Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Linagliptin

Proprietary Product Name: Trajenta

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
ACPM	Australian Committee for Prescription Medicines
ADA	American Diabetes Association
AE	adverse event
ANCOVA	analysis of covariance
AUCG	area under glucose curve
BI	Boehringer Ingelheim
BMI	body mass index
CEC	clinical event committee
CER	clinical evaluation report
CI	confidence interval
CMI	consumer medicine information
CTD	common technical document
DPP-4	dipeptidyl peptidase 4
EASD	European Association for the Study of Diabetes
eGFR	estimated glomerular filtration rate
FAS	full analysis set
FDC	fixed dosage combination
FPG	fasting plasma glucose
GIP	glucose-dependent inhibitory peptide
GLP-1	glucagon-like peptide 1
HbA1c	haemoglobin A1C
IVRS	interactive voice response system
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
MDRD	modification of diet in renal disease

Abbreviation	Meaning
NPH	Neutral Protamine Hagedorn
OHA	oral hypoglycaemic agent
PCSA	possibly clinically significant laboratory abnormality
PI	product information
PK	pharmacokinetic
PPS	per protocol set
PV	protocol violation
RMP	risk management plan
SAE	serious adverse event
SCS	Summary of Clinical Safety
SD	standard deviation
SI	Systeme Internationale
SOC	system organ class
SU	sulphonylurea
SWS	switched set
TGA	Therapeutic Goods Administration
TZD	thiazolidinedione
T2DM	type 2 diabetes mellitus

I. Introduction to product submission

Submission details

Type of Submission	Extension of Indications
Decision:	Approved
Date of Decision:	9 May 2013
Active ingredient(s):	Linagliptin
Product Name(s):	Trajenta
Sponsor's Name and Address:	Boehringer Ingelheim Pty Ltd 78 Waterloo Rd, North Ryde, NSW 2113
Dose form(s):	Film-coated tablet
Strength(s):	5 mg
Container(s):	Blister pack
Pack size(s):	30's
Approved Therapeutic use:	*Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise,* *as monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or* *as add on to metformin, sulfonylureas or metformin plus sulfonylureas, or to insulin (with or without metformin).*
Route(s) of administration:	Oral
Dosage:	5 mg once daily. May be taken with or without food
ARTG Number (s)	175499

Product background

Linagliptin is a synthetic non-peptide competitive reversible inhibitor of dipeptidyl-peptidase-4 (DPP-4). Renal excretion is a minor pathway of elimination of linagliptin at therapeutic doses *(see Pharmacokinetics section of PI; no dosage adjustment is necessary in renal insufficiency).* Linagliptin acts to lower blood glucose by extending the half-life of glucagon-like peptide-1 (GLP-1). GLP-1 augments glucose-stimulated insulin release, limits glucagon secretion and slows gastric emptying.

This AusPAR describes the application by the sponsor to extend the indications for Trajenta to include use as:

· *a monotherapy and*

- *an add on to insulin (with or without metformin and/or pioglitazone and/or sulphonylurea)*

Regulatory status

Linagliptin ('Trajenta®') 5 mg tablet once daily was approved for registration in October 2011 for the following indication:

> *Trajenta is indicated 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.*

Monotherapy indication for linagliptin was approved in European Union (EU), USA, Canada and Switzerland in the initial registration. The extension of indication for "add-on to insulin" was approved in the USA on 14 August 2012 and in the EU on 24 October 2012. Applications in Canada and Switzerland are still in progress. The current approved indications (monotherapy and add-on to insulin) for EU and USA are summarised in Table 1 below.

Table 1. International Regulatory Status for Trajenta

Country	*Submission Date and status*	*Indication*
European Union	March 2012 Approved: 24 October 2012	Trajenta is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults: as **monotherapy** • in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment. as **combination therapy** • in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control. • in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. • in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.
United States of America	October 2011 Approved: 13 August 2012	1.1 Monotherapy and Combination Therapy TRADJENTA tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see Clinical Studies (14.1)]. 2.2 Concomitant Use with an Insulin Secretagogue (e.g., Sulfonylurea) or with Insulin When TRADJENTA is used in combination with an insulin secretagogue (e.g., sulfonylurea) or with insulin, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia [see Warnings and Precautions (5.1)].
Canada	15 June 2012	Ongoing
New Zealand	Not submitted	
Switzerland	11 April 2012	Ongoing

Product Information

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

II. Quality findings

There was no requirement for a quality evaluation in a submission of this type.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

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

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder principally characterised by hyperglycaemia. Its incidence and prevalence is increasing in developed countries, associated with a parallel increase in obesity contributed to by excessive and qualitatively inappropriate food intake and reduced physical activity. The pathogenesis of T2DM includes insulin resistance together with a relative impairment of insulin secretion which tends to progress over time. Part of the insulin deficiency is represented by a diminution in the "incretin effect", the physiological mechanism by which post-prandial insulin secretion is enhanced as a result of insulin secretagogues (incretins) being released into the circulation from the upper gastrointestinal tract following feeding. Linagliptin is an inhibitor of DPP-4, the enzymatic activity of which includes as substrates the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent inhibitory peptide (GIP). Levels of these incretins are therefore increased following administration of linagliptin, which thus lowers blood glucose by enhancing insulin response to feeding.

This action of linagliptin and other DPP-4 inhibitors in improving post-prandial insulin secretion is different from and is complementary to the actions of other oral hypoglycaemic agents (OHA) currently in use and mentioned in the current and proposed indications for Trajenta. Metformin improves glucose disposal by mechanisms which are not entirely clear but which are not dependent on insulin, and can be regarded as improving insulin sensitivity. Sulphonylureas (SU) stimulate insulin secretion more directly and can do so in the fasting state or at normal blood glucose levels, hence being more prone than other OHA to cause hypoglycaemia. Thiazolidinediones (TZD) counter insulin resistance by improving response to insulin at the post-receptor level. Combinations of these classes of OHA, including DPP-4 inhibitors such as linagliptin, are therefore rational as their various actions are all directed at improving the quantum of insulin action on its target metabolic pathways; as is the supplementary administration of insulin itself, hence combination of any OHA class with insulin also is a hypothetically rational basis for therapy.

Appropriate medical management of T2DM is guided by clinical algorithms such as that contained within the consensus statement of the American Diabetes Association and

European Association for the Study of Diabetes.[1] This, like other similar guidelines, gives primacy to the introduction of lifestyle measures and to metformin as the drug of first choice for pharmacotherapy. The role of the other drug classes mentioned above, and the hierarchy which might govern their order of introduction into T2DM Management, is less clearly defined. Metformin (except in the United States) and SU have both been in use for over 50 years, whereas TZD and incretin based therapies, including GLP-1 analogues as well as DPP-4 inhibitors, have been introduced much more recently and best practice with regard to their appropriate use remains in a state of evolution. To further compound the situation, there remains some use of other OHA classes introduced earlier such as glinides (such as repaglinide) and alpha glucosidase inhibitors such as acarbose which is registered in Australia and voglibose which is not but which is used in one of the studies in the submission. Additionally, the recognition that the pathogenesis of T2DM includes a variable but significant element of insulin deficiency has led to an increasing use of insulin in the management algorithm. This in turn has led to the need for studies, such as some of those included in this submission, which examine the efficacy and safety of OHA used in conjunction with insulin therapy.

Contents of the clinical dossier

Scope of the clinical dossier

There was a complex overlap of datasets supporting this application and three related submissions (for changes to the Clinical trials section of the PI and registration of the fixed dosage combination (FDC), in addition to the original registration application).

The submission was well presented and indexed and easy to navigate in electronic format. In order to address the rather complex overlap between the datasets supporting this application and three related submissions, a detailed tabular listing of the clinical studies submitted in support of all four applications was provided by the sponsor. The sponsor has provided annotations indicating which studies have already been evaluated by the TGA in the related submissions.

Throughout the application, each clinical trial report has two identifying numbers, one in the format 1218.xx and the other in the format Uxx-xxxx-xx. In this evaluation report, the 1218.xx format only is used.

The submission contained the following clinical information:

- A single newly submitted pivotal efficacy/safety study, 1218.36, supporting the addition of linagliptin to insulin with or without various combinations of other OHA.
- Six other efficacy/safety studies. Five of these support various aspects of the application for extension of indications; four of these (1218.40, 1210.43, 1218 .50 and 1218.52) have been previously evaluated but are now presented with final extension data; and one (1218.63) is newly presented. The sixth (1218.20) is the final 104 week report of a study evaluated for a previous submission to the TGA and is presented in support of an update to the clinical trials section unrelated to this application for extension of indications.
- Pooled safety analysis
- Literature references

[1] Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman R, Sherwin R, Zinman B. (2009). Medical management of hyperglycaemia in type II diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 32 (1): 193.

Pharmacokinetics

Studies providing pharmacokinetic data

No studies providing evaluable analyses of PK data were included in the submission. PK measurements were nevertheless obtained in some of the included studies. Linagliptin concentrations in trough samples were obtained in pivotal Study 1218.36 but the results are not provided in the interim report included with this submission. It is stated that they will be provided in the final report. Trough linagliptin measurements were also obtained, with particular reference to level of renal dysfunction, in supporting studies 1218.43 and 1218.63, and are referred to in the relevant study summaries below.

Summary of pharmacokinetics

The limited PK data referenced in the previous paragraph is discussed below in relation to safety in the renally impaired population.

Evaluator's overall conclusions on pharmacokinetics

Conclusions are limited to the above referenced discussion on renal safety.

Pharmacodynamics

Studies providing pharmacodynamic data

No pharmacodynamic studies have been submitted with or are relevant to this application.

Summary of pharmacodynamics

Not applicable.

Evaluator's overall conclusions on pharmacodynamics

Not applicable. The pharmacodynamic action of linagliptin has been well characterised in previous submissions, particularly the initial registration application.

Efficacy

Dosage selection for the pivotal studies

As indicated above, a single dosing schedule of 5 mg once daily applies to all current indications for linagliptin and has been continued in the pivotal Study 1218.36 and all of the other studies in the submission.

Studies providing efficacy data

A single newly submitted pivotal efficacy/safety study, 1218.36, supporting the addition of linagliptin to insulin with or without various combinations of other OHA.

Six other efficacy/safety studies were also submitted. Five of these support various aspects of the application for extension of indications; four of these (1218.40, 1210.43, 1218 .50 and 1218.52) have been previously evaluated but are now presented with final extension data; and one (1218.63) is newly presented. The sixth (1218.20) is the final 104 week report of a study evaluated for a previous submission to the TGA and is presented in

support of an update to the clinical trials section unrelated to this application for extension of indications.

Evaluator's conclusions on clinical efficacy

For use with insulin

Efficacy of linagliptin for T2DM is supported by Study 1218.36. With regard to this being a single pivotal study, it should be noted with respect to the relevant guideline[2] that this finding was statistically robust, with a clinically significant treatment effect, measured as change in HbA1c, of 0.62%. Although presented as a 24 week interim report, the submission contained sufficient data for the full 52 week duration of the study to conclude that the treatment response was enduring for that period. Efficacy with or without metformin and in the presence or absence of moderate renal insufficiency was also shown. Importantly, this was a study of adding linagliptin to insulin therapy, rather than vice versa and is therefore relevant to the most likely sequence of clinical use, as discussed below. Efficacy for this indication, with unimpaired treatment effects on HbA1c in the range 0.64-0.73%, is further supported in the population of renally impaired T2DM patients by Study 1218.43 and by Study 1218.63 in patients in the age groups over 70 and over 75. Study 1218.63 also shows that efficacy of linagliptin is maintained when added to insulin when metformin and sulphonylurea are both already being given.

For use as monotherapy

Newly submitted evidence of efficacy of linagliptin for T2DM is restricted to the long-term extension (total 52 weeks) of Study 1218.50 carried out on patients ineligible for metformin due to intolerance or contraindication. The previously evaluated finding of efficacy as monotherapy in this setting, with a HbA1c treatment margin of 0.57% is confirmed, along with observational evidence that the response is maintained at 52 weeks. This observational evidence also leaves open the question of whether the size of this treatment response might be less than that obtained with a sulphonylurea (glimepiride) used as active comparator in the study. Study 1218.40 did not provide new evidence of efficacy as monotherapy, although the subset of its subjects who were recruited from Study 1218.16 did demonstrate evidence of such efficacy when that study was originally evaluated.

This evaluation does not concur with the sponsor's proposal that the final results of Study 1218.43 provide supportive evidence for use as monotherapy. However, it is felt that use as monotherapy in patients in whom metformin is contraindicated or not tolerated is adequately supported by the data evaluated in the original registration submission along with the findings in the final report of Study 1218.50.

Safety

Studies providing safety data

- Pivotal efficacy Study 1218.36

Pivotal studies that assessed safety as a primary outcome

- No studies of this type submitted.

[2] EMEA points to consider on application with one pivotal study, CPMP/EWP/2330/99, 31 May 2001

Dose-response and non-pivotal efficacy studies

The non-pivotal efficacy studies provided safety data, as follows:

- Study 1218.63 provided data on 162 patients treated with linagliptin and 79 with placebo.
- Study 1218.50 provided data on 137 patients treated in Part 2 of the study with linagliptin and 64 with the active comparator glimepiride (safety data for Part 1 was reviewed in the previous CER).

Pivotal studies that assessed safety as a primary outcome

- No studies of this type submitted.

Patient exposure

Patient numbers and exposure to placebo and linagliptin for the study groupings reviewed in this report, as described above, are shown below (Table 2).

Table 2. Patient exposure

	SAF-3		SAF-4	
	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
Number of patients, N (%)	700 (100.0)	720 (100.0)	630 (100.0)	631 (100.0)
Exposure categories, N (%)				
≥24 weeks	631 (90.1)	664 (92.2)	580 (92.1)	598 (94.8)
≥52 weeks	218 (31.1)	229 (31.8)	186 (29.5)	197 (31.2)
Duration of treatment exposure [days]				
Mean (±SD)	292 (116.5)	297 (111.8)	295 (114.5)	303 (110.0)
Median (minimum, maximum)	295 (1, 531)	298 (3, 531)	292 (4, 531)	304 (3, 531)
Overall patient years	559.0	585.1	508.8	523.6

	SAF-5		SAF-6	
	Placebo	Linagliptin 5 mg	Placebo	Linagliptin 5 mg
Number of patients, N (%)	55 (100.0)	54 (100.0)	121 (100.0)	126 (100.0)
Exposure categories, N (%)				
≥24 weeks	42 (76.4)	47 (87.0)	103 (85.1)	109 (86.5)
≥52 weeks	32 (58.2)	32 (59.3)	34 (28.1)	26 (20.6)
≥78 weeks	0	0	0	0
≥102 weeks	0	0	0	0
Duration of treatment exposure [days]				
Mean (±SD)	290 (132.6)	315 (103.9)	283 (122.0)	265 (107.5)
Median (minimum, maximum)	364 (1, 384)	364 (29, 396)	293 (4, 527)	244 (11, 531)
Overall patient years	43.6	46.6	93.8	91.3

Note that exposure data for SAF-5 (Study 1218.43) will have been included in the previous evaluation.

Postmarketing experience

The data on cardiovascular safety referred to in the previous section was the only post marketing information contained in the submission.

Safety issues with the potential for major regulatory impact

No new issues were identified in this evaluation. Adverse effects previously identified as potential risks for this drug class (such as hypersensitivity reactions and pancreatitis) were not observed to be of any greater incidence in the data reviewed for this submission.

Other safety issues

Safety in special populations

The study populations in the submission contained a significant proportion of subjects in older age groups and with impaired renal function. No specific safety issues were identified for these populations, although it should be observed that in each case the number of subjects exposed to linagliptin was relatively small: 54 in the case of the renally impaired population SAF-5, and 126 for the elderly population SAF-6 (Table 12 in AusPAR Attachment 2).

Evaluator's overall conclusions on clinical safety

The profile of adverse events by comparison with placebo shows no pattern to suggest any newly emergent safety concern regarding linagliptin. There was a minor incidence of specified adverse effects (hypersensitivity, pancreatitis) which have been previously identified as being associated with this drug. Linagliptin shows a low incidence of hypoglycaemia, particularly by comparison with a sulphonylurea which is a therapeutic alternative choice in the proposed usage. The findings on cardiovascular risk do not suggest any adverse effect of linagliptin in this respect and invite continuing analysis for the possibility of a beneficial effect.

List of questions

Safety

No questions, although the cardiovascular safety information in the draft PI should be updated.

Clinical summary and conclusions

First round benefit-risk assessment

First round assessment of benefits

The benefits of linagliptin in the proposed usage are:

- Improved diabetes control as measured by HbA1c reduction.
- Availability of a therapeutic alternative for patients unable to take metformin, whether because of intolerance or contraindication due to impairment of renal function.
- Consequent likelihood (yet to be proven for this class of drugs) of reduced risk of diabetes complications.
- Reduced risk of hypoglycaemia and weight gain by comparison with most likely therapeutic alternative (sulphonylurea), at least in the monotherapy usage.
- In the insulin usage, reduction in insulin dosage; although whether that is beneficial *per se* is arguable.

First round assessment of risks

The risks of linagliptin in the proposed usage are:

- A low level of risk of described class specific side-effects including hypersensitivity reactions and pancreatitis.

- Safety of use in patients aged 70 or above, and in those with impaired renal function, is at this stage dependent on the observation of relatively limited exposure.
- Potential (and inestimable) future risk of presently unforeseen side-effects for this relatively new drug by comparison with therapeutic alternatives with long safety records (for example, insulin, sulphonylureas).

First round assessment of benefit-risk balance

The benefit-risk balance of linagliptin in both aspects of the proposed indication was considered favourable assuming that the proposed monotherapy usage is adjusted to include only patients ineligible for metformin.

First round recommendation regarding authorisation

As mentioned above, clinical practice regarding the positioning of recently introduced blood glucose lowering agents, including DPP-4 inhibitors, is in a state of evolution. Currently, three DPP-4 inhibitors in addition to linagliptin (sitagliptin, saxagliptin and vildagliptin) are registered for use in Australia with differing approved indications. All three are approved as add-on therapy to metformin, a sulphonylurea or a thiazolidinedione. Sitagliptin is also approved as monotherapy when metformin cannot be used. Sitagliptin and saxagliptin are each approved for initial combination therapy with metformin in specific clinical circumstances (high initial HbA1c and poor prospects of response to monotherapy). Most recently (TGA approval 19 September 2012), a limited indication for use with insulin (basal and pre-mixed insulin only, with or without metformin) has been approved for saxagliptin. These differences, which may be confusing to the prescriber, appear to be related not so much to differences in the properties of the various drugs as to variations in the trial design and types of evidence presented in submissions for registration.

Given the evaluation and regulatory process involved, it can be concluded from the above discussion that there is an evidence base and a positive benefit/risk balance supporting the use of DPP-4 inhibitors as a class in the following therapeutic situations: monotherapy when metformin cannot be used, add-on therapy to the other OHA classes mentioned, initial combination with metformin in defined clinical circumstances, and use with insulin. Consideration of any of these indications for other members of the class such as linagliptin is therefore reasonable provided there is adequate supporting evidence. In this particular application, use as monotherapy and use with insulin are the additional indications requested and these are discussed separately below.

Use as monotherapy

Consideration of this aspect of the application was initially influenced by uncertainty as to the sponsor's intentions. Although the letter of application includes in the proposed new indication the use "as monotherapy", without qualification, it goes on, on the following page, to indicate that the company now accepts that monotherapy should be restricted to metformin-ineligible patients, and this intention is clearly supported by the summary in the sponsor's Clinical Overview, as discussed above. In view of this, it will be assumed for the purpose of this evaluation report that the application is in fact for monotherapy in metformin-ineligible patients. The letter of application and the sponsor's Clinical Overview requests consideration of the resubmission for monotherapy on the basis of the final results of Studies 1218.43 and 1218.50, *"together with the previously submitted data"*. The pivotal study for the unrestricted monotherapy application in the original submission was Study 1218.16 which was evaluated in the CER for the submission but not included amongst the data for the present submission. The study was carried out on treatment-naive patients and demonstrated superiority to placebo with a treatment difference in HbA1c of 0.69%. However, the evaluator did not recommend first-line treatment based on

this data on the basis that other submitted data showed linagliptin to be inferior to sulphonylurea in this situation and that there was no data comparing it with metformin as initial monotherapy. The evaluator recommended that an alternative indication suitable for approval might be *"…. as monotherapy (where both metformin and sulphonylureas are either ineffective or contraindicated)…."* Apart from the reference to sulphonylureas, this is effectively what is now being requested.

The findings of Studies 1218.43 and 1218.50, which support efficacy in monotherapy for metformin-ineligible patients, together with the benefit-risk balance for use in that situation, have been reviewed above.

Positioning linagliptin relative to sulphonylureas

The recommendation of the previous evaluator that monotherapy only be considered where both metformin and sulphonylureas are either ineffective or contraindicated cannot be lightly dismissed. Sulphonylureas were the first class of oral hypoglycaemic agent to be used and apart from the important possibility of causing hypoglycaemia, have a well-established safety as well as efficacy profile. Prior to the introduction of new classes of oral agents including thiazolidinediones and DPP-4 inhibitors, most treatment algorithms placed sulphonylureas as first choice for add-on treatment to metformin, or even first-line treatment for the small proportion of non-obese T2DM patients. The fact that they are much less costly might also be a factor in circumstances not relevant to this evaluation report.

No evidence has been produced in this submission or to the evaluator's knowledge in any of the related submissions for linagliptin, that when used alone it has efficacy superior to that of sulphonylureas. If anything, the reverse may be the case; as discussed above, in a long-term double-blind controlled study greater HbA1c reduction was seen with glimepiride than with linagliptin. This was in the context of add-on treatment to metformin but given the differing and complementary actions of the three drugs, it is as likely as not that the same effect would be observed in the absence of metformin. Phase 2 Study 1218.6, reviewed in the CER of the original submission for registration showed in drug naive T2DM patients a HbA1c reduction at 12 weeks of 0.73% in subjects randomised to 5 mg double-blind linagliptin by comparison with 0.90% with open label glimepiride; and in a similar study with open label metformin as the active comparator (1218.5) the HbA1c reduction was 0.46% for 5 mg linagliptin by comparison with 0.85% for metformin.

On the basis of efficacy alone, therefore, it is difficult to recommend linagliptin (or possibly other DPP-4 inhibitors) as monotherapy in preference to sulphonylureas in the absence of intolerance or contraindication to the latter, something which occurs much less frequently than with metformin. However, there are safety risks to be considered, particularly the much greater incidence of hypoglycaemia with sulphonylureas. The nature of the risk/benefit equation will vary between individuals, either due to their personal history of hypoglycaemia, or occupation (for example, heavy transport driver) or other medical conditions (such as epilepsy). In view of this, it is felt that the choice between linagliptin and sulphonylurea is best left to the treating clinician, taking account of the patient's circumstances. The situation regarding the choice between linagliptin and metformin is different, as the contraindication and intolerance issues are more clearly defined and in their absence, there is no reason to favour linagliptin.

In summary, it is recommended that use as monotherapy in patients ineligible for metformin be approved, without qualification with regard to sulphonylurea use. With regard to clarity for the prescriber, it may be of some benefit that this is equivalent, as discussed above, to the conditions for the only other DPP-4 inhibitor currently approved for use as monotherapy in Australia.

Use with insulin

In the introduction to the summary of the submission in the sponsor's Clinical Overview, it is stated that "With the present submission, Boehringer Ingelheim is applying for the use of linagliptin as combination therapy with insulin in adult patients with T2DM when insulin with or without oral antidiabetic drugs (metformin, pioglitazone, sulphonylurea) does not provide adequate glycaemic control". It is thus defined that the target population for this combination therapy includes patients whose treatment includes various combinations of metformin, pioglitazone, and sulphonylureas. The inclusion of all of these drug classes in the proposed indication once linagliptin is added, however, demands evidence of efficacy with regard to each of them.

With regard to **metformin**, pivotal Study 1218.36 provides adequate evidence that linagliptin is effective when added to insulin whether in the presence of or in the absence of metformin. It would in any case be therapeutically irrational to prefer linagliptin to metformin as an add-on therapy to insulin, unless metformin was contraindicated or not tolerated.

The submitted evidence does not support the inclusion of **pioglitazone** in the therapeutic equation proposed. The only relevant study was 1218.36, which included small subsets of subjects taking pioglitazone (1% of study population) or pioglitazone and metformin (7.4% of study population) as well as insulin. Analysis of the primary efficacy parameter, HbA1c change from baseline, showed that the treatment margin of linagliptin over placebo was unchanged and remained significant in the pioglitazone + metformin subset, by comparison with the majority subset taking metformin alone with insulin (see Table 4 in AusPAR Attachment 2). The pioglitazone therapy was pre-existing and not determined by randomisation. The data does not exclude the possibility of additional therapeutic benefit from pioglitazone in combination with linagliptin, metformin and insulin but neither does it prove it. The subset of subjects taking pioglitazone alone with insulin was too small to allow any conclusions about the benefit of linagliptin in that combination. Furthermore, there is no existing approval for use of linagliptin in any combination with pioglitazone, and to allow its use specifically in this situation together with insulin with or without metformin would require much stronger evidence than is found in this study.

The situation with regard to **sulphonylurea** is somewhat similar. This class of drug was not used in pivotal Study 1218.36 and no sub-analyses by class of background therapy were performed in Study 1218.43. Some evidence of efficacy for the linagliptin + sulphonylurea + metformin + insulin combination is seen in Study 1218.63, in which the group so treated achieve the greatest effect size in terms of HbA1c change but again there is no randomisation to the sulphonylurea component or statistical analysis by comparison with the linagliptin + metformin combination with insulin. The situation is nevertheless slightly different in that there is evaluated evidence supporting an existing indication for the triple linagliptin + sulphonylurea + metformin combination, or linagliptin + sulphonylurea, without insulin.

It is therefore recommended that on the basis of the evidence submitted, use of linagliptin be approved as add-on treatment to insulin with or without metformin. This evaluator would have no objection to this being extended to use as add-on to insulin with or without metformin and/or sulphonylurea, although the evidence is marginal. Use with pioglitazone in any combination was not supported.

Proposed indication

In line with the above comments, it was recommended that the proposed indication be altered to the following:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when*

> *metformin is not tolerated or contraindicated, or as add on to metformin, sulphonylureas or metformin plus sulphonylureas, or to insulin (with or without metformin **and/or sulphonylureas**).*

The phrase "and/or sulphonylureas" in bold should be removed if it is felt inappropriate to include it on the basis of marginal evidence.

The above could be slightly simplified and shortened, if thought appropriate, as follows:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when metformin is not tolerated or contraindicated, or as add on to metformin and/or sulphonylureas, or to insulin (with or without metformin and/or sulphonylureas). This would assume that the phrase metformin and/or sulphonylureas can legitimately be taken to include the combination of the two drugs/classes.*

If the recommendation of this report to approve monotherapy without qualification as to sulphonylurea use is not accepted, the words *"metformin and sulphonylureas are"* could be substituted for *"metformin is"* in the second line of either version.

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).

The following table (Table 3) 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 3. Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
1. Safety considerations may be raised by the clinical and non-clinical evaluators through the consolidated TGA request for information and/or the nonclinical and clinical Evaluation Reports respectively. It is important to ensure that the information provided in response to these includes consideration of the relevance for the Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	The sponsor has not commented on this recommendation	No additional safety concerns were raised.
It was recommended to the Delegate that the sponsor:		
2. Provide comprehensive details of the Trajenta educational program planned for Australia. This should include but may not be limited to the following: **2(i)-Aims:** It is unclear if this educational program will inform prescribers of any safety concerns	*The Trajenta educational program planned for Australia include:* · *product specific promotional materials (i.e. detail aids and the approved Trajenta* *Product Information(PI)) and* · *disease specific educational activities (online training and face to face*	It was recommended the sponsor submit to the TGA when available, draft materials for the proposed RACGP (Category 1) accredited program, including the questionnaires given before and after to measure the effectiveness of

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
associated with the use of Trajenta. It is recommended that the sponsor provide details of which safety concerns the program addresses and how it addresses them. **2(ii)-Implementation:** The sponsor proposes the educational program to be delivered via face to face and online activities. It is recommended the sponsor provide drafts of these educational materials to the TGA prior to marketing and also 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, the intended duration of this program should also be provided. **2(iii)-Evaluation of the effectiveness:** The sponsor proposes that the effectiveness of the educational activities will be reviewed quarterly, based on checklists gathered from face to face activities and outcomes from online activities. It is recommended that the sponsor provide a robust plan to	*meetings)* *Details of the delivery of the promotional materials, proposed educational activities and evaluation of effectiveness were provided.*	the program.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
assess the effectiveness of the educational program in Australia and how this will be demonstrated to the Office of Product Review, TGA.		
3. Provide the protocols/details study synopses to the TGA Office of Product Review, for **3(i)** the FDA PMR 1766-3 and **3(ii)** FDA PMR 1766-4, when available.	**3(i)** *Boehringer Ingelheim has been released from providing Post-marketing requirement (PMR) 1766-3 requested by the FDA. A copy of the FDA letter notifying Boehringer Ingelheim of their release from this post-marketing requirement is provided.* The FDA states in their letter to the Sponsor *"...We have reviewed your submission and have determined that you are released from PMR 1766- 3 because to date, postmarketing adverse event data have not shown hypersensitivity or severe cutaneous reactions safety signals with Tradjenta (linagliptin) Tablets. Additionally, the risk of hypersensitivity and severe cutaneous events can be further assessed through PMR 1766-4, your large cardiovascular outcome trial. We remind you that assessments of the long-term effects of Tradjenta (linagliptin) Tablets on these adverse events are secondary objectives of your required cardiovascular outcome trial (PMR 1766-4), as stated in the May 2, 2011, approval letter."*	This was considered acceptable.
	3(ii) *b) PMR 1766-4 The latest draft of the clinical trial protocol for Study 1218.22 (CARMELINA) is provided*.	This was considered acceptable.
5. List the frequency that *"Immune system disorders"* occur (i.e Common, uncommon or rare) in the proposed Australian PI as this information is missing (see page 12).	*Immune system disorders is classified as the system organ class (SOC), and therefore is not assigned a frequency. To reduce confusion, Boehringer Ingelheim proposes the following* *layout of the post-marketing adverse events listing:* *Immune System Disorders: Rare: Angioedema, urticaria.*	This is considered acceptable.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
	The Australian product information will be updated if OPR is in agreement with this proposed layout.	
It was recommended that the Delegate consider:		
6. The updated indication sought for Trajenta as a monotherapy in the EU (see below; also proposed Summary of Product Characteristics (SmPC) Module 1.10.2.3 of current package) is only for patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment	*Boehringer Ingelheim acknowledges the RMP evaluator's recommendation that the proposed Australian monotherapy indication wording be similar to the EU monotherapy indication. As we have not received the clinical evaluation report, we propose that further discussions on the wording of the proposed indication occur after we have received the Clinical evaluator's and Delegate's recommendations.*	It remains the OPR's recommendation that the Delegate consider updating the indication for Trajenta as a monotherapy (in the EU approved as of 24 OCT 2012) for patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.
7. For the important potential risk 'Infections'-The FDA Product Label includes information on increased rates of urinary tract infection with linagliptin when used in combination with sulfonylurea *"Rates for other adverse reactions for TRADJENTA 5 mg versus placebo when TRADJENTA was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when TRADJENTA was used as add-on to*	*Boehringer Ingelheim provides the following explanation of the observed differences of the listed adverse reactions under the System Organ Class (SOC) 'Infections and infestation' when linagliptin is used in combination with sulfonylurea. The RMP evaluator identified that 'urinary tract infections' was reported at an increased rate in the US product label but this was not included in the Australian Product information (PI).* *In the initial submission the term 'urinary tract infection' was unintentionally not provided in the label documents, although it was identified by the applied algorithm. When the mistake was discovered, a larger data set of placebo controlled trials was available. In this updated data set (placebo N=2364, and linagliptin N=4302) 'urinary tract infection' was reported more frequently in the placebo group (N=95, 4.0%) compared to linagliptin (N=135, 3.1%) [Integrated Summary of Safety, U11-2599-01, Table 5.2.2.1.1.1]. Based on these new data, the event 'urinary tract*	It is remains the OPR's recommendation that the Delegate consider including information on increased rates of urinary tract infection with linagliptin when used in combination with sulfonylurea. The sponsor's response only includes data for linagliptin vs placebo not linagliptin + sulfonylurea vs placebo.

Recommendation in RMP evaluation report	Sponsor's response	OPR evaluator's comment
sulfonylurea;..." (see FDA Product Label page 2). The proposed Australian PI does not include this information.	*infection' was not considered as listed event. As the USPI displayed the algorithm for the side effect identification, the term was subsequently added. The term 'urinary tract infection' is not considered to be listed, therefore no updated was carried out for the EU SmPC or other labels (including the Australian PI).*	
8. The important potential risk 'Worsening of renal function' is not assigned any risk minimisation activities. The FDA Product Label and EU SmPC also do not include any information on this potential risk.	*Boehringer Ingelheim, supports the RMP evaluator's recommendation that the important potential risk 'Worsening of renal function' is not assigned any risk minimisation activities.* *As supported by Study 1218.43 [U11-3170-01], the use of linagliptin as add-on to pre-existing anti-diabetic therapy, the reported safety and laboratory results were comparable between linagliptin and placebo with no distinct safety concerns observed. A statistically significant and clinically relevant reduction in the change from baseline in HbA1c of -0.72% after 52 weeks of treatment was observed for linagliptin compared to placebo. The reduction in HbA1c observed for the linagliptin treatment group was sustained throughout the 52 weeks of the study.* *This study supports the assumption that renal impairment would not significantly alter the exposure of linagliptin and that no dose adjustment would be required in patients with any degree of renal impairment.*	This was considered acceptable.

SmPC=Summary of Product Characteristics

The following table (Table 4) contains the Summary of the Risk Management Plan from the Australian Specific Annex RMP dated 21 May 2012.

Table 4. From Australian Specific Annex (dated 21 May 2012)- Summary of Risk Management Plan. Addendum to EU RMP U10-1739-05.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risk		
Hypoglycaemia	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section '**ADVERSE EFFECTS**' of AUS PI).
Pancreatitis	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section '**ADVERSE EFFECTS**' of AUS PI).
Angioedema/urticaria hypersensitivity	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section '**ADVERSE EFFECTS**' of AUS PI).
Important potential risks		
Skin lesions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Infections	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Worsening of renal function	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Important missing information		
Safety in subpopulations		
High risk patients with recent CV events	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV-safety study and 1218.63 [U09-2389-01]). Ongoing CV meta-analyses of Phase III and IV programme at appropriate time points	Appropriate labelling (Section '**CLINICAL TRIALS, Cardiovascular Risk**' of AUS PI).

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Old patients (>80 years)	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV safety study and 1218.63 [U09-2389-01])	Appropriate labelling (Sections '**PHARMACOLOGY, Pharmacokinetics in special patient groups**, Elderly:' and '**CLINICAL TRIALS, Linagliptin as add on therapy in elderly patients (age ≥ 70 years) with type 2 diabetes**' of AUS PI).
Severe renally impaired patients	Routine pharmacovigilance and analysis of ongoing clinical trial safety data (study 1218.43 [U08-1995-01])	Appropriate labelling (Sections '**PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics In Special Patient Groups**, Renal Impairment:' and '**CLINICAL TRIALS, Linagliptin as add on therapy in patients with severe renal impairment**' of AUS PI).
Paediatric use	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section '**PRECAUTIONS, Paediatric Use**' of AUS PI).
Pregnant and lactating patients	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Sections '**PRECAUTIONS, Use in Pregnancy**' and '**PRECAUTIONS, Use in Lactation**' of AUS PI).
Hepatic impaired patients	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section '**PHARMACOLOGY, Pharmacokinetics, Pharmacokinetics In Special Patient Groups**, Hepatic Impairment' of AUS PI).
Oncological adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Idiosyncratic adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Immunological adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Concomitant P-gp and CYP3A4 inhibitors	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.

Summary of OPR recommendations

OPR suggested wording for conditions of registration

RMP

- Implement EU RMP Version 5.0, dated 16 February 2012 [Data lock point 29 November 2011] with Australian Specific Annex dated 21 May 2012 and any future updates as a condition of registration.

PSUR

- Post marketing reports are to be provided annually 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 Practices (GPP) relating to PSURs. Unless agreed separately between the supplier, who is the recipient of the approval and the TGA, the first report must be submitted to the TGA no later than 15 calendar months after the date of this approval letter. The subsequent reports must be submitted no less frequently than annually from the date of the first submitted report. 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

Outstanding issues

Educational program

The information provided on the educational program is considered acceptable. However, it was recommended to the Delegate that the sponsor submit to the TGA, when available, draft materials for the proposed Royal Australian College Of General Practitioners (RACGP) (Category 1) accredited program, including the questionnaires given before and after to measure the effectiveness of this program.

Proposed indication

The recommendation that the Delegate consider the updated indication, for Trajenta as a monotherapy for patients whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment, in the EU (approved as of 24 October 2012) still applies. The proposed updated indication for Australia does not include this restriction (see proposed updated indication for Australia with changes in *underline italics*):

Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, *as monotherapy or* as add on to metformin, sulphonylureas*, insulin (with or without metformin and/or pioglitazone and/or sulphonylurea)* or metformin plus sulphonylureas.

Adverse event: Urinary tract infections

For the important potential risk 'Infections'-The FDA Product Label includes information on increased rates of urinary tract infection with linagliptin when used in combination with sulfonylurea *"Rates for other adverse reactions for TRADJENTA 5 mg versus placebo when TRADJENTA was used in combination with specific anti-diabetic agents were: urinary tract infection (3.1% vs 0%) and hypertriglyceridemia (2.4% vs 0%) when TRADJENTA was used as add-on to sulfonylurea;..."* (see FDA Product Label page 2). The proposed Australian PI does not include this information.

The recommendation that the Delegate consider including information on increased rates of urinary tract infection with linagliptin when used in combination with sulfonylurea still applies. The sponsor's response to this recommendation includes reference to data and

concludes 'urinary tract infection' is not considered to be a listed event and therefore no update was carried out for the EU Summary of Product Characteristics (SmPC) or other labels (including the Australian PI). However, the data the sponsor gives references to only includes events for linagliptin versus placebo not linagliptin + sulfonylurea versus placebo.

Precaution - Hypoglycaemia

It is recommended the Delegate consider requesting the sponsor to add information in the Precautions-Hypoglycaemia section to inform Healthcare professionals that when linagliptin is used in combination with insulin to consider using a lower dose of insulin to reduce the risk of hypoglycaemia. Severe and life-threatening events of hypoglycaemia in clinical trials were reported with Trajenta + insulin treated versus placebo treated patients. It is noted both the EU SmPC and the FDA Product label include similar precautions (see Table 5 below).

Table 5. EU SmPC and US Product label

EU SmPC	US Product label
"4.4 Special warnings and precautions for use *Hypoglycaemia...* *...Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when* *linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin, may be considered (see section 4.2)."* (page 3)	***WARNINGS AND PRECAUTIONS*** ***5.1 Use with Medications Known to Cause Hypoglycemia*** *Insulin secretagogues and insulin are known to cause hypoglycemia. The use of TRADJENTA in combination with an insulin secretagogue (e.g., sulfonylurea) was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial [see Adverse Reactions (6.1)]. The use of TRADJENTA in combination with insulin in subjects with severe renal impairment was associated with a higher rate of hypoglycemia [see Adverse Reactions (6.1)]. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with TRADJENTA.*
"4.2 Posology and method of administration *Posology* *The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of* *metformin should be maintained, and linagliptin administered concomitantly.* *When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the* *sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia (see section 4.4)"* (page 2)	***6 ADVERSE REACTIONS*** ***6.1 Clinical Trials Experience...*** *...Hypoglycemia...* *... In the study of patients receiving TRADJENTA as add-on therapy to a stable dose of insulin for up to 52 weeks (n=1261), no significant difference in the incidence of investigator reported hypoglycemia, defined as all symptomatic or asymptomatic episodes with a self measured blood glucose ≤70 mg/dL, was noted between the TRADJENTA (31.4%) and placebo (32.9%) treated groups. During the same time period, severe hypoglycemic events, defined as requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions, were reported in 11 (1.7%) of TRADJENTA treated patients and 7 (1.1%) of placebo treated patients. Events that were considered life-threatening or required hospitalization were reported in 3 (0.5%) patients on TRADJENTA and 1 (0.2%) on placebo.*

VI. Overall conclusion and risk/benefit assessment

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

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The data included a single pivotal efficacy/safety Study 1218.36 supporting addition of linagliptin to insulin with or without other OHA, and a supportive Study 1218.63 in T2D patients 70 years or older.

Studies 1218.40, 1210.43, 1218.50 and 1218.52 were previously evaluated; extension data were presented in the current submission. Study 1218.20 was evaluated by the TGA previously and the final 104 week report was presented to support an update to the clinical trials section of the PI.

There is a complex overlap of datasets supporting this application and three related submissions (for changes to the Clinical trials section of the PI and registration of the FDC, in addition to the original registration application).

Pharmacokinetics

There were no new studies; trough linagliptin measurements were obtained in subsets in 1218.43 and 1218.63. From *Study 1218.43,* the CER provides the following summary '*Linagliptin trough concentrations were stable over time and, in patients with severe renal impairment, the lowest geometric Mean levels were observed at Week 48 (6.78 nmol/L; n = 40) and the greatest geometric Mean levels were observed at Week 30 (8.80 nmol/L; n = 41)*.' From *Study 1218.63* the CER shows mean (standard deviation (SD)) linagliptin values: subjects with normal renal function (n=4), 5.67 (2.76) nmol/L; mild renal impairment (n=20), 6.86 (2.60) nmol/L; moderate renal impairment (n=11), 7.21 (2.22) nmol/L.

Clinical efficacy

Add on to insulin

Pivotal study

The CER identified *Study 1218.36* as the pivotal study. This was an international multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the efficacy and safety of add-on treatment with linagliptin 5 mg compared with placebo, in T2DM patients (n = 1263) with insufficient glycaemic control on basal insulin therapy. The primary efficacy endpoint was at 24 weeks; basal insulin was to remain stable until 24 weeks; during the next 28 week phase insulin was adjusted by the study investigator. Only the interim report until 24 weeks was provided.

Included were T2DM patients ≥18 years treated with subcutaneous (SC) basal insulin (included glargine, detemir and Neutral Protamine Hagedorn (NPH)) alone or in

combination with metformin and/or pioglitazone. No subjects were on background medication with a sulfonylurea. Important exclusions were uncontrolled fasting hyperglycemia >13.3 mmol/L, impaired hepatic function, gastric bypass surgery and systemic corticosteroid therapy. There were 630 randomised to placebo and 633 to linagliptin 5 mg daily. More than 50% had some degree of renal impairment; baseline data were similar between groups. The disposition of patients up to the 24 week cut-off shows comparable discontinuations.

The primary efficacy outcome was the change from baseline in HbA1c after 24 weeks of double-blind therapy, determined as a superiority analysis on the full analysis set (all treated subjects with baseline and on-treatment HbA1c value, LOCF). The adjusted mean difference linagliptin-placebo (95% CI), -0.65%(-0.74,-0.55), was statistically and clinically significant (CER p 16-17). The evaluator notes from sub-analyses that the statistically and clinically significant effect is preserved both in the presence of metformin and in subjects with moderate renal dysfunction.

Secondary efficacy variables included the proportion achieving target HbA1c <7.0% and <6.5%, or ≥0.5 % reduction from baseline, all significantly in favour of linagliptin. Other secondary variables were change in HbA1c over time and change in fasting plasma glucose. The Kaplan-Meier plot of first use of rescue therapy over 52 weeks was consistent with these results. Hypoglycaemic episodes were 24% for placebo and 27% for the linagliptin treated group. Median weight changes were close to 0 for both groups.

Study 1218.43

This was a double blind randomised placebo-controlled study in T2DM patients with severe chronic renal impairment. Subjects were on a range of background diabetes therapies, including insulin, to remain unchanged for the first 12 weeks. Subjects were randomised to linagliptin (n = 68) or placebo (n = 65). Between 12 and 52 weeks, 52% of placebo subjects had at least one change in background therapy, most frequently increased insulin (mean increase 9.7%), versus 39% of linagliptin subjects (mean decrease insulin 24.3%). Data for 52 weeks were presented. The result for HbA1c treatment difference (mean, 95% CI) was -0.72% (-1.03, -0.41), showing superiority of linagliptin over placebo (p<0.0001). The evaluator notes that this study demonstrated a durable clinically significant reduction in HbA1c in patients with renal impairment and combined with background therapies, mostly insulin and/or sulfonylurea (in the linagliptin arm, 37/66 insulin only, 9/66 insulin + sulfonylurea, 9 sulfonylurea only). It is therefore relevant to the extension of indication to add on to insulin therapy and in those unable to use metformin due to renal impairment.

As there were no subjects taking no background medication, it is not relevant specifically to linagliptin as monotherapy, although it supports linagliptin use in patients with renal impairment.

Study 1218.63

This multinational randomised, double-blind, placebo-controlled, parallel group study (linagliptin 5 mg n = 160, placebo n = 78) examines the efficacy and safety of linagliptin 5 mg daily over 24 weeks in T2DM patients aged ≧70 with insufficient glycaemic control (HbA1c ≧7.0%) despite treatment with metformin and/or sulphonylurea and/or insulin.

Randomisation was stratified by baseline HbA1c level and by use of insulin prior to the study. Most subjects (81.3%) had baseline HbA1c <8.5%, 68.5% were males and 96.7% white. Mean age was 74.9 years; 44.4% were ≧75 years. The majority had renal impairment; 51.9% mild (eGFR 60 to ≦ 90), 25.7% moderate (eGFR 30 to ≦60), 1.2% severe (eGFR ≤30).

The primary efficacy parameter analysis on the full analysis set (FAS) (last observation carried forward (LOCF)) results showed an adjusted mean HbA1c% treatment difference

(standard error (SE)) (95% CI) of -0.64% (0.08) (-0.81, -0.48), both statistically and clinically significant. Secondary variables were supportive.

The evaluator noted that hypoglycaemia findings appeared to indicate a decrease in those with insulin as background therapy, which seemed unlikely. The overall finding that investigator-reported hypoglycaemia was more common in the linagliptin group (24.1% versus 16.5% placebo) was plausible in view of generally improved glycaemic control.

Efficacy conclusion for linagliptin added to insulin

The evaluator concluded that the data from pivotal trial 1218.36, supported by 1218.43 and 1218.63, demonstrated efficacy of linagliptin added to insulin therapy in T2D treatment, including for the treatment of patients with renal impairment, and in patients over 70 years. The dataset included patients already receiving combination metformin and sulfonylurea.

Monotherapy

Study 1218.50

This was a study of linagliptin as monotherapy in T2DM patients with intolerance or contraindications to metformin. *Part 1* has previously been evaluated by the TGA. It consisted of an 18 week period of double-blind therapy in which linagliptin (151 randomised subjects) was compared with placebo (76 subjects). It demonstrated superiority of linagliptin over placebo after 18 weeks, with an adjusted mean difference in HbA1c % (95% CI) of -0.57(-0.86, -0.29). A reduction in HbA1c from baseline of 0.5% or greater was achieved by 36.1% of linagliptin subjects by comparison with 17.8% of placebo subjects.

Delegate's Comment: Study 1218.50 Part 1 was placebo-controlled rather than comparison with established therapy had a small number of patients and was of short duration. The effect size was not large. The EU Guideline states monotherapy studies should be 6 months, with a maintenance period of at least 16 weeks; 'for oral antidiabetic agents with an original mechanism of action a 12 month controlled overall duration may be required.'[3]

Additional data Study 1218.50

In the newly submitted *1218.50 Part 2*, the study population had a median age of 57 years, was 65% female, 71% White, median body mass index (BMI) was 29; 93% were metformin intolerant due to gastro-intestinal side-effects and only 7% were contraindicated for metformin due to renal impairment. Placebo subjects from Part 1 were switched to glimepiride, started at 1 mg daily and titrated upwards at weekly intervals to a maximum of 4 mg; titration was based on pre-specified blood glucose targets and titration was not to be continued past Week 12. Double-blind treatment, using a double dummy technique, then continued for 34 weeks as a comparator controlled trial; 119/137 linagliptin and 58/64 glimepiride subjects completed Part 2 of the study. Although Table 8 CER (Attachment 2), shows a higher proportion of discontinuations in the linagliptin arm (11.9% versus 7.9%), including 'lack of efficacy', the evaluator states the difference relates to protocol issues and does not suggest bias in tolerability.

In the final study report (Part 1 + Part 2) the primary efficacy parameter was HbA1c % change from baseline to 18 weeks, as for Part 1. A repeat analysis of FAS with adjustment for stratification factors (previous anti-diabetes therapy and reason for metformin

[3] Note for Guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus <http://www.tga.gov.au/pdf/euguide/ewp108000en.pdf>

intolerance) and baseline HbA1c % resulted in a mean difference (95%CI) of -0.60 (-0.88, -0.32). This was similar to the original estimate.

According to the CER, there was no statistical analysis of the HbA1c and FPG changes during Part 2. The overall change in HbA1c from baseline to Week 52 was -0.44% for the linagliptin group and -0.72% for the placebo/glimepiride group. A qualitatively similar pattern for FPG was seen in the two groups. Results included average weight change during Part 2; +1.3 kg glimepiride versus -0.2 kg linagliptin.

The evaluator commented that from the graph provided at Figure 6 in the CER, it appears that the reduction in HbA1c following switching from placebo to glimepiride is greater than that following commencement of linagliptin in Part 1. Subjects continuing on linagliptin appeared to maintain the original reduction in HbA1c seen from Week 12 onwards, although the data are not clearly displayed

Delegate's Comment*:* This study does not strongly support the use of linagliptin as an alternative monotherapy to a sulfonylurea, based on efficacy . The active comparator extension was not statistically analysed but results suggest a greater treatment effect for glimepiride.

Study 1218.40 was evaluated in the CER for the fixed dose combination of linagliptin with metformin. Data to 78 weeks were provided for this study, the open label extension phase of 4 placebo-controlled studies (1218.15, 1218.16. 1218.17, 1218.18) evaluated for a previous submission. Overall, for those who continued linagliptin in 1218.40 ('old lina' group) the mean (SD) change in HbA1c from baseline to Week 78 was +0.12 (0.76%), versus -0.49 (0.85%) for those who changed to linagliptin from placebo treatment over the entire study population ('new lina'); the majority were subjects previously on combination therapies. In *1218.16* (n = 496) the adjusted mean (95% CI) difference linagliptin-placebo for change from baseline HbA1c% was -0.69(-0.85 to -0.53). [4] Entering *1218.40* from *Study 1218.16* were 443 patients who received linagliptin 5 mg monotherapy. The evaluator states no sub-analysis could be found in *1218.40* for monotherapy patients in the open label extension.

Study 1218.20 was previously evaluated by the TGA. It is not directly relevant to the extension of indications data but the evaluator states that 104 week data confirm the previous findings from the 52 week data, that is, glimepiride added to metformin was superior to linagliptin added to metformin; the quoted HbA1c reduction from baseline remains at 0.4% for linagliptin and 0.6% for glimepiride. The between-treatment difference in HbA1c%, after 104 weeks of double-blind therapy, was 0.20 (97.5% CI: 0.094, 0.299) ($p<0.0001$ for superiority in favour of glimepiride). The differential in the proportions of subject experiencing hypoglycaemia remained; 7.5% for linagliptin compared with 36.1% for glimepiride, and there was a mean weight loss of 1.39 kg for linagliptin by comparison with a weight gain of 1.29 kg for glimepiride. The evaluator notes that these updated figures have been included in the proposed PI.

Delegate's Comment: Although linagliptin added to metformin was non-inferior to glimepiride for efficacy in this trial this was superseded by a finding of superiority for glimepiride; that finding persisted to 104 weeks. See also *Cardiovascular Safety*.

Analyses across trials

The evaluator mentions pooled efficacy datasets described in the submission (Module 2.5) that included subjects from 1218.36, 1218.43 and 1218.63 and states that the conclusions are consistent with those for the individual studies as above.

[4] Delegate's Overview and request for ACPM advice for previous submission.

Efficacy conclusions for linagliptin monotherapy

The evaluator concluded that data from 1218.50 Part 2, with the data from 1218.50 Part 1 and 1218.16 originally evaluated for registration, supported linagliptin use as monotherapy in patients in whom metformin is contraindicated or not tolerated.

Clinical safety

Safety data from newly submitted studies was reviewed. The sponsor's Summary of Clinical Safety summarised the database for linagliptin with respect to 6 safety sets based on groupings of studies with similar design. The evaluator identified the datasets SAF-3 (placebo-controlled studies) SAF-4 (1218.36), SAF-5 (1218.43), and SAF-6 (1218.63) as relevant. Exposure in these study groupings is shown in the CER.

A summary is provided in Table 6 below.

Table 6. Patient exposure

	SAF-3	SAF-4	SAF-5	SAF-6
N	linagliptin 720 placebo 700	Lng 631 Plac 630	Lng 54 Plac 55	Lng 126 Plac 121
Overall patient years	Lng 585 Plac 559	Lng 523 Plac 508	Lng 47 Plac 44	Lng 91 Plac 94

In pivotal ***Study 1218.36*** data was collected on general adverse events (AEs) and AEs of particular interest including hypersensitivity reactions, renal AEs, increased liver enzymes, cutaneous skin reactions and pancreatitis, laboratory tests, physical examination (PE), vital signs and electrocardiogram (ECG). Hypoglycemia was specifically documented.

Overall incidence of AEs was similar (72.5% placebo, 71.0% linagliptin). AEs of special interest included urticaria (linagliptin 4 placebo 1) and pancreatitis (linagliptin 3 placebo 1), thyroid neoplasms (linagliptin 4 placebo 0). Treatment-related AEs occurred in 18% of placebo patients versus 15.8% linagliptin. There were no imbalances in deaths or serious AEs (SAEs). Discontinuations were 2.4% linagliptin and 3.3% placebo.

One patient in the placebo developed liver function abnormalities fulfilling Hy's law and was diagnosed with hepatitis B. There was no imbalance with regard to renal function or albuminuria. There were imbalances in the possibly clinically significant abnormalities of decreased haemoglobin (Hb) (frequency of reporting 6.4% linagliptin versus 3.1% placebo), decreased red cell count (RCC) (2.4% versus 1.3%), and decreased white cell count (WCC) (6.4% versus 1.0%). The evaluator stated mean values and minimums/variance were similar and there were no AEs of anaemia or neutropenia.

Other studies

In *1218.50* AEs occurred in 62.5% of glimepiride and 59.9% of linagliptin patients. One case of hypersensitivity occurred in each group. In *1218.63*, 75.9% in both placebo and linagliptin group reported AEs. In this group aged ≥ 70 years, in the linagliptin group 2 patients had deterioration in renal function that resolved spontaneously without ceasing the trial medication, 1 had eczema and 1 had moderate contact dermatitis. Treatment related AEs in *1218.63* were reported by 21% linagliptin versus 13.9% placebo patients. The hypoglycaemia events reported as AEs were more common in linagliptin than placebo (14.8% versus 8.9%). There were no deaths in this study and no imbalances for deaths or SAEs.

Discontinuations appeared unrelated to study drug in *1218.50.* In *1218.16* the evaluator considered that although there was apparent imbalance in withdrawals, these were related to incidental conditions occurring with relatively high frequency in this age group. For linagliptin versus placebo there were 3.2% versus 2.6% with possibly significant increases in GGT. Increased creatinine occurred in 7.6% versus 3.9%.

Postmarketing safety data

The submission contained the report dated 19 December 2011 on a pooled safety analysis of cardiovascular risk drawn from all Phase III studies then available in the sponsor's database for linagliptin. Included subjects totalled 7907, comprising 4893 on linagliptin 5 mg daily or 2.5 mg twice daily, 2081 on placebo and 937 on active control with either voglibose or glimepiride.

The analysis employed individual patient data from 13 trials. An independent clinical event committee (CEC) adjudicated major cardiovascular events occurring during the studies, including cardiovascular death, non-fatal stroke, non-fatal myocardial infarction, unstable angina pectoris with and without hospitalisation, stable angina pectoris and transient cerebral ischaemic attacks. These collectively represent clinical consequences of coronary and cerebrovascular disease. The primary composite endpoint for the meta-analysis comprised the more severe events of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or unstable angina pectoris with hospitalisation.

For this primary endpoint, 44 events were observed in the linagliptin group and 45 in the combined placebo/active control comparator group, yielding incident event rates of 12.0 and 16.9 per 1000 years of exposure respectively. Using a variety of statistical methods, cardiovascular risk by comparison between these two groups were calculated with 95% CI, and a Forrest plot of these data is shown at Figure 7 of the CER. The possible emergence of a difference over time was shown by a Kaplan-Meier plot of the data (Figure 8 in CER).

A number of secondary endpoints were analysed, including an FDA defined criterion of major adverse cardiovascular events (MACE). The individual risk event categories listed earlier were also analysed as tertiary endpoints. Of these, events of stroke and transient cerebral ischaemic attack were observed by Cox regression to be significantly lower for linagliptin compared with the combined comparators.

The evaluator accepted the conclusion that treatment with linagliptin, with or without background therapy, did not increase cardiovascular risk compared with a combined comparator group (placebo, glimepiride and voglibose). The evaluator also noted that in the report on active controlled *Study 1218.20* an adjudicated analysis showed an overall lower incidence of cardiovascular events (6.4%) in the linagliptin/metformin group of 776 subjects by comparison with 9.5% in the glimepiride group of 775 subjects.

Table 7. Cardiovascular events

	Linagliptin		Glimepiride		p-value[1,2]	Relative risk[3]	95% Confidence interval[4]
	N	(%)	N	(%)			
Combined cardiovascular events[5]	12	(1.6)	26	(3.4)	0.0213	0.46	(0.23, 0.91)
Individual events							
CV death (including fatal stroke)	2	(0.3)	2	(0.3)	0.9990	1.00	(0.14, 7.07)
Non-fatal MI	6	(0.8)	10	(1.3)	0.3136	0.60	(0.22, 1.64)
Non-fatal stroke	3	(0.4)	11	(1.4)	0.0315	0.27	(0.08, 0.97)
Stable angina	11	(1.4)	12	(1.6)	0.8312	0.92	(0.41, 2.06)
Unstable angina							
with hospitalisation	3	(0.4)	3	(0.4)	0.9987	1.00	(0.20, 4.93)
without hospitalisation	0	(0.0)	0	(0.0)	0.9995	1.00	(0.02, 50.27)
Transient ischaemic attack	1	(0.1)	5	(0.7)	0.1015	0.20	(0.02, 1.71)
Total mortality	4	(0.5)	4	(0.5)	0.9985	1.00	(0.25, 3.98)

All events were independently adjudicated by CEC and analysed as part of the planned cardiovascular meta-analysis on the project level

[1] From chi-squared test

[2] With continuity correction of 0.5

[3] Including cardiovascular death, myocardial infarction, stroke, and hospitalisation due to unstable angina

[4] 2-sided 95% confidence interval on a logarithmic scale

Safety in special populations

The study populations in the submission contained subjects in older age groups and with impaired renal function. No specific safety issues were identified for these populations, although it should be observed that in each case the number of subjects exposed to linagliptin was relatively small: 54 in the case of the renally impaired population SAF-5 and 126 for the elderly population SAF-6.

Evaluator's overall conclusions on clinical safety

No newly emergent safety concerns regarding linagliptin were suggested. There was a minor incidence of specified adverse effects (hypersensitivity, pancreatitis) which have been previously identified as being associated with this drug. Linagliptin showed a low incidence of hypoglycaemia, particularly by comparison with a sulphonylurea. The findings provided on cardiovascular risk did not suggest any adverse effect of linagliptin.

Evaluator's risk-benefit balance conclusion

The benefits of linagliptin in the proposed usage (as listed by the clinical evaluator) included:

- Improved diabetes control as measured by HbA1c reduction
- Availability of a therapeutic alternative for patients unable to take metformin, whether because of intolerance or contraindication due to impairment of renal function.
- Reduced risk of hypoglycaemia and weight gain by comparison with most likely therapeutic alternative (sulphonylurea), at least in the monotherapy usage

The risks of linagliptin in the proposed usage were listed as

- Previously described class specific side-effects including hypersensitivity reactions and pancreatitis
- Safety of use in patients aged 70 or above, and in those with impaired renal function, is at this stage dependent on the observation of relatively limited exposure
- Risk of presently unforeseen side-effects for this relatively new drug by comparison with therapeutic alternatives with long safety records (such as insulin, sulphonylureas)

The evaluator concluded that the benefit-risk balance was favourable for the extensions of indication to monotherapy in patients unable to use metformin, and use with insulin with or without metformin and/or sulphonylureas.

Risk management plan

The RMP evaluator advice was that monotherapy with linagliptin should be for use in patients for whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment. The addition of hypoglycaemia with insulin to the PI under *Precautions* was recommended.

Risk-benefit analysis

Delegate considerations

Issues identified by the Delegate

Monotherapy

Although sponsor's letter of application included, in the proposed new indication, the use "as monotherapy", without qualification, on the next page of the letter it goes on to indicate that the company now accepts that monotherapy should be restricted to metformin-ineligible patients. This should be confirmed by the sponsor in their pre-ACPM response.

The findings support efficacy in monotherapy, for metformin-ineligible patients. Sulphonylureas have a well-established efficacy and safety profile that includes risk of hypoglycaemia. The sponsor has requested linagliptin as a monotherapy alternative to the use of sulfonylurea, with no direct comparison available. In add on treatment to metformin, glimepiride appears to be more efficacious.

It appears therefore, based on available data, that linagliptin monotherapy should only be considered where both metformin and sulphonylureas are either ineffective or contraindicated.

The proposed *Clinical trials* section of the PI is large and requires editing for relevance. It includes descriptions relevant to the unqualified use of linagliptin as monotherapy and comparing efficacy to voglibose. These do not appear relevant to the indication.

Use with insulin

In the introduction to the sponsor's Clinical Overview, it is stated that "*With the present submission, Boehringer Ingelheim is applying for the use of linagliptin as combination therapy with insulin in adult patients with T2DM when insulin with or without oral antidiabetic drugs (metformin, pioglitazone, sulphonylurea) does not provide adequate glycaemic control*".

With regard to *metformin*, pivotal Study 1218.36 provides adequate evidence that linagliptin is effective when added to insulin whether in the presence of or in the absence of metformin.

The submitted evidence does not support the inclusion of *pioglitazone* in the therapeutic equation proposed. The only relevant study was 1218.36, which included small subsets of subjects taking pioglitazone (1% of study population) or pioglitazone and metformin (7.4% of study population) as well as insulin. The subset of subjects taking pioglitazone alone with insulin was too small to allow any conclusions about the benefit of linagliptin in that combination. There is no existing approval for use of linagliptin in any combination with pioglitazone.

No *sulphonylurea* was included as background in pivotal Study 1218.36 and no sub-analyses by class of background therapy were performed in Study 1218.43.

In summary, on the basis of the evidence submitted, *use of linagliptin as add-on treatment to insulin with or without metformin* was supported**.**

There appear to be insufficient long-term data to support use of linagliptin in combination with insulin and sulphonylureas or pioglitazone. Hypoglycaemia in combination with insulin and/or sulfonylurea might be expected. Subjects excluded from the pivotal study included those with hepatic or renal impairment, or gastric surgery.

New/emerging CVS data also appear to warrant caution. A 'Safety Related Notification' was received from the sponsor in January to 'update' cardiovascular safety information. The summary provided with the Safety related notification (SRN) for inclusion in the PI includes a hazard ratio markedly different from that in the current PI and from that provided with this submission; the HR now proposed for inclusion is 0.78(CI 0.55-1.12). No data were provided. The sponsor should clarify this and provide the most recent information with their pre-ACPM response.

Proposed action

It was proposed that linagliptin could be approved for the amended extension of indications:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or as add on to metformin, sulphonylureas or metformin plus sulphonylureas, or to insulin (with or without metformin).*

The application was submitted to the Advisory Committee on Prescription Medicines (ACPM) for advice.

Response from sponsor

TGA Delegate recommendation

Boehringer Ingelheim Pty Limited welcomed the Delegate's recommendation to approve **the sponsor's** proposal to extend the current indications for Trajenta (linagliptin). Boehringer Ingelheim accepted the proposed wording put forward by the Delegate:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise,*
>
> *as monotherapy when metformin and sulphonylureas are not tolerated, or are contraindicated, or*
>
> *as add on to metformin, sulphonylureas or metformin plus sulphonylureas, or to insulin (with or without metformin).*

Comments to issues raised by the TGA Delegate

The Delegate has also requested in their overview for Boehringer Ingelheim to provide the following:

- clarify the update to cardiovascular safety information provided as a safety related notification and provide the most recent information

Cardiovascular (CV) safety information

In December 2008, the Food and Drug Administration (FDA) issued a guidance for the assessment of CV morbidity/mortality associated with new drugs for the treatment of

diabetes. Boehringer Ingelheim in 2010, in line with these regulatory requirements, performed a formal pre-specified CV meta-analysis, with prospective independent adjudication of all potential CV events for the linagliptin Phase III programme.

The first meta-analysis report [U10-1736-01] was provided as part of the registration package for Trajenta. Data from this report demonstrated that linagliptin treatment was not associated with an increase in CV risk and that the occurrence of time to first occurrence of specific CV events were significantly lower for linagliptin compared to the active and placebo comparators [Hazard ratio 0.34 (95% Confidence interval 0.17;0.70)]. This data is included in the currently approved PI.

In 2011 an updated analysis was completed which included data from four more Phase III trials and one Phase IIb trial. The updated analysis report [U11-2802-01] was provided as part of the data package supporting this application. The overall conclusion from this second analysis report also demonstrated that linagliptin treatment was not associated with an increase in CV risk. However the increase in number of patients and studies included in the analysis, resulted in the previously observed significant difference between linagliptin and the comparator now became non-significant [Hazard ratio 0.79 (95% confidence interval 0.52;1.20)].

The final analysis report was completed in December 2012 [U12-2369-01]. Data from this final report was used to update the *Clinical Trial – Cardiovascular Risk* section of the PI, included in the Safety Related Notification submitted in January 2013. The overall conclusion has not changed, in that linagliptin treatment is not associated with an increase in CV risk. However, the increase in patient numbers used in the final report, has changed the initial primary endpoint outcome for linagliptin from being "significantly lower" to being "non-significantly lower" when compared to the combined active and placebo comparators. [Hazard ratio 0.78 (95% Confidence interval 0.55;1.12)].

A copy of the final meta-analysis report [U12-2369-01] was also provided with the sponsor's response.

Changes to Product Information (PI)

The suggested amendments by the two clinical evaluators for application 'extension of indications' and application 'update to the PI' have been incorporated in the PI. Each amendment includes a reference of the source of the change. In addition, changes that were proposed in the Safety Related Notification submitted on the17 January 2013 have also been included in annotated PI. With regard to recommendations made by the Delegate, these have also been incorporated in the amended PI.

Conclusion

Boehringer Ingelheim appreciated the opportunity given by the Delegate to provide the latest data from the ongoing meta-analysis report.

The latest data from the ongoing meta-analysis report has altered the initial observation that Trajenta significantly lowers the occurrence of CV events when compared to active and placebo comparators. However, the overall conclusion remains the same. Trajenta does not increase CV risk.

Trajenta has demonstrated beneficial effects on efficacy, safety and also with cardiovascular risk. This application and the recommendation to approve the extension of indications, allows for physicians to be able to use Trajenta as an alternative treatment option when treating their type 2 diabetes patients.

Advisory committee considerations

The ACPM resolved to recommend to the TGA delegate of the Minister and Secretary that:

Resolution 2747

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered this product to have an overall positive benefit–risk profile for the Delegate's proposed indication**;**

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or as add on to metformin, sulphonylureas or metformin plus sulphonylureas, or to insulin (with or without metformin).*

Proposed PI/CMI amendments

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI).

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration.

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 the product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Trajenta (linagliptin) 5 mg film-coated tablet for oral administration, indicated for:

> *Trajenta is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise,*
>
> *as monotherapy when metformin and sulfonylureas are not tolerated, or are contraindicated, or*
>
> *as add on to metformin, sulfonylureas or metformin plus sulfonylureas, or to insulin (with or without metformin).*

Specific conditions of registration applying to these therapeutic goods

1. The implementation in Australia of the Trajenta linagliptin EU Risk Management Plan Version 5.0, dated 16 February 2012 [Data lock point 29 November 2011], with Australian Specific Annex dated 21 May 2012, included with submission 2011-01168-3-5 and any subsequent revisions with any accompanying caveats and requests for pharmacovigilance activities as agreed with the TGA and its Office of Product Review.

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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