PUBLIC SUMMARY DOCUMENT
Product: Linagliptin, tablet, 5 mg, Trajenta®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought an Authority required (STREAMLINED) listing for treatment of patients with type 2 diabetes in combination with metformin or a sulfonylurea.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

Linagliptin was TGA registered on 1 November 2011 and is indicated for treatment of 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.

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Dual oral combination therapy with metformin or a sulfonylurea.

Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date and level of the qualifying HbA_{1c} must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances: (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records.

The PBAC noted the requested restriction was consistent with those for other medicines currently listed on the PBS for this condition.

5. Clinical Place for the Proposed Therapy

Type 2 diabetes is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and exercise are the first steps in managing the disease, followed by the addition of drug therapy with

metformin. When diet and exercise modifications and metformin monotherapy is inadequate in controlling blood glucose, current treatment guidelines recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, insulin can be added. Other options include glucagon like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, or meglitinides.

The submission proposed that the place in therapy of linagliptin is an alternative therapy to sitagliptin or vildagliptin in the current clinical treatment algorithm for Type 2 diabetes, after diet and exercise, metformin and then a sulfonylurea have failed.

6. Comparator

The submission nominated sitagliptin as the main comparator. The PBAC agreed that this is appropriate.

7. Clinical Trials

Linagliptin plus metformin

The submission presented a meta-analysis of two randomised trials (1218.6 and 1218.17) comparing linagliptin plus metformin with placebo plus metformin. This meta-analysis was compared to three meta-analyses using four randomised trials comparing sitagliptin plus metformin with placebo plus metformin (Charbonnel 2006, Goldstein 2007; Raz 2008 and Scott 2008).

A supplementary analysis of linagliptin plus metformin compared to sitagliptin plus metformin was also included in the submission. This indirect comparison has a different comparator arm and for that reason was not included in the primary analysis. This indirect comparison used meta-analysed Trials 1218.20 and 1218.6 and compared it to Nauck 2007.

Linagliptin plus a sulfonylurea

The submission compared one randomised trial (1218.35) comparing linagliptin plus a sulfonylurea and placebo plus a sulfonylurea to one randomised trial (Hermansen 2007) with sitagliptin plus a sulfonylurea and placebo plus a sulfonylurea.

Details of the trials and associated reports published at the time of the submission are shown in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Placebo controlled sitagliptin trials with metformin		
Charbonnel 2006	Randomised, double blind, parallel group study evaluating the efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone.	*Diabetes care* 29, 2638-2643.
Goldstein 2007 Goldstein, B. J. et al	Randomised, double blind, parallel group study evaluating the effect of initial combination therapy with sitagliptin, and metformin on glycemic control in patients with type 2 diabetes. A 24 Week Study.	*Diabetes care* 30, 1979-1987.

Williams-Herman, D. et al.	Randomised, double blind, parallel group study evaluating the efficacy and safety of initial combination therapy with sitagliptin and metformin in patients with type 2 diabetes: A 54-week study.	*Current Medical Research and Opinion* 25(3), 569-583.
Williams-Herman, D. et al	Randomised, double blind, parallel group study evaluating the efficacy and safety of sitagliptin and metformin as initial combination therapy and as monotherapy over 2 years in patients with type 2 diabetes.	*Diabetes, Obesity and Metabolism* 12(5), 442-451.
Raz 2008	Randomised, double blind, parallel group study evaluating the efficacy and safety of sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes. A 30 Week study.	*Current Medical Research and Opinion* 24, 537-550
Scott 2008	Randomised, double blind, parallel group study evaluating the efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes.	*Diabetes, Obesity and Metabolism* 10(10), 959-969.
Placebo controlled sitagliptin trials with a sulfonylurea		
Hermansen 2007	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin.	*Diabetes, obesity & metabolism* 9, 733-745.
Nauck 2007	Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with a sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: A randomised, double-blind, non-inferiority trial.	*Diabetes, Obesity and Metabolism* 9(2), 194-205.
Seck 2010	Safety and efficacy of treatment with sitagliptin or glipizide in patients with type 2 diabetes inadequately controlled on metformin: A 2-year study.	*International Journal of Clinical Practice* 64(5), 562-576.

8. Results of Trials

Linagliptin in combination with metformin

The submission undertook a full analysis set comparison as well as a per protocol comparison. Both comparisons of linagliptin plus metformin resulted in significant reductions in HbA1c compared to placebo. Similarly, the trials comparing sitagliptin plus metformin and placebo plus metformin (Charbonnel 2006, Scott 2008) demonstrated significant reductions for HbA1c for the sitagliptin arm. The indirect comparison resulted in a reduction in HbA1c, below the 0.4% minimum clinically important difference (MCID).

The submission suggested that the proportion of patients that reported an adverse event was similar in the linagliptin plus metformin arms compared to the placebo plus metformin arms. The submission undertook relative risk and risk difference analyses for all adverse events, serious adverse events or adverse events leading to discontinuation and suggested that there is no significant difference between the linagliptin plus metformin arm or the placebo plus metformin arm. In addition, indirect comparisons were undertaken comparing the proportion of subjects reporting any adverse event, serious adverse event, cardiovascular adverse events

and serum lipids, between linagliptin and sitagliptin. These indirect analyses showed that there were no significant differences between linagliptin and sitagliptin.

Linagliptin in combination with a sulfonylurea

The submission undertook a full analysis set comparison as well as a per protocol comparison. The comparison of linagliptin plus sulfonylurea resulted in a significant reduction in HbA1c compared to placebo. Similarly the comparison of sitagliptin plus a sulfonylurea and placebo plus a sulfonylurea demonstrated significant reductions in HbA1c for the sitagliptin arm. The indirect comparison resulted in a weighted mean difference just exceeding the 0.4% MCID.

The submission suggested that the proportion of patients that reported an adverse event was similar in the linagliptin plus a sulfonylurea arm compared to the placebo plus a sulfonylurea arm. The submission undertook relative risk and risk difference analyses for all adverse events, serious adverse events or adverse events leading to discontinuation and claimed that there is no significant difference between the linagliptin plus a sulfonylurea arm or the placebo plus a sulfonylurea arm. Indirect comparisons were undertaken comparing the proportion of subjects with adverse events and serious adverse events between linagliptin and sitagliptin. These analyses showed that there was no significant difference between linagliptin and sitagliptin.

The submission provided data from four trials in the extended assessment of safety of linagliptin. A 54-week interim report of trial 1218.20, a final report of 1218.23 and an interim report at 42-54 weeks of a 78 week study (trial 1218.40). Trial 1218.PI was a pre-specified meta-analysis of cardiovascular safety. It combined data from eight linagliptin trials. The submission also provided a summary of clinical safety presented to the TGA which included over 30 studies representing over 6,000 subjects. These studies indicated that there were comparable rates of adverse events in linagliptin treated participants compared to placebo treated participants. These do not appear to identify any additional adverse events not reported in the pivotal studies.

For PBAC's comments on these results, see Recommendation and Reasons.

9. Clinical Claim

The submission claimed linagliptin plus metformin is non-inferior in terms of efficacy and safety to sitagliptin plus metformin.

The submission claimed linagliptin plus a sulfonylurea is non-inferior in terms of efficacy compared to sitagliptin plus sulfonylurea. The submission claimed that linagliptin plus a sulfonylurea is non-inferior in terms of safety compared to sitagliptin plus sulfonylurea.

For PBAC's view, see Recommendation and Reasons.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as linagliptin 5mg daily and sitagliptin 100mg daily. This was accepted by the PBAC on the basis of the clinical data.

11. Estimated PBS Usage and Financial Implications

The likely number of prescriptions per year was estimated in the submission as between 100,000 and 200,000 in Year 5 of listing at a net cost per year to the PBS of less than $10 million in Year 5.

The submission estimated small additional costs to the PBS on the basis that linagliptin is presented in a 30-day pack compared with sitagliptin in a 28-day pack resulting in a requirement to fill 12.2 prescriptions of linagliptin per year instead of 13.0 prescriptions per year with sitagliptin, and therefore on average one less co-payment each year.

12. Recommendation and Reasons

The PBAC was of a mind to recommend listing of linagliptin on a cost minimisation basis compared with sitagliptin. However, in the absence of a decision by the TGA Delegate on the registration of linagliptin, the PBAC deferred a final recommendation. The PBAC agreed to finalise its decision on the listing of linagliptin following the receipt of a positive TGA Delegate's Summary.

On the basis of the clinical data, the equi-effective doses are estimated as linagliptin 5mg daily and sitagliptin 100mg daily.

For the comparison with sitagliptin when both are used in comparison with metformin, the submission presented one meta-analysis of two randomised trials (1218.6, 1218.17) comparing linagliptin plus metformin with placebo plus metformin. This meta-analysis is compared to three meta-analyses using four randomised trials comparing sitagliptin plus metformin with placebo plus metformin (Charbonnel 2006, Goldstein 2007; Raz 2008 and Scott 2008). The PBAC noted that the pooled indirect comparison of effect based on the primary outcome of change in HbA1c was within the pre-specified non-inferiority margin for MCID in HbA1c of 0.4% and that it also fell within a MCID of 0.3%. This indirect analysis therefore demonstrates that linagliptin is non-inferior to sitagliptin with respect to diabetes control when both are used in combination with metformin.

For the comparison with sitagliptin when both are used in combination with a sulfonylurea, the submission presented one randomised trial (1218.35) comparing linagliptin plus a sulfonylurea and placebo plus a sulfonylurea to one randomised trial (Hermansen 2007) with sitagliptin plus a sulfonylurea and placebo plus a sulfonylurea. The confidence interval of the indirect analysis for HbA1c was outside the MCID and thus non-inferiority was not demonstrated. The submission suggested that the reason for not being able to demonstrate non-inferiority of linagliptin with a sulfonylurea is that there was only one trial, per arm, available to analyse and that there was a difference in the drugs and dose of the sulfonylurea. Whilst non-inferiority is neither demonstrated nor excluded by this comparison the PBAC accepted that linagliptin is likely to be non inferior to sitagliptin when both are use in combination with a sulfonylurea.

The PBAC agreed that the safety results for linagliptin and sitagliptin suggested non inferiority in this regard but noted there is uncertainty as long term data are lacking.

The submission estimated small additional costs to the PBS on the basis that it is presented in a 30 day pack compared with sitagliptin in a 28-day pack.

The PBAC also recommended that linagliptin be included in the PBS medicines for prescribing by nurse practitioners.

Recommendation:
Defer

ADDENDUM
Product: Linagliptin, tablet, 5 mg, Trajenta®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: November 2011

Purpose of Application:
The re-submission provided a TGA Delegate Summary for linagliptin, which was previously considered at the July 2011 PBAC meeting under the TGA/PBAC parallel process for an Authority Required (STREAMLINED) listing for treatment of patients with type 2 diabetes in combination with metformin or a sulfonylurea.

Background:
At the July 2011 meeting, the PBAC was of a mind to recommend listing of linagliptin on a cost minimisation basis compared with sitagliptin. However, in the absence of a decision by the TGA Delegate on the registration of linagliptin, the PBAC deferred a final recommendation.

Recommendation and Reasons:
The PBAC recommended listing linagliptin on the PBS on a cost-minimisation basis compared with sitagliptin. On the basis of the clinical data, the equi-effective doses are estimated as linagliptin 5mg daily and sitagliptin 100mg daily.

The PBAC noted that the TGA Delegate has proposed to approve linagliptin for the treatment of adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylurea, or metformin plus sulphonylurea.

The PBAC considered that the requested listing for linagliptin is consistent with the proposed TGA Delegate's indication.

The PBAC recommended that linagliptin is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners within collaborative arrangements.

Recommendation:
LINAGLIPTIN, tablet, 5 mg

Restriction:	<u>Authority Required (STREAMLINED)</u> Dual oral combination therapy with metformin or a sulfonylurea. Type 2 diabetes, in combination with either metformin or a sulfonylurea, in a patient whose HbA_{1c} is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), a thiazolidinedione (glitazone) or a glucagon-like peptide-1 despite

treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The date and level of the qualifying HbA_{1c} must be documented in the patient's medical records at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA_{1c} must be no more than 4 months old at the time treatment with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated.

Blood glucose monitoring may be used as an alternative assessment to HbA_{1c} levels in the following circumstances: (a) clinical conditions with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or (b) red cell transfusion within the previous 3 months.

A patient in these circumstances will be eligible for treatment where blood glucose monitoring over a 2 week period shows blood glucose levels greater than 10 mmol per L in more than 20% of tests. The results of this blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a gliptin, a glitazone or a glucagon-like peptide-1, must be documented in the patient's medical records.

Note
Linagliptin is not PBS-subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1.

Maximum qty: 30
Rpt: 5

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The sponsor does not wish to provide any comments.