recommended for immediate release products. A single dose study is generally considered as most sensitive to detect formulation differences, whereas a multiple dose study is only required for extended release products where the accumulation might depend on the formulation if flip-flop kinetics[13] are present. The primary endpoints for these single dose studies were C_{max} for both linagliptin and metformin, and AUC_{0-72} for linagliptin and AUC_{0-inf} for metformin. Due to the long terminal half-life of linagliptin of more than 100 h, a truncated AUC_{0-72} was used instead of AUC_{0-inf} for linagliptin for the primary endpoint (which is in line with the TGA adopted European Union (EU) *Guideline on the investigation of bioequivalence*[14]).

In contrast, Study 1218.55 was a multiple dose study to determine the pharmacokinetic/pharmacodynamic characteristics of linagliptin (without metformin) in Afro-American subjects. The primary endpoints of $AUC_{\tau,ss}$ and $C_{max,ss}$ were at steady state. In addition, the accumulation factors reported for linagliptin in this study (1.40 for AUC and 1.49 for C_{max}) are similar to the previously reported values.

No dedicated drug-drug interactions studies were performed with the FDC. Extensive data exists on the drug-drug interaction of the individual actives (linagliptin and metformin) of the FDC. Data was provided during the initial evaluation of linagliptin that co-administration with metformin did not impact on the pharmacokinetics of either linagliptin or metformin in healthy volunteers. Therefore in the proposed Australian Product Information, the section "*Interaction with other medicines*" has combined the same information from the linagliptin (Trajenta) PI and metformin (Diabex) PI.

[13] Flip-flop kinetics definition: In pharmacokinetics, flip-flop phenomenon happens when the rate of absorption is slower than the rate of elimination. The decline of the terminal slope during flip-flop pharmacokinetics will depend greatly on how fast absorption is taking place. In this case, the terminal slope is not controlled by the usual clearance and volume of distribution, but instead by bioavailability and the ka.

[14] CPMP/EWP/QWP/1401/98Rev.1/Corr** <http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>
Adopted by TGA with the following notation:
"While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.
The procedure for abridged applications claiming essential similarity to a reference product (ie, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia."

Evaluator's response to the sponsor

Regarding evaluator's precaution in Afro-American subjects with T2DM

Very little new data were provided by the sponsor in regards to the effects of intrinsic and extrinsic factors on the PK of the new FDC. As the sponsor states in their response Study 1218.55 examined the single dose and steady state PKs of linagliptin 5 mg in patients with T2DM of African-American (AA) origin (Table 7).

Table 7. Study 1218.55. Geometric mean (%gCV) and mean (%CV) noncompartmental PK parameters of linagliptin after single and multiple oral administration of 5 mg linagliptin to AA T2DM patients n(N=41 (single dose) and N=39 (steady state).

	Unit	gMean	gCV[%]	Mean	CV[%]
AUC_{0-24}	[nmol·h/L]	137	32.4	144	33.5
C_{max}	[nmol/L]	10.9	57.6	12.7	63.1
t_{max}^*	[h]	1.50	1.00 - 8.00		
fe_{0-24}	[%]	0.504	214	1.16	137
CLR_{0-24}	[mL/min]	6.45	151	11.6	115
$AUC_{\tau,ss}$	[nmol·h/L]	194	25.8	200	26.4
$C_{max,ss}$	[nmol/L]	16.4	40.9	17.8	46.6
$t_{max,ss}^*$	[h]	1.50	0.500 - 4.00		
$C_{24,ss}$	[nmol/L]	5.94	25.5	6.12	25.5
$t_{1/2,ss}$	[h]	119	22.4	122	28.0
$V_Z/F_{,ss}$	[L]	9400	36.0	10000	40.7
$CL/F_{,ss}$	[mL/min]	911	25.8	940	24.8
$MRT_{po,ss}$	[h]	102	20.3	104	20.6
$fe_{0-24,ss}$	[%]	4.42	45.2	4.82	42.0
$CLR_{0-24,ss}$	[mL/min]	40.3	33.7	42.4	31.7
RA,AUC_{0-24}	[.]	1.40	22.8	1.44	23.6
RA,C_{max}	[.]	1.49	52.8	1.67	47.8
$Accumulation,t_{1/2}$	[h]	13.1	44.0	14.3	42.2

* for tmax and tmax,ss, the median and range (min-max) is given

This study indicates that in patients of AA origin with T2DM the gMean C_{max} and AUC_{0-24} following a single 5 mg dose of linagliptin was 10.9 nM/L (5.15 ng/mL, assuming the molecular weight (MW) of linagliptin = 472.54)and 137 nM.h/L (64.7 ng.h/mL), respectively. At steady-state in these subjects the gMean C_{maxss} and $AUC_{t,ss}$ of linagliptin was 16.4 nM/L (7.74 ng/mL) and 194 nM.h/L (91.67 ng.h/mL), respectively.

By contrast, Study 1218.2, from the initial Category 1 application for linagliptin tablets 5 mg, examined the PKs of linagliptin 5 mg following a single dose and at steady-state in 8 Caucasian subjects with T2DM (Tables 8 and 9). This study demonstrated that in patients of Caucasian origin with T2DM the gMean C_{max} and AUC_{0-24} following a single 5 mg dose of linagliptin was 3.93 ng/mL and 56 ng.h/mL, respectively and at steady-state in these subjects the gMean C_{maxss} and $AUC_{t,ss}$ of linagliptin were 5.24 ng/mL and 74.7 ng.h/mL, respectively.

Table 8. Study 1218.2. Individual noncompartmental PK parameters of linagliptin after single oral administration of 5 mg linagliptin to patients with T2DM with descriptive statistics.

	$AUC_{0\text{-}24}$ [ng·h/mL]	$AUC_{0\text{-}24,norm}$ [(ng·h/mL)/mg]	$AUC_{0\text{-}tz}$ [ng·h/mL]	t_z [h]	C_{max} [ng/mL]	$C_{max,norm}$ [(ng/mL)/mg]	t_{max} [h]	$Ae_{0\text{-}24}$ [µg]	$fe_{0\text{-}24}$ [%]	$CL_{R,0\text{-}24}$ [mL/min]
	62.7	12.5	61.7	23.5	4.57	0.914	3.00	36.7	0.734	9.76
	46.1	9.21	45.4	23.5	2.53	0.506	6.02	7.22	0.144	2.61
	47.9	9.58	47.1	23.5	2.81	0.562	2.00	6.83	0.137	2.38
	58.1	11.6	57.2	23.5	3.45	0.690	6.00	53.4	1.07	15.3
	46.2	9.23	45.4	23.5	2.65	0.530	1.50	25.1	0.502	9.07
	63.1	12.6	62.0	23.5	6.05	1.21	0.917	30.4	0.609	8.04
	69.2	13.8	68.1	23.5	7.79	1.56	1.50	95.9	1.92	23.1
	59.9	12.0	58.9	23.5	4.07	0.814	1.50	9.73	0.195	2.71
N	8	8	8	8	8	8	8	8	8	8
Mean	56.6	11.3	55.7	23.5	4.24	0.848	2.80	33.2	0.663	9.12
SD	8.84	1.77	8.70	0.0151	1.86	0.371	2.07	30.1	0.602	7.21
Median	46.1	9.21	45.4	23.5	2.53	0.506	0.917	6.83	0.137	2.38
Max	59.0	11.8	58.1	23.5	3.76	0.752	1.75	27.8	0.555	8.55
CV [%]	69.2	13.8	68.1	23.5	7.79	1.56	6.02	95.9	1.92	23.1
gMean	15.6	15.6	15.6	0.0644	43.8	43.8	73.7	90.8	90.8	79.1
gVC [%	56.0	11.2	55.1	23.5	3.93	0.786	2.26	22.6	0.453	6.73
	16.0	16.0	16.0	0.0644	42.4	42.4	78.0	125	125	106

Table 9. Study 1218.2. Individual noncompartmental PK parameters of linagliptin at steady state after multiple oral administration of 5 mg linagliptin to patients with T2DM with descriptive statistics.

	$AUC_{\tau,ss}$ [ng·h/mL]	$AUC_{\tau,ss,norm}$ [(ng·h/mL)/mg]	$C_{max,ss}$ [ng/mL]	$C_{max,ss,norm}$ [(ng/mL)/mg]	$t_{max,ss}$ [h]	$C_{min,ss}$ [ng/mL]	$t_{min,ss}$ [h]	$C_{pre,ss}$ [ng/mL]	$C_{pre,2}$ [ng/mL]	$C_{pre,3}$ [ng/mL]	$C_{pre,4}$ [ng/mL]
	80.1	16.0	5.05	1.01	1.50	2.85	23.5	2.89	2.06	2.04	2.14
	79.6	15.9	4.89	0.978	1.00	2.74	0.00	2.74	1.50	1.85	2.30
	70.5	14.1	4.73	0.946	1.00	2.36	23.5	2.46	1.63	2.07	2.36
	85.0	17.0	4.85	0.970	3.00	2.48	0.00	2.48	1.84	1.85	1.95
	61.4	12.3	3.75	0.750	3.00	1.94	23.5	1.99	1.58	1.62	1.61
	78.2	15.6	7.88	1.58	1.50	2.37	0.00	2.37	2.11	2.16	2.36
	73.3	14.7	5.70	1.14	1.00	2.35	0.00	2.35	2.26	2.53	2.40
	72.0	14.4	5.92	1.18	1.50	2.33	0.00	2.33	2.16	2.22	2.13
N	8	8	8	8	8	8	8	8	8	8	8
Mean	75.0	15.0	5.35	1.07	1.69	2.43	8.81	2.45	1.89	2.04	2.16
SD	7.30	1.46	1.22	0.243	0.843	0.278	12.2	0.273	0.294	0.277	0.269
Median	61.4	12.3	3.75	0.750	1.00	1.94	0.00	1.99	1.50	1.62	1.61
Max	75.7	15.1	4.97	0.994	1.50	2.37	0.00	2.42	1.95	2.06	2.22
CV [%]	85.0	17.0	7.88	1.58	3.00	2.85	23.5	2.89	2.26	2.53	2.40
gMean	9.73	9.73	22.7	22.7	49.9	11.4	138	11.1	15.5	13.6	12.5
gVC [%	74.7	14.9	5.24	1.05	1.53	2.41	---	2.44	1.87	2.03	2.14
	10.1	10.1	21.7	21.7	48.0	11.7	---	11.3	16.0	13.6	13.5

The evaluator's comparison of these results indicated that the exposure to linagliptin is increased following both single doses and at steady-state in Afro-American subjects with T2DM compared to Caucasians with T2DM, for example, at steady state the C_{max} and AUC of linagliptin 5 mg is approximately 1.48 and 1.23 fold higher in Afro-American subjects compared with Caucasians.

Therefore in the absence of a single study that directly compared linagliptin PKs in Afro-American and Caucasian subjects with T2DM, as recommended in the first round, the evaluator suggests that the precautions section of the PI should be modified and a new part should be added stating that:

"Race

Studies in Afro-American and Caucasian subjects with T2DM have identified that at steady state linagliptin AUC and Cmax were approximately 23% and 48% higher, respectively, in Afro-American subjects compared to Caucasians. Although this increase is unlikely to be clinically significant Afro-American subjects may require a reduction in dose."

In addition, the sponsor's *Summary of Clinical Pharmacology Studies* indicates that there is a similar increase in steady-state linagliptin exposure in Japanese and Chinese subjects with T2DM compared to Caucasians with T2DM and although this is unlikely to affect the efficacy of linagliptin in Asian subjects it may result in an increase in adverse drug-drug interactions. Therefore, a similar statement to the one above should be made in regards to Japanese and Chinese subjects.

In regards to drug-drug interaction studies with the FDC

This question was asked to establish whether the effects of drugs like cimetidine on metformin excretion or simvastatin on linagliptin metabolism were potentiated following administration of the FDC or free combination compared with when metformin or linagliptin were administered alone. The evaluator accepted that in the absence of these data then the listing of the drug-drug interactions of the two active components separately as it currently appears in the proposed PI was not ideal but was considered to be satisfactory.

Second round clinical summary and conclusions

Second round benefit-risk assessment

Second round assessment of benefits

No change in the assessment has occurred as a result of a final review following the sponsor's responses to the clinical questions (see *First Round Assessment of benefits above*).

Second round assessment of risks

No change in the assessment has occurred as a result of a final review following sponsor's responses to the clinical questions (see *First Round Assessment of risks above*).

Second round assessment of benefit-risk balance

No change in the assessment has occurred as a result of a final review following sponsor's responses to the clinical questions (see *First Round Assessment of benefit-risk balance above*).

Second round recommendation regarding authorisation

Authorisation is recommended for the fixed dose combination tablets containing linagliptin and metformin 2.5/500, 2.5/850 and 2.5/1000 mg as indicated below:

> *Trajentamet is an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or in those already being treated and well controlled with the free combination of linagliptin and metformin.*
>
> *Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

V. Pharmacovigilance findings

Risk management plan

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

Safety specifications

Subject to the evaluation of the nonclinical aspects of the Safety Specification by the Toxicology area of the Office of Scientific Evaluations (OSE) and the clinical aspects of the Safety Specification by the Office of Medicines Authorisation (OMA), the summary of the Ongoing Safety Concerns as specified by the sponsor was as shown in Table 10.

Table 10. Ongoing Safety Concerns

Important identified risks	Hypoglycaemia (linagliptin/metformin and sulphonylurea) Pancreatitis Lactic acidosis
Important potential risks	Skin lesions Hypersensitivity reactions Infections
Important missing information	Safety in subpopulations · high risk patients with recent CV events · old patients (> 80 years) · paediatric patients · pregnant and lactating patients · oncological adverse reactions · idiosyncratic reactions · immunological adverse reactions · concomitant P-gp and CYP3A4 inhibitors

Proposed pharmacovigilance

The following table (Table 11) summarises the pharmacovigilance activities proposed by the sponsor.

Table 11. Proposed Pharmacovigilance activities (Table presented in two columns)

Safety concern	Proposed pharmacovigilance activi (routine and additional)
Important identified risk	
Hypoglycaemia	Routine pharmacovigilanc and analysis of clinical tria safety data
Pancreatitis	Routine pharmacovigilanc and analysis of clinical tria safety data
Lactic acidosis	Routine pharmacovigilanc and analysis of clinical tri safety data
Important potential risks	
Skin lesions	Routine pharmacovigilan and analysis of clinical t safety data
Hypersensitivity reactions	Routine pharmacovigilan and analysis of clinical t safety data

Safety concern	Proposed pharmacovigilance activities (routine and additional)
Infections	Routine pharmacovigilance and analysis of clinical trial safety data
Worsening of renal function	Routine pharmacovigilance and analysis of clinical trial safety data (planned CV-safety study 1218.74 [U10-2169])
Important missing information	
Safety in subpopulations	
High risk patients with recent CV events	Routine pharmacovigilance and analysis of clinical trial safety data. Planned CV-safety study 1218.74 [U10-2169]
Elderly patients (> 80 years)	Routine pharmacovigilance and analysis of clinical trial safety data (planned CV-safety study 1218.74 [U10-2169])
Paediatric use	Routine pharmacovigilance
Pregnant and lactating patients	Routine pharmacovigilance and analysis of clinical trial safety data
Oncological adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data
Idiosyncratic adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data
Immunological adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data
Concomitant P-gp and CYP3A4 inhibitors	Routine pharmacovigilance and analysis of clinical trial safety data

Risk minimisation activities

In regard to the proposed routine risk minimisation activities, the draft product information and consumer medicine information documents were considered satisfactory.

Proposed risk minimisation activities will achieve a reduction in risk of identified safety concerns primarily through the provision of information and education. Routine risk minimisation activities will include warnings/notification of undesirable effects in the Australian Product Information (PI) for the identified safety concerns.

An educational program will be developed to inform the Australian doctors about the role of Trajentamet in glycaemic control for patients with type 2 diabetes. One of the aims of the educational programme is to enhance understanding of the identified safety concerns *hypoglycaemia* and *pancreatitis*.

The following table (Table 12) summarises the OPR's evaluation of the RMP, the sponsor's responses to issues raised by the OPR and the second round OPR evaluation of the sponsor's responses.

Table 12. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
It is recommended that the Delegate: · Implement RMP Version 1.0 dated 8 June 2011 with Australian Specific Annex Version 1.0 and any future updates as a condition of registration.	Provided updated RMP Version 4.0 dated 13 Jul 2012 [data lock point 15 October 2010] with their response.	It was recommended that the Delegate implement EU RMP Version 4.0 dated 13 July 2012 [data lock point 15 October 2010] including Annex VIII, Australian Specific Annex, and any future updates as a condition of registration.
It is recommended to the Delegate that the sponsor: · Update the RMP of the current submission to include the missed ongoing safety concerns from the linagliptin (Trajenta) RMP Version 5.0 and also include use with insulin as an area of important missing information, with relevant pharmacovigilance and risk minimisation (consider the Australian education programme) activities.	***1) Update of the linagliptin and metformin RMP to include missing ongoing safety concerns*** *a) Worsening of renal function* *Boehringer Ingelheim is providing the updated the linagliptin and metformin RMP (version 4.0). In this updated version, "worsening of renal function" has been included as an "Important potential risks".* *b) Hypersensitivity* *Hypersensitivity was a search category which includes angioedema and urticaria."Hypersensitivity reactions" has been included as an "Important potential risks" within the linagliptin and metformin RMP (version 4.0).* A justification to include hypersensitivity as an "Important potential risk" was provided in Part II 3. Evaluation of the need for risk assessment activities: *c) Hepatic impairment* It was discussed in the linagliptin and metformin RMP that hepatic insufficient patients will be contraindicated for the use of the linagliptin/metformin combination product due to the metformin component:	**Changes to the RMP and PI have been made and this was considered acceptable.**

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	<u>Other special population: renal impairment, hepatic impairment, and elderly</u> *The available nonclinical data do not indicate any risk associated with use of linagliptin to renal or hepatic function [U10-1492]. Metformin is contraindicated in renal impaired and hepatic insufficient patients [R10-5537]. Because of the metformin component of the fixed dose combination, linagliptin/metformin will be contraindicated in renal impaired and hepatic insufficient patients. Data of the individual compounds do not indicate an increased risk for elderly [U07-1910, U08-1185, R10-5239]. Therefore, no additional nonclinical data for linagliptin/metformin will be obtained.* [Part I section 1.1.2 "Specification of need for additional non-clinical data if the product is to be used in special population"] Boehringer Ingelheim proposes to update the Australian Product Information to include "Hepatic insufficiency, acute alcohol intoxication, alcoholism (due to the metformin component)" in the *Contraindication* section, and a statement in the *Dosage and Administration* section related to Hepatic impairment. Therefore "hepatic impaired patients" is not required to be included as an "Important potential risk" in the linagliptin and metformin RMP. ***2) Include use with insulin as an area of important missing information***	It was noted the sponsor proposes a precautionary PI statement "*The use of TRAJENTA DUO in combination with insulin has not been adequately studied.*"
It was recommended to the Delegate that the sponsor: Australian educational programme: · Expand this programme to include the other **Important identified risk** - lactic acidosis, which may occur due to the metformin component of the fixed	*The Australian Specific Annex has been amended to include lactic acidosis as an identified safety concern (section 3a). Boehringer Ingelheim as part of the Australian education programme is developing a diabetes CME program which will include information on Trajenta Duo.*	Although the sponsor concludes in the RMP routine risk minimisation activities are sufficient and no risk minimisation plan is needed, they provide details of an educational programme for Australian healthcare professionals (specialist physicians and general practitioners) in the Australian Specific Annex.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
dose combination. · Provide the proposed educational materials to the Office of Product Review (OPR) prior to marketing and additional detail on how they will be implemented. That is, which representatives from the sponsor will deliver face to face activities and how will the sponsor ensure they have the appropriate training/knowledge. In addition, confirm if the outcomes of the evaluation of educational activities will be provided to the OPR via Period Safety Update Reports or another mechanism.	A general outline of the proposed CME program was provided in the Sponsor's response.	The sponsor has not provided a copy of the draft educational materials with their response or details on the knowledge and training those who will deliver the programs. If this submission is approved it is recommended the sponsor provide within 6 months of registration - copies of the educational materials - how these will be implemented and the training and knowledge of the presenters - the intended duration of this program
It was recommended to the Delegate that the sponsor: · Provide an update on the progress of the study report for study 1218.63. The sponsor states that the estimated/actual completion date for study 1218.63 was November 2011.	*The study report for study 1218.63 was completed in December 2011, with revisions in February 2012. The complete study report was provided in the ongoing extension of indications application for Trajenta (linagliptin) [submission ID: PM-2012-01168-3-5].*	**This was considered acceptable**.

Summary of OPR recommendations

The OPR's suggested wording for RMP and PSUR conditions of registration and Outstanding issues in relation to the RMP are shown below.

Please note that the sponsor provided an updated EU RMP Version 4.0 with their response (RMP evaluation report refers to EU RMP Version 1.0). Key changes to the updated RMP are outlined below. The sponsor has not provided a summary of changes, however, key changes in this updated RMP are as shown in Table 13 below.

Table 13. Key changes to the EU-RMP

Safety specification	Addition of 'Worsening of renal function' as an Important potential risk^.
Pharmacovigilance activities	Assigned 'Worsening of renal function' to long term CV-safety study 1218.74.
	Removed study 1218.63* from pharmacovigilance plan which was assigned to the area of Important missing information 'High risk patients with recent CV events' (long-term CV safety study 1218.74 is still assigned).
	Removed study 1218.63* from pharmacovigilance plan which was assigned to the area of Important missing information elderly patients (> 80 years; long-term CV safety study 1218.74 is still assigned).

^ The important potential risk 'Worsening of renal function' is not assigned any risk minimisation activities.
* The study report was provided in the ongoing extension of indications application for Trajenta (linagliptin) [submission ID: PM-2012-01168-3-5], which is currently under review by the TGA (also see Sponsor's response).

Suggested wording for conditions of registration

RMP

- Implement EU RMP Version 4.0 dated 13 July 2012 [data lock point 15 October 2010] including Annex VIII, Australian Specific Annex, and any future updates as a condition of registration.

PSUR

- Post marketing reports are to be provided in line with the current published list of European Union (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 periodic Safety Update Reports each covering six months.

Reasons

It is noted that below information is included in the released European Medicines Agency (EMA) list of reference dates for Jentadueto (linagliptin/metformin).[15]

Table 14. Reference dates for Jentadueto

EU approval date	PSUR Submission Frequency	Data lock point
20/07/2012	6 months	19/07/2013

[15] EMA reference dates and frequency of PSUR submission

Outstanding issues

Education program

If approved the sponsor should provide within 6 months of registration:

- the educational materials;
- who will deliver these and the training required;
- intended duration of this program.

VI. Overall conclusion and risk/benefit assessment

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

Quality

The linagliptin used in the proposed products is manufactured and controlled in the same manner as for the single agent linagliptin 'Trajenta' tablets. The metformin is covered by a European Directorate of Quality medicines certificate of suitability. The proposed tablets are unscored film-coated immediate-release products, distinguished by differing colours, sizes and markings.

The evaluator considered 6 bioavailablity studies. Study 1288.4 investigated relative bioavailability of 2.5 mg linagliptin + 1000 mg metformin hydrochloride fixed dose tablet with and without food. Food had no significant effect on C_{max} and AUC of linagliptin and AUC metformin but the C_{max} of metformin was reduced by about 20%.

Studies 1288.1, 1288.2, 1288.3 showed bioequivalence of the fixed dose combinations 2.5 mg /500 mg, 2.5 mg /850 mg, and 2.5 mg /1000 mg with free combinations of the corresponding doses.

Study 1218.45 compared linagliptin 2.5 mg b.d. with linagliptin 5 mg once daily in a two period crossover study where each period was 7 days. Bioequivalence was demonstrated. Study 1288.6 indicated that 'fast' and 'slow' dissolving batches of the proposed 2.5 mg/1000 mg tablets were bioequivalent.

The EU Glucophage innovator product used in studies was accepted as equivalent to the Australian innovator product.

Increased colour intensity on labels corresponds to increasing strength of metformin. Active ingredient strengths in the PI were included in the trade name as part of the product description, presentation, and dosage and administration, although the active ingredient names do not have equal prominence with the trade name.

The quality evaluator stated that all issues were satisfactorily resolved including changes to the PI and registration was recommended with respect to chemistry, quality control and biopharmaceutics. The application was not considered by the Pharmaceutical Sub-Committee.

Delegate's comment

It was considered unsatisfactory that only two of the trade names proposed give any hint that the tablet is a fixed dose combination with metformin.

Nonclinical

The evaluator notes the daily doses proposed and the combinations proposed are currently approved for individual components.

Studies in diabetic mice supported proposed clinical use. No PK interactions were observed in rats. Repeat-dose toxicities and embryofetal toxicity studies revealed no novel or exacerbated clinically relevant toxicities in combination; the majority of toxicities were due to metformin.

PI changes were recommended under PD/PK and Precautions: Fertility, Pregnancy and Lactation. In particular, the toxicology evaluator recommended Pregnancy Category C.

The arginine component was considered toxicologically acceptable.

Clinical

Pharmacokinetics

PK studies 1288.1, 1288.2, 1288.3 demonstrated bioequivalence of FDC tablets with relevant doses of free linagliptin and metformin.

The CER identifies Study 1218.57 as establishing bioequivalence of innovator metformin tablets BMS Glucophage and Merck Glucophage.

Study 1288.4 showed a high fat meal with the FDC tablet had little effect on linagliptin AUC0-72 and C_{max}; Mean AUC_{0-72} of linagliptin was 162 nM.h/L and 164 nM.h/L under fed and fasted conditions, respectively with mean C_{max} 4.56 and 4.99 nM/L, respectively. There was little effect on metformin AUC_{0-inf} (fasted: 12000 ng.h/mL, fed: 11500 ng.h/mL). It prolonged the time to reach maximum plasma concentrations by about 2 hours (median T_{max} increased from 2.00 h to 4.00 h) and lowered the C_{max} by about 18.1% (fasted: 1820 ng/mL; fed: 1490 ng/mL)(Tables 4.22, p60 and 4.23, p60).

Delegate's comment

> Metformin is given with food and overall exposure is unaffected for the fixed dose combination. The proposed PI does not accurately reflect the information from this study, describing the tablet as 5/1000 when a single 2.5 mg linagliptin/1000 mg metformin FDC was given, and stating the peak serum concentration of metformin was reduced by 12% instead of 18%. This should be amended. The effect is not likely to be clinically significant.

Study 1288.55 investigated the PK of 5 mg Linagliptin in patients with Type 2 diabetes mellitus of African American origin. The T_{max} following 5 mg oral linagliptin was 1.5 hours and at steady state the $AUC_{\tau,ss}$ was 194 nmol.h/L and $C_{max,ss}$ was 16.4 nmol/L. Compared to the results for Caucasian men in Study 1218.2, the evaluator considered the AUC_{ss} and $C_{max\ ss}$ were approximately 23% and 48% higher, respectively, in Afro-American subjects.

No studies examined bioequivalence of free and FDC combinations at steady state, or drug-drug interactions between proposed FDC tablets and other drugs.

Pharmacodynamics

There was no information specific to the FDC tablets.

In Study 1218.55 in Afro-American subjects with Type II diabetes mellitus, inhibition of plasma DPP-4 activity correlated with linagliptin plasma concentrations. In these subjects at steady-state, the enzyme activity assays at 24 hours and steady state (E_{24} and E_{ss}) showed plasma DPP-4 inhibition was 75% and 85%, respectively. This was comparable to

values in Study 1218.2 in Caucasians, suggesting that increased exposure in Afro-Americans did not increase inhibition of plasma DPP-4 activity.

Dose finding

Study 1218.6 was previously evaluated for linagliptin registration. It demonstrated that linagliptin 5 mg, as add-on to metformin, was similar to linagliptin 10 mg for outcome variables including HbA1c and DPP-4 inhibition, with both superior to linagliptin 1 mg.

Clinical efficacy

The CER identified Study 1218.46 as the pivotal study. In summary, this was a randomised, double-blind, placebo-controlled parallel group multicentre study comparing the efficacy and safety of twice daily administration of the free combination of linagliptin (Lina) 2.5 mg + metformin (Met) 500 mg or of Lina 2.5 mg + Met 1000 mg, with the individual components of metformin (500 mg or 1000 mg twice daily), and linagliptin (5 mg once daily) over 24 weeks in drug naive or previously treated type 2 diabetic patients with inadequate glycaemic control. It was designed as a superiority study. The double-blind period was followed by an optional open-label extension study for a further 24 weeks.

Patients pre-treated with one oral antidiabetic agent (OAD) underwent a 6 week washout period including 2 weeks placebo run-in. Patients not pre-treated with an oral anti-diabetic treatment had a 2 week placebo run-in period. Patients with poor glycaemic control, that is, baseline HbA1c ≥11% were enrolled into an open-label arm. All patients randomised to metformin 1000 mg underwent a forced titration phase. Key inclusion criteria included: males and females with T2DM, treatment naive or previously treated with not more than one oral antidiabetic drug; age range ≥18 to ≤80 years; BMI ≤40 kg/m^2; HbA1c ≥7.5 to <11.0% (for treatment naive patients) and ≥7.0 to ≤10.5% (for treatment washout patients).

The primary efficacy outcome variable was change in HbA1c from baseline to Week 24. Secondary outcomes included treat-to-target efficacy response and use of rescue medication. The full analysis set (n = 756) was all randomised patients who received at least one dose of study drug, had a baseline HbA1c, and had at least one HbA1c on treatment. The CER describes baseline demographic data reflecting the target population. Results for the primary outcome are described in the CER. Free combinations linagliptin 2.5 mg + met 1000/met 500 were superior to the individual components alone to 24 weeks. Mean treatment differences in HbA1c from baseline to week 24 (95% CI) were -0.51% (-0.73, -0.30) for linagliptin 2.5 mg + met 1000 compared to met 1000 alone, and -1.14% (-1.36, -0.92) for linagliptin 2.5 mg + met 1000 compared to lina 5 mg alone. Secondary efficacy variables were consistent with these results.

Study 1218.62 was a Phase IIb randomised, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin 2.5 mg twice daily versus 5 mg once daily over 12 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes and insufficient glycaemic control. The objective was to demonstrate non-inferiority of linagliptin 2.5 mg BID. to linagliptin 5 mg once daily; the pre-specified non-inferiority margin for treatment difference HbA1c % change from baseline was 0.35. A total of 451 randomised patients were planned and 771 patients were enrolled at 81 sites. Patients treated with one previous OAD stopped treatment while background metformin therapy continued. Patients were randomised 5:5:1 to linagliptin 2.5 mg: linagliptin 5 mg: placebo.

Both linagliptin groups were superior to placebo in HbA1c reduction from baseline to 12 weeks. The adjusted mean difference in HbA1c change from baseline to week 12 for

linagliptin 2.5 mg BID minus linagliptin 5 mg once daily was 0.06% (95% CI -0.07, 0.19), confirming non-inferiority.

Study 1218.43 compared linagliptin to placebo as add on to pre-existing antidiabetic therapy, including insulin, in T2D patients with chronic renal failure. The CER notes that as metformin is contra-indicated in patients with renal impairment this study was not supportive of the FDC application.

There were two long-term open label extension studies, 1218.40 (extension up to 78 weeks of completers from studies 1218.15, 1218.16, 1218.17, and 1218.18) and 1218.52 (extension over 54 weeks of completers from 1218.46), the latter still ongoing at the time of submission.

In Study 1218.40 patients treated with linagliptin with or without other OADs ('old' lina) continued the same treatment; patients treated with placebo in previous trials were treated with linagliptin 5 mg ('new' lina). Statistical analyses were descriptive; efficacy endpoint was change from baseline in Hba1c over time. The 'old' linagliptin group (n = 1532) maintained HbA1c% at 78 weeks and the 'new' linagliptin group (n = 589) had a reduction (mean change from baseline 0.02% versus -0.54%).

In Study 1218.52 patients who completed the entire double-blind treatment period of 1218.46 without rescue medication were included. Those previously randomised to lina 2.5 + met 500, lina 2.5 + met 1000, or met 1000, continued the same medication; those previously receiving metformin 500 mg BID, linagliptin 5 mg once daily or placebo were randomised to one of lina 2.5 + met 500, lina 2.5 + met 1000, or met 1000. The results described in the CER were from a second interim analysis.

Meaningful patient numbers from the first 30 weeks of treatment showed a modest benefit in HbA1c change from baseline in linagliptin compared to metformin 1000; this is shown on pp 99-100 of the CER. Overall, treatment benefit was suggested for lina 2.5 + met 1000, compared to lina 2.5 + met 500 or met 1000.

Delegate's comment

> Additional data to 54 weeks were mentioned in the CER; overall the change from baseline appeared small (-0.24% for lina 2.5 + met 1000, -0.28% for lina + met 500, -0.06% for met 1000) and it was only in the group that switched (after 24 weeks in 1218.46) that a treatment difference effect > 0.5% in favour of lina + met 1000 was maintained.

The CER conclusion for clinical efficacy was that free combination of 2.5 mg linagliptin with metformin 500 mg or 1000 mg showed clinically meaningful benefit compared with either component alone. It is noted the intermediate dose 2.5 mg/850 mg was not tested in efficacy studies.

Clinical safety

Exposure

The sponsor provided various analyses of data using an 'SAF-C' nomenclature for different groupings of studies for the assessment of data relevant to the combination of linagliptin + metformin. Mean exposure in long-term placebo controlled trials (SAF-C2) was 891.5 patient years for lina+ metformin versus 567.9 patient years for linagliptin alone. In the pivotal study 1218.46, 286 patients received linagliptin + metformin for 24 weeks and in extension 1218.52 mean exposure was comparable across groups, with about 50% having exposure of 24 weeks or more at the time of interim analysis.

Adverse events

Pivotal study 1218.46

AEs were very common for GI disorders, infections, metabolic and nervous system disorders. Diarrhoea was the most frequently reported individual GI AE, with the highest frequency in the group lina 2.5 + met 1000, that is, highest dose of metformin.

In a study grouping (SAF-M1) for long term safety of linagliptin as monotherapy, the CER indicates higher rates of GI disorders and hypoglycaemia for the combination lina + met versus lina (26.2% versus 17.3% and 6.3% versus 2.4% respectively).

The group (SAF-C8) of all Phase II and III studies with linagliptin + metformin included 3529 patients of whom 2603 reported AEs; 6.1% severe and < 1% for any organ system. Events of special interest were for linagliptin+ metformin were renal (≤1.3%), hypersensitivity (≤ 1.2%) and pancreatitis, (≤0.2%).

Adverse drug reactions were reported at similar rates across all groups in the pivotal study (8-14%). The frequency of serious adverse events ranged from 1.4% in both lina+ met groups and placebo to 4.2% in lina 5 group. One fatality in the met 1000 group was considered unrelated. In SAF-C8, a grouping of all studies with linagliptin + metformin, drug related AEs were reported in 17% of all patients. There were 9 deaths while receiving lina + met and 5 reported in patients receiving metformin as monotherapy or with glimepiride; causes were mainly cardiovascular and considered unrelated to study medication. Discontinuations due to AEs were at similar rates across the pivotal study (<5% for lina, met, and lina+ met) and combined groups; for lina + met 3.4% in SAF- M1 and 5.2% in SAF-C8.

Laboratory tests

The evaluator considered there was no evidence of hepatic toxicity, or clinically relevant differences between groups. In Study 1218.46 the proportion transitioning to > ULN ALT in Lina 2.5 + met 1000 group was 15.7%, and in the open label subset 11.1%, that is, very common; however no patients fulfilled the criteria for Hy's law. In the study grouping for safety for lina+ met, SAF-C8, there were 129 hepatic events in 3529 patients.

There was a suggestion that for small numbers renal impairment increased from normal/mild to moderate in Study 1218.46. In SAF-C8, only 47.6% had normal renal function at the end of treatment; 22.4% with normal renal function at baseline developed mild renal impairment, 0.7% moderate and 2 patients (0.1%) developed severe renal impairment.

Delegate's comment

> Metformin is contraindicated in hepatic insufficiency and renal impairment, and in conditions likely to alter renal function such as shock, sepsis or dehydration, and these aspects should be clear in the PI for the fixed dose combination product.

Hypoglycaemia reports in 1218.46 were 5 in lina 2.5 + met 500 and 0 in lina 2.5 + met 1000. In SAF-C8 14% of patients reported hypoglycaemic events and 3.8% reported severe hypoglycaemic events.

Cardiovascular safety

The CER describes a meta-analysis of 8 trials with a total of 5239 diabetic patients. The primary endpoint was the adjudicated composite of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke and angina requiring hospitalisation. Median drug exposures were 175 days for linagliptin, 367 days for placebo and 619 days for active comparator groups. The difference of events (11 linagliptin, 23 in comparator groups), incidence rate/1000 patient years and Kaplan-Meier plots indicated no risk

increase for linagliptin; differences were non-significant when all placebo–controlled trials versus linagliptin were plotted.

Delegate's comment

This is included in the currently approved PI for the single agent Trajenta. However there appear to be additional analyses available, associated with an altered overall hazard ratio and the sponsor should provide updated analyses with the ACPM response.

CER safety conclusions

The combination linagliptin + metformin was assessed in 3529 patients with T2D, with combined study datasets resulting in information for exposure ≥ 24 weeks of n = 2694, and ≥ 78 weeks of n = 1756, for all strengths of linagliptin (2.5 mg BID, 5 mg once daily, or 10 mg once daily), in combination with metformin given either as background therapy or free combination therapy (500 mg or 1000 mg BID).

Overall the adverse event profiles including for SAEs were similar across groups and the evaluator was satisfied the AE profile was as known for linagliptin and metformin and there was no evidence to suggest and increased incidence of AEs when used in combination.

Meta-analysis of 8 trials, provided with this submission, did not suggest increased risk of serious cardiac disorders for linagliptin as assessed by adjudicated composite endpoint.

CER benefit-risk

The evaluator identifies the only benefit of the FDC compared to free combination as 'increased convenience and compliance'.

The risks include the adverse events of both components, as well as prescription of the combination product without sufficient attention to metformin precautions and contra-indications.

Authorisation was recommended by the evaluator for the requested indications.

Risk-benefit analysis

Issues identified by the delegate

- There were no data supporting increased safety or clinical benefit for the fixed dose combination in a clinical setting. The argument for registration of Trajentamet relies on the possibility that taking fewer tablets that is, 1 BID could improve compliance versus 1 BID for metformin and one daily for linagliptin.
- The Indication as stated could be interpreted as including first line therapy with linagliptin + metformin. This was not explicitly proposed, and may be made less ambiguous by moving the comma after 'appropriate' to follow 'metformin alone'.
- The draft PI did not include adequate reference to metformin; for example it does not contain the boxed warning for metformin with respect to risk of lactic acidosis or a complete list of contraindications, or advice for review of metformin dosage. Circumstances where metformin would be discontinued should be described. PK information for metformin for special populations appears to be missing, and the PK food study for the combination appears inaccurate. The pregnancy categorisation should be amended as per thenonclinical report.

- Tradenames should indicate the product is a fixed dose and the strength of components.
- The clinical evaluator recommended amended statements on possible increased exposure to linagliptin in African-American and Asian subjects, as identified by the evaluator from steady state PK studies, as it may result an increase in adverse drug-drug interactions.
- The proposed PI included the same statement about cardiovascular risk as for the approved PI for Trajenta. However it appears in subsequent analyses that the estimated hazard ratio has changed substantially. The sponsor should clarify this in the pre-ACPM response.

Summary

Based on the available data and evaluations the Delegate proposed to approve registration of FDC linagliptin + metformin tablets all strengths, provided the PI was amended appropriately.

This Delegate's Overview was submitted to ACPM for advice.

Response from sponsor

Boehringer Ingelheim Pty Limited (BI) provided the following response to the Delegate's Overview.

Amendments to the proposed indication

BI accepted the Delegate's proposed amendment to the indication. The amended indication for the linagliptin/metformin fixed dose combination is now:

> *Trajentamet is an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or in those already being treated and well controlled with the free combination of linagliptin and metformin.*
>
> *Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

Change to the proposed tradename

BI considered the Delegate's comment "*It is unsatisfactory that only two of the tradenames proposed give any hint that the tablets is a fixed dose combination with metformin.*"

BI proposed to adopt Trajentamet as the primary tradename for the linagliptin/metformin hydrochloride fixed dose combination tablets.

Safety and clinical benefit for the fixed dose combination in clinical setting

BI supported that the primary rationale of using a fixed dose combination product is:

- For patient convenience; for this product the number of daily tablet intake will reduce from 3 tablets (2 metformin tablets and 1 Trajenta (linagliptin) tablet) to 2 Trajentamet tablets a day.
- To facilitate compliance in a patient population with commonly co-morbid conditions like hypertension and hyperlipidemia requiring polypharmacy.

However, the sponsor disagreed with the Delegate's comment that there are no data supporting increased safety or clinical benefit for the fixed dose combination in a clinical setting.

Bioequivalence (BE) studies [Studies 1288.1, 1288.2 and 1288.3] were performed in T2DM patients for the three proposed fixed-dose strengths to bridge the clinical trial results performed with linagliptin and metformin given as separate tablets. The BE studies demonstrated that the fixed-dose combination tablets were bioequivalent to the free combinations of linagliptin and metformin tablets. Therefore, clinical efficacy has been established for the fixed-dose combination tablets on the basis of these BE studies.

Twice daily posologies of linagliptin plus metformin were used in Study 1218.46 (24 week factorial design study with initial therapy) and Study 1218.62 (12 week add-on to metformin study). These studies have confirmed efficacy and safety of the linagliptin 2.5 mg/metformin twice daily combinations versus metformin monotherapy. Furthermore, Study 1218.62 showed non-inferiority of linagliptin 2.5 mg twice daily versus linagliptin 5 mg once daily on top of metformin background therapy (primary endpoint of HbA1c reduction from baseline) in patients with T2DM. This study (1218.62) was powered for non-inferiority of linagliptin 2.5 twice daily versus 5 mg once daily with regard to primary endpoint HbA1c. Pooled analyses of placebo controlled studies of linagliptin+metformin (versus placebo+metformin) did not reveal any clinically meaningful difference in the safety profile for the linagliptin twice daily versus once daily posology.

Discussion of possible impact of ethnicity with increased exposure to linagliptin

BI did not consider a statement with regard to an increased exposure in African Americans or Asian subjects as necessary for the following reasons:

- The differences in exposure observed between African Americans or Asians in comparison to Caucasian subjects were of minor magnitude (in general about 30%) and are therefore not relevant considering the large safety margin of linagliptin (note that doses of up to 600 mg well tolerated in the SRD trial).
- Also when compared to the totality of Caucasian data, the exposures seen in Asians and African Americans are contained within the range seen in Caucasian subjects (healthy volunteers and patients).

Finally and most importantly, the DPP-4 inhibition in Caucasians, African Americans and Asians was absolutely comparable indicating that the same efficacy is reached despite a slightly different exposure. The most likely explanation for this is that a slightly different number of DPP-4 binding sites between races, which are the main driver of linagliptin PK.

As a consequence it was assumed that:

1. the unbound concentrations, which would be safety relevant for off-target effects were not different between races (note that only 1% of linagliptin is unbound at trough)
2. the minor differences in exposure is even needed to achieve full efficacy in all populations, that is, that the PK-PD relationship was slightly different between studies.

Finally it has to be also noted that the Trajenta (linagliptin) 5 mg dose was found to be safe and efficacious in all investigated races including Asians and African Americans.

Cardiovascular (CV) risk data in PI

The Delegate requested a clarification by BI regarding the change in the estimate hazard ratio that has been described for CV risk for Trajenta (linagliptin). Three meta-analysis reports are available on the investigation of CV risk in T2DM patients treated with linagliptin.

The CV risk statement in the current Trajenta PI incorporated data from the initial meta-analysis report (U10-1736-01) submitted during the registration of Trajenta (approved 21 October 2011). Two additional meta-analysis reports have subsequently been completed as more study data has become available.

The second report was provided as part of the ongoing Trajenta extension of indications application. Data from the third and final report, U12-2369-01 was supported the Safety related notification (SRN) application to update of the CV risk statement in the Trajenta PI. The third and final report meta-analysis report was not supplied to the TGA when the SRN was submitted. At the time the Trajentamet application was prepared the second meta-analysis report was not available therefore the report and the conclusions were not included in this application. A copy of the final meta-analysis report [U12-2369-01] was provided with the sponsor's Pre-ACPM response.

The overall conclusion from all three reports remains the same; linagliptin treatment was not associated with an increase in CV risk. However the increase in number of patients and studies included in the analysis, has resulted in the previously observed significant difference between linagliptin and the comparator now became non-significant (Table 17 below).

Table 17. CV risk meta-analysis

	Current Trajenta PI wording	Proposed Trajenta wording
Number of studies	8	17
Number of patients	5,239	9,462
Reported Hazard Ratio [linagliptin versus active and placebo comparators]	0.34 (95% CI 0.17;0.70)	0.78 (95% CI 0.55;1.12)
Reference (date of report)	U10-1736-01 (May 2010)	U12-2369-01 (Dec 2012)

Furthermore, the statement on CV risk meta-analysis in the Trajentamet PI will be updated to be consistent with the wording proposed in the ongoing Trajenta Safety related notification.

Conclusion

Boehringer Ingelheim Pty Limited agreed with the Delegate's recommendation to approve the registration of the new fixed dose combination product of linagliptin and metformin hydrochloride (Trajentamet®) film-coated tablets for the following indications:

> *Trajentamet is an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or in those already being treated and well controlled with the free combination of linagliptin and metformin.*
>
> *Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

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**:**

An adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or in those already being treated and well controlled with the free combination of linagliptin and metformin.

Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

The proposed dosing instructions are also supported.

Proposed amendments to the PI /CMI include:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and specifically advised on the inclusion of the following:

- a statement in the *Precautions* and *Contraindications* sections of the PI to clarify the renal function contraindication which is not in line with Australian Prescriber advice, standard clinical practice, the Australian Medicines Handbook 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 approve the registration of the products Trajentamet (linagliptin/metformin hydrochloride at 2.5/500 mg, 2.5/850 mg and 2.5/1000 mg) film coated tablets in blister pack and bottles to be administered orally twice daily with meals, indicated for:

Trajentamet is indicated as an adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus when treatment with both linagliptin and metformin is appropriate in patients inadequately controlled on metformin alone, or those already being treated and well controlled with the free combination of linagliptin and metformin.

Trajentamet is indicated in combination with a sulfonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulfonylurea.

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the Trajentamet 2.5 mg/500 mg, Trajentamet 2.5 mg/850 mg and Trajentamet 2.5 mg/1000 mg (linagliptin/metformin HCl EU Risk Management Plan (RPM) Version 4.0, dated 13 July 2012 [data lock point 15 October 2010] with Australian Specific Annex VIII, included with submission 2011-03536-3-5, and any subsequent revisions with any accompanying caveats and requests for pharmacovigilance activities as agreed with the TGA and its Office of Product Review.
2. Post marketing reports are to be provided in line with the current published list of European Union (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 periodic Safety Update Reports each covering six months.

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

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