PUBLIC SUMMARY DOCUMENT
Product: LINAGLIPTIN, tablet, 5 mg, Trajenta®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

To extend the current Authority Required (STREAMLINED) listing to include treatment of patients with type 2 diabetes in combination with metformin and a sulfonylurea (triple therapy).

2. Background

This drug had not previously been considered by the PBAC for this indication.

At the November 2011 meeting, the PBAC recommended listing linagliptin on the PBS as an Authority required (STREAMLINED) listing for treatment of patients with type 2 diabetes in combination with metformin or a sulfonylurea (dual therapy) on a cost-minimisation basis compared with sitagliptin dual therapy. On the basis of the clinical data, the equi-effective doses were estimated as linagliptin 5 mg daily and sitagliptin 100 mg daily. Listing was effective from 1 March 2012.

3. Registration Status

Linagliptin was TGA registered on 1 November 2011 for the indication:

> Linagliptin 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, sulphonylurea, or metformin plus sulphonylurea.

4. Listing Requested and PBAC's View

Note

Linagliptin is not PBS-subsidised for use as monotherapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1.

Authority Required (STREAMLINED)

Triple oral combination therapy with metformin and a sulfonylurea

Type 2 diabetes, in combination with metformin and 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 maximally tolerated doses of metformin and a sulfonylurea.

The date and level of the qualifying HbA1c 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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

There is estimated to be between 45,000 and 100,000 new diagnoses of diabetes each year in Australia, with Type 2 making up the majority. 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 or 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 triple therapy (linagliptin plus metformin and a sulfonylurea) is as an alternative oral treatment option to pioglitazone triple therapy (pioglitazone plus metformin and a sulfonylurea) for the treatment of type 2 diabetes.

6. Comparator

The submission nominated pioglitazone triple therapy as the comparator.

The PBAC agreed that pioglitazone is the appropriate comparator for the proposed listing of linagliptin as it is the only product currently listed for 'triple oral' therapy.

However, the PBAC noted that the post market review of oral hypoglycaemics may inform future considerations of the comparator; for example, insulin or exenatide maybe alternatives that are in fact replaced in clinical practice for this patient population.

7. Clinical Trials

No head-to-head studies were available. The submission was based on an indirect comparison of linagliptin triple therapy (Study 1218.18) with pioglitazone triple therapy (Charpentier et al 2009, Pan et al 2002, and Scheen et al 2009) using placebo (with metformin and a sulfonylurea) as the common comparator.

Details of the trials published at the time of submission are in the table below.

Trial ID / First author	Protocol title/ Publication title	Publication citation
Linagliptin triple therapy trials		
Study 1218.18		
Owens et al (2011)	Efficacy and safety of linagliptin in persons with Type 2 diabetes inadequately controlled by a combination of metformin and sulfonylurea: A 24-week randomized study.	Diabetic Medicine 28: 1352-1361
Pioglitazone triple therapy trials		
Charpentier et al (2009)	Earlier triple therapy with pioglitazone in patients with type 2 diabetes.	Diabetes, Obesity and Metabolism.11: 844-854
Pan et al (2002)[a]	The efficacy and safety of pioglitazone hydrochloride in combination with sulfonylureas and	Chinese Journal of Internal Medicine 41:

Trial ID / First author	Protocol title/ Publication title	Publication citation
	metformin in the treatment of type 2 diabetes mellitus a 12-week randomized multi-centres placebo-controlled parallel study.	388-392
Scheen et al (2009)	Long-term glycaemic control with metformin-sulfonylurea-pioglitazone triple therapy in PROactive (PROactive 17).	Diabetic medicine 26: 1033-1039
Dormandy et al (2005)	Secondary prevention of macrovascular events in patients with type 2 diabetes: a randomized trial of pioglitazone. The PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events).	Lancet 366:1279-1289
Charbonnel et al (2004)	The Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive): Can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5,238 patients.	Diabetes Care 27: 1647-1653

[a] The study by Pan et al (2002) was only published in Chinese

8. Results of Trials

The results for the primary outcome of mean change in HbA1c levels are shown in the table below:

Results of the indirect analysis comparing mean change in HbA1c (%) levels from baseline

Trial	Mean (SD) change in HbA1c (%) levels			Treatment effect WMD (95% CI)
	Linagliptin	Placebo	Pioglitazone	
Study 1218.18 24 week	-0.72 (0.84) (N = 778)	-0.10 (0.81) (N = 262)	-	-0.62 (-0.73, -0.51)
Charpentier (2009) 28 week	-	+0.28 (0.9) (N = 147)	-0.9 (0.9) (N = 142)	-1.18 (-1.39, -0.97)
Pan (2002) 12 week	-	-0.4 (0.83) (N = 142)	-0.7 (0.96) (N = 141)	-0.30 (-0.51, -0.09)
Scheen (2009) 26 week	-	-0.2 (1.4) (N = 660)	-0.9 (1.3) (N = 654)	-0.70 (-0.85, -0.55)

Abbreviations: CI, confidence interval; SD, standard deviation; WMD, weighted mean difference

For the primary outcome of mean change in HbA1c levels from baseline, the PBAC noted that the indirect comparison of Study 1218.18 vs Pan suggested that linagliptin triple therapy is non-inferior to pioglitazone triple therapy while the submission claimed superiority. Differences between the treatments were statistically significant with the results favouring linagliptin. The short treatment duration (12 weeks) and fixed dosing schedule (vs. flexible dosing in PI) used in the Pan et al (2002) trial may bias the results of the indirect analysis in favour of linagliptin. There are also concerns about the comparability of the Pan et al (2002) trial population with the other trial populations (due to inadequate reporting of patient characteristics).

The PBAC also noted that the indirect comparison of Study 1218.18 vs Charpentier indicated that linagliptin triple therapy is inferior to pioglitazone triple therapy. Differences between treatments were statistically significant with results favouring pioglitazone. An indirect comparison of HbA1c responders (< 7.0%) between linagliptin and pioglitazone showed that differences were statistically significant in favour of pioglitazone.

The submission claimed that the use of the higher 45 mg dose in the Charpentier et al (2009) study may bias the results of the indirect analysis against linagliptin. Although aggressive (30 mg up-titrated to 45 mg if HbA1c >6.5% at 12 weeks), the flexible dosing schedule used in the Charpentier et al (2009) trial is within those recommended in the relevant product information documents.

The indirect comparison between Study 1218.18 and Scheen et al (2009) is likely to be confounded by patients in the Scheen et al (2009) study altering their other diabetes medications over time (including insulin, metformin and sulfonylureas). Other issues with Scheen et al (2009) include the rapid forced titration dosing schedule (vs. flexible dosing in PI) and uncertain risk of bias due to being a post-hoc subgroup analysis.

The submission argued that on balance linagliptin is likely to be non-inferior to pioglitazone in terms of glycaemic control.

The PBAC noted that the differences in the study design of the linagliptin and pioglitazone trials (e.g. trial duration, dosage regimens, co-administered therapies and patient populations/trial locations) add additional uncertainty to the indirect comparison of HbA1c outcomes. Therefore, the PBAC was not convinced that non-inferiority of linagliptin compared with pioglitazone was established on glycaemic control.

Adverse events rates appear to be broadly similar between linagliptin and pioglitazone triple therapy based on the trial data presented.

A Periodic Safety Update Report (PSUR) for linagliptin indicated that the sponsor is continuing to monitor all adverse events, including the risk of pancreatitis, hypersensitivity events and severe cutaneous reactions. Median duration of exposure for patients in the linagliptin clinical trial program was 400 days (minimum 1 day, maximum 685 days). There has only been limited post-marketing exposure as linagliptin was only approved for diabetes in 2011 (FDA/EMA/TGA). Therefore, the long-term safety profile of linagliptin is still relatively unknown. Pioglitazone has been marketed for over a decade and only recently has the full spectrum of adverse events been observed.

Potential safety concerns associated with pioglitazone treatment are cardiovascular events (congestive heart failure), hypoglycaemia, oedema, weight gain, bladder cancer, bone fracture, hepatic impairment. The TGA, FDA and EMA have issued warnings about the increased risk of bladder cancer in patients taking pioglitazone for more than one year. The French Medicines Agency has suspended use of pioglitazone based on the risk of bladder cancer. The German drug regulatory agency also recommended that new patients do not initiate pioglitazone.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described linagliptin triple therapy as non-inferior in terms of efficacy and non-inferior in terms of safety compared to pioglitazone triple therapy.

Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submission's clinical claim that linagliptin triple therapy is non-inferior in terms of

comparative effectiveness to pioglitazone triple therapy. The PBAC accepted that linagliptin triple therapy is probably non-inferior to pioglitazone triple therapy in terms of safety based on current information.

10. Economic Analysis

The submission presented a cost-minimisation analysis of linagliptin triple therapy compared to pioglitazone triple therapy. The analysis was based on the clinical claim that linagliptin is non-inferior to pioglitazone in terms of efficacy and safety.

The submission presented two alternative equi-effective dose calculations based on using either the pioglitazone trial data or the pioglitazone Medicare data. The 2008 PBAC Guidelines (version 4.3) state a preference for using trial data over observational data (such as pharmacy claims data) when calculating equi-effective dosing due to potential biases and confounders associated with observational data.

The submission did not demonstrate that linagliptin is non-inferior to pioglitazone dosing in triple therapy regimens used in clinical practice (which include 15, 30, 45 mg doses). Instead, the submission argued that the fixed 30 mg dose used in the Pan et al (2002) trial was the most appropriate for clinical purposes.

The submission proposed a weighted linagliptin PBS price based on the predicted utilisation of linagliptin in dual and triple therapy. The submission predicted proportional utilisation for dual therapy and for triple therapy.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the overall net cost to the PBS/RPBS over five years will be less than $10 million. The increased costs associated with listing linagliptin are primarily due to differences in pack sizes between linagliptin (30 days treatment) and pioglitazone (28 days treatment) that translate to different numbers of prescriptions required and copayments. These estimates are uncertain as they rely on the predicted patterns of use for pioglitazone (based on 2010 Medicare pharmacy claim data). The submission did not address the potential for linagliptin to preferentially replace lower strengths of pioglitazone (particularly in those populations where there are safety concerns about pioglitazone) over higher strengths of pioglitazone.

12. Recommendation and Reasons

The PBAC agreed that pioglitazone is the appropriate comparator for the proposed listing of linagliptin as it is the only product currently listed for 'triple oral' therapy. However, the PBAC noted that the post market review of oral hypoglycaemics that is being undertaken may inform future considerations of the comparator; for example, insulin or exenatide maybe alternatives that are in fact replaced in clinical practice for this patient population.

The PBAC noted that the basis of the submission was an indirect comparison of linagliptin triple therapy (Study 1218.18) with pioglitazone triple therapy (Charpentier et al 2009, Pan et al 2002, and Scheen et al 2009) using placebo (with metformin and a sulfonylurea) as the

common comparator. The submission nominated a non-inferiority margin of 0.4% for the indirect analysis of the primary outcome, change in HbA1c from baseline.

The PBAC did not accept the submission's claim that the comparison between Study 1218.18 and Pan et al (2002) is relevant to the Australian clinical setting based on the 30 mg daily fixed dose regimen. The PBAC considered that the Charpentier trial was more relevant because in clinical practice patients may have their pioglitazone dose titrated to 45 mg daily if a greater therapeutic response is required. The PBAC noted that the Charpentier trial was the pivotal trial used in the listing of pioglitazone for triple therapy. Further, the PBAC was concerned that the short duration of the Pan trial (12 weeks) may not have been sufficient to achieve optimal glycaemic control with pioglitazone. The PBAC did not consider there was a strong basis for the selective inclusion of trials particularly as this could significantly affect the conclusions drawn from the indirect analysis results.

For the primary outcome of mean change in HbA1c levels from baseline, the PBAC noted that the indirect comparison of Study 1218.18 vs Pan suggests linagliptin is non-inferior to pioglitazone triple therapy. However, the indirect comparison of Study 1218.18 vs Charpentier indicates that linagliptin is inferior to pioglitazone triple therapy. The PBAC noted the differences in the study design of the linagliptin and pioglitazone trials (e.g. trial duration, dosage regimens, co-administered therapies and patient populations/trial locations) add additional uncertainty to the indirect comparison of HbA1c outcomes. Therefore, the PBAC was not convinced that non-inferiority of linagliptin compared with pioglitazone was established on glycaemic control.

The PBAC noted that, based on the data presented in the submission, the adverse events rates are similar between linagliptin and pioglitazone triple therapy but the long term safety profile of linagliptin is still relatively unknown. The PBAC considered that due to ongoing long term safety concerns with pioglitazone, there may be a clinical need for an alternative oral treatment to pioglitazone.

Based on the evidence presented, the PBAC considered there was insufficient evidence to accept the submission's clinical claim that linagliptin triple therapy is non-inferior in terms of comparative effectiveness to pioglitazone triple therapy. The PBAC accepted that linagliptin triple therapy is probably non-inferior to pioglitazone triple therapy in terms of safety based on current information.

The PBAC noted the submission presented a cost minimisation analysis of linagliptin versus pioglitazone. The PBAC considered that on the basis of inadequate clinical evidence to support a claim of non-inferiority with the nominated comparator, the cost minimisation analysis was not valid.

The PBAC considered that both the equi-effective dose calculations presented in the submission, based on either the pioglitazone trial data (Pan and Charpentier) or the pioglitazone Medicare data, were uncertain. The PBAC recalled that the 2008 PBAC Guidelines (version 4.3) state a preference for using trial data over observational data (such as pharmacy claims data) when calculating equi-effective dosing due to potential biases and confounders associated with observational data. Further, the PBAC considered that using the combined pioglitazone trial data (Pan and Charpentier) is inappropriate as the indirect analysis from the Charpentier trial indicates that linagliptin triple therapy is inferior to

pioglitazone triple therapy and therefore an equi-effective dose cannot be determined from this data if the Charpentier trial is included.

The PBAC noted that the submission proposed a weighted price for linagliptin based on the assumption of utilisation for dual therapy and utilisation for triple therapy. The PBAC considered that these estimates were highly uncertain particularly as there may be a rapid and large uptake in triple therapy use due to the safety concerns associated with pioglitazone.

Therefore, the PBAC rejected the submission on the basis of uncertain comparative clinical effectiveness and considerable economic uncertainty.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

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 has no comment.