PUBLIC SUMMARY DOCUMENT

Product: Linagliptin with metformin hydrochloride, tablets, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, Trajentamet®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: March 2013

1. Purpose of Application

The submission requested an Authority required (STREAMLINED) listing for treatment of type 2 diabetes mellitus (T2DM) in a patient whose HbA_{1c} is greater than 7% prior to initiation of a gliptin, glitazone or a glucagon-like peptide-1 despite treatment with metformin and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

2. Background

The PBAC had not previously considered this fixed dose combination (FDC) product. Linagliptin tablets and metformin tablets are both currently TGA registered and PBS listed.

3. Registration Status

The submission was considered under the TGA/PBAC parallel process. At the time of PBAC consideration, the Clinical Evaluation Report and TGA Delegate's overview were available.

Linagliptin with metformin was registered by the TGA on 21 May 2013.

4. Listing Requested and PBAC's View

Authority required (STREAMLINED)
Type 2 diabetes 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 metformin and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

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.

Authority required (STREAMLINED)
Continuation of therapy in type 2 diabetes mellitus in a patient who has previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and linagliptin.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Linagliptin/metformin FDC will provide a treatment alternative to concurrent use of linagliptin and metformin for T2DM patients with inadequate glycaemic control despite using metformin alone. There are currently three other FDCs involving a dipeptidyl peptidase-4 (DPP-4) inhibitor or a thiazolidinedione in combination with metformin for the treatment of T2DM listed on the PBS:

- rosiglitazone/metformin FDC;
- sitagliptin/metformin FDC; and
- vildagliptin/metformin FDC.

The submission presented a clinical management algorithm which was based on treatment guidelines published by Diabetes Australia and the Royal Australian College of General Practitioners.

The submission proposed that the listing of the linagliptin/metformin FDC on the PBS would be prescribed to patients who would otherwise be prescribed linagliptin and metformin as separate tablets.

6. Comparator

The submission nominated linagliptin and metformin constituent tablets as the comparator. The PBAC accepted this as the appropriate comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented four randomised pharmacokinetics trials comparing the bioavailability of linagliptin/metformin FDC with linagliptin and metformin constituent tablets (1218.47, 1288.2, 1288.3 and 1288.1), and one randomised controlled trial comparing linagliptin and metformin taken concomitantly with metformin or linagliptin monotherapy, and placebo in patients with type 2 diabetes mellitus (1218.46).

Study 1218.47 was a single dose crossover study aimed at examining the relative bioavailability of a pilot formulation of linagliptin 2.5 mg/metformin 1,000 mg FDC compared to the free combination of linagliptin 5 mg and metformin 1,000 mg.

Studies 1288.2, 1288.3 and 1288.1 were single dose crossover studies that evaluated whether the proposed FDC formulations linagliptin 2.5 mg/metformin 500 mg, linagliptin 2.5 mg/metformin 850 mg and linagliptin 2.5 mg/metformin 1,000 mg were bioequivalent to the respective free dose combinations of linagliptin 2.5 mg and metformin 500 mg/850 mg/1,000 mg.

The primary endpoints for these pharmacokinetics studies were AUC_{0-72h} and C_{max} for linagliptin and $AUC_{0-\infty}$ and C_{max} for metformin. The acceptable range for bioequivalence was the 90% confidence interval of the geometric mean ratios between 80% and 125%.

Study 1218.46 assessed the efficacy of concomitant linagliptin 2.5 mg and metformin 500 mg (bid) and linagliptin 2.5 mg and metformin 1,000 mg (bid) compared with linagliptin 5 mg monotherapy (qd) and metformin 500 mg/1,000 mg monotherapy (bid).

The bioequivalence studies were unpublished internal study reports. Publication details of study 1218.46 are presented in the table below.

1218.46 Haak T et al 2012	Initial combination of linagliptin and metformin improves glycaemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled study	*Diabetes, Obesity & Metabolism* 2012; 14(6), 565-

For PBAC's view, see Recommendation and Reasons.

8. Results of Trials

Bioequivalence was demonstrated with linagliptin 2.5 mg/metformin 500 mg FDC, linagliptin 2.5 mg/metformin 850 mg FDC, and linagliptin 2.5 mg/metformin 1,000 mg FDC compared to the use of individual tablets, as the 90% confidence intervals for all parameters were within the bioequivalence acceptable range of 80% to 125%.

Trial 1218.46 only assessed the efficacy of the free dose combination of concomitant linagliptin and metformin against monotherapy. The primary outcome was the change in HbA_{1c} from baseline to week 24. The primary results are presented in the table below.

Results of HbA_{1c} from baseline to 24 weeks of the randomised trial

Trial ID	Linagliptin/ Metformin adjusted mean (SE)	Metformin alone (500 or 1000mg) adjusted mean (SE)	Linagliptin alone 5mg[a] adjusted mean (SE)	Adjusted mean difference (95% CI)	p-value
Trial 1218.46					
M 500 mg bid	-1.2(0.1)	-0.6(0.1)		-0.6 (-0.8, -0.4)	<0.0001
M 500 mg bid	-1.2(0.1)		-0.5(0.1)	-0.8 (-1.0, -0.5)	<0.0001
M 1,000 mg bid	-1.6(0.1)	-1.1(0.1)		-0.5 (-0.7, -0.3)	<0.0001
M 1,000 mg bid	-1.6(0.1)		-0.5(0.1)	-1.1 (-1.5, -0.9)	<0.0001

Source: Haak 2012, Table 2
Abbreviations: SE = standard error, bid=twice daily
[a]Linagliptin was administered as 2.5mg twice daily when combined with metformin 500mg or 1,000mg

The results of 1218.46 demonstrated that linagliptin taken in combination with metformin was superior to linagliptin alone, and metformin alone based on the change in HbA1c from baseline at week 24.

The PBAC recalled it had previously accepted the relevance of the change in mean HbA1c as a surrogate outcome for assessing efficacy[1]. The PBAC noted that linagliptin is currently

[1] PBAC (March 2009) Sitagliptin with metformin FDC, extract of March 2009 PBAC minutes.

reimbursed for use as a dual therapy with metformin and/or sulfonylurea but it is not registered or reimbursed for use as a monotherapy. The PBAC further noted that trial participants included treatment naïve patients which was not representative of the intended population for the linagliptin/metformin FDC. These study characteristics reduced the applicability of this trial for assessing the FDC.

There were no differences between the adverse events (AE) reported for subjects who received single tablets compared with the linagliptin/metformin FDC in trials 1288.2, 1288.3 and 1288.1. Only trial 1288.1 indicated a greater number of patients experiencing severe AEs whilst receiving the FDC compared to the single tablets.

The most commonly experienced treatment-related AEs in the single dose trials were headache, followed by nasopharyngitis, diarrhoea or vomiting, consistent with the safety profile described in the Product Information.

The proportion of subjects reporting any AE in trial 1218.46 was similar in the placebo arm (54.2%) compared with the linagliptin and/or metformin arms (49.0%-56.6%). The proportion of subjects exhibiting SAE was low, ranging from 1.4% in subjects randomised to placebo and both linagliptin and metformin study arms, to 4.1% in subjects randomised to metformin 1,000 mg bid.

The PBAC considered that the submission failed to address the issue of the difficulty of managing two sets of adverse events with the combined drugs in the FDC since both of the medications would need to be stopped if the patient is required to discontinue the FDC. In addition, since trial 1218.46 included treatment naïve patients, the trial participants may have presented with less advanced disease and therefore less likely to present with adverse events.

9. Clinical Claim

The submission described linagliptin/metformin FDC as bioequivalent with respect to both effectiveness and safety when compared with linagliptin and metformin taken separately.

The PBAC considered the submission's claim that linagliptin/metformin FDC as bioequivalent to linagliptin and metformin taken separately, was adequately supported. However, noting that the final TGA registration was not yet available, the PBAC also noted that the final assessment of acceptable bioequivalence was a matter for the TGA.

The PBAC considered that claims regarding the effectiveness and safety of the FDC compared to the constituent tablets could not be determined from the studies provided, as they were single dose studies and did not directly assess a course of multi-dose treatment over time.

The submission claimed that concomitant linagliptin and metformin was significantly more effective than linagliptin or metformin single tablets taken as monotherapy alone based on the change in HbA1c from baseline at week 24. The PBAC accepted that the submission provided adequate evidence (Study 1218.46) that there is an additional clinical effect compared to metformin alone, in terms of reduction in HbA1c.

10. Economic Analysis

The submission presented a cost-minimisation analysis based on the bioequivalence of linagliptin/metformin FDC compared to the constituent drugs.
The equi-effective doses were estimated as follows:

- Linagliptin in the FDC (2.5 mg twice daily) is the same as linagliptin single tablets (5 mg once daily)
- The daily dose of metformin in the linagliptin 2.5 mg/metformin 500 mg FDC tablet is 1,000 mg. It is assumed that patients prescribed the FDC would have previously taken a single tablet of 1,000 mg prior to switching to the FDC.
- The daily dose of metformin in the linagliptin 2.5 mg/metformin 850 mg FDC tablet is 1,700 mg, with the assumption that patients would have previously received two single tablets of 850 mg metformin.
- The daily dose of metformin for patients taking the linagliptin 2.5 mg/metformin 1,000 mg FDC tablet is 2,000 mg, with patients previously receiving two single tablets of 1,000 mg metformin

The proposed price of the linagliptin/metformin FDC was calculated using the equivalent reimbursed prices for the linagliptin and metformin components of the combination tablet.

The PBAC accepted the estimated equi-effectiveness doses and considered the cost-minimisation analysis reasonable based on the submission's claim of bioequivalence.

11. Estimated PBS Usage and Financial Implications

The submission estimated the likely number of prescriptions per year of linagliptin/metformin FDC (all strengths) to be between 100,000 and 200,000 in Year 5. The submission estimated a greater reduction (while within the same range) in the number of prescriptions for the constituent products and other gliptin/metformin FDCs. The net costs to the PBS/RPBS and the Government (taking into account cost savings to the MBS) were both estimated in the submission to be less than $10 million in Year 5.

The PBAC noted the submission's claim that patients likely to be prescribed the linagliptin/metformin FDC, would be patients switching from a current combination treatment of the components, as well as a small number of patients switching from existing listed gliptin/metformin FDCs. The estimated cost savings to the MBS were based on a reduction in liver function tests from patients switching to the linagliptin/metformin FDC from the vildagliptin/metformin FDC. The PBAC considered that this cost saving was uncertain as the assumption that patients will switch from vildagliptin/metformin FDC to linagliptin/metformin FDC was unsupported.

The PBAC considered that the submission's estimate of usage was uncertain and was a likely underestimate on the basis of the potential for leakage beyond the requested PBS population for the linagliptin/metformin FDC, from third line use, to first line use in patients unable to tolerate or contraindicated to sulfonylurea therapy. In addition, the PBAC noted experience with other PBS listed gliptin/metformin FDCs indicated that there is potential for higher uptake than anticipated, and that a proportional decrease in the proposed substituted therapies, may not eventuate in practice.

The PBAC noted the potential for other use outside of the PBS subsidy criteria, including as triple oral therapy with sulphonylurea, metformin and a gliptin, and a proportion of patients

where a gliptin is added to metformin, and where the patient does not have a contraindication or intolerance to a sulphonylurea.

The PBAC noted the following concerns with the linagliptin/metformin FDC with respect to completely meeting the guidelines for FDCs:

- Criterion (f) requires that the combination not encourage or result in an inappropriate increase in overall utilisation of the components, nor inappropriate use of one or both components in specific patient groups**.** The PBAC considered that there is a risk that linagliptin/metformin FDC may be used earlier in the treatment algorithm than specified in the PBS restriction based on sources of information provided by the DUSC relating to predicted versus actual use of combination drugs.
- Criterion (g) requires that the combination product does not result in inappropriate dosing of either component, nor contain components which require individual dose titration. The PBAC considered that there was risk of inappropriate dosing with linagliptin/metformin FDC as the metformin component requires titration.
- Criterion (h) requires that the combination product does not result in unnecessary proliferation of product and/or dose forms. The PBAC was not convinced of a pressing clinical need for a linagliptin/metformin FDC as there are currently two PBS listed gliptin/metformin FDCs.

12. Recommendation and Reasons

The PBAC deferred consideration of this submission pending finalisation of the TGA registration process, particularly the final indication, and further consideration of predicted utilisation and financial implications based on the Drug Utilisation Sub-Committee (DUSC) utilisation analysis.

The PBAC noted the requested restriction was consistent with current restrictions for other gliptin with metformin FDC products.

The PBAC also noted a PBS post market review (PMR) of products used in the management of diabetes was currently underway. It noted that one of the terms of reference of this review was to describe the utilisation and patterns of treatment of PBS listed drugs for type 2 diabetes mellitus, and to compare these with PBS restrictions. Hence, the findings of this review may impact the PBS restrictions for medicines for the treatment of diabetes mellitus.

The PBAC noted a preliminary report from the Drug Utilisation Sub-Committee from its February 2013 meeting on the utilisation of gliptins and gliptin-metformin FDCs. The DUSC utilisation analysis, that had been provided to sponsors for comment, suggested that at least 30% of current use of gliptins and gliptin-FDCS is not consistent with existing restrictions. The PBAC considered that new products of this class would need to be assessed in this context.

The PBAC considered that it would be essential to consider the final report from DUSC before defining the appropriate restrictions for linagliptin/metformin as a new FDC. There may also be implications for the current restrictions for existing gliptin/metformin FDCs following consideration of the DUSC report. If there is in fact evidence to support what appears to be the evolving clinical use of gliptins higher up the treatment algorithm, including as an alternative to sulfonylureas as second line therapy, then this use is not consistent with the cost-effective use that was previously accepted by the PBAC for gliptins or

gliptin/metformin FDCs. The PBAC also considered that the addition of another FDC of gliptin with metformin could promote the current rapid growth in utilisation of gliptins.

The PBAC noted that the final report from DUSC would be provided to PBAC for consideration at its Special meeting in April 2013, and agreed to re-consider the PBS-listing of linagliptin/metformin FDC at that meeting.

The application was subsequently considered at the April 2013 PBAC Special PBAC meeting and the outcome will be published at a later date.

Based on the DUSC utilisation analysis, the PBAC considered that the submission's estimates of utilisation and financial implications were highly uncertain and likely to be significantly underestimated, should the linagliptin/metformin FDC be used in the same way as the currently PBS listed DPP-4 inhibitor (gliptin)/metformin FDCs.

The PBAC agreed it would be reasonable to extrapolate the risk of use outside the restriction seen for currently listed gliptin/metformin FDCs as it would also apply to linagliptin/metformin FDC, should the PBS indication be approved as proposed.

The PBAC noted that whilst the requested listing of linagliptin/metformin FDC on the PBS would allow prescribing to patients who would otherwise be prescribed linagliptin and metformin as separate tablets, preliminary results from the DUSC utilisation review suggest gliptins are being used earlier in the treatment algorithm.

The PBAC considered the submission's cost minimisation approach based on bioequivalence of the FDC against the individual components to be reasonable.

The PBAC considered the nominated comparator was appropriate and consistent with comparators previously accepted for other gliptin/metformin FDCs. However, the PBAC also noted that the two currently PBS-listed gliptin/metformin FDCs may also be considered as comparators.

Recommendation:
Deferred

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 had no further comment.

ADDENDUM – APRIL 2013

Product: Linagliptin with metformin hydrochloride, tablets, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, Trajentamet®
Sponsor: Boehringer Ingelheim Pty Ltd
Date of PBAC Consideration: April 2013

1. Purpose of Application

To reconsider the submission, deferred at the March 2013 PBAC meeting, requesting an Authority required (STREAMLINED) listing for treatment of type 2 diabetes mellitus (T2DM).

2 Background and Requested listing

Refer to the March 2013 Public Summary Document to which this addendum is appended.

3. Registration status

As at 21 May 2013, linagliptin with metformin FDC was TGA registered for the following indications:

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

4. Clinical place for the proposed therapy

Refer to the March 2013 Public Summary Document.

5. Comparator

Refer to the March 2013 Public Summary Document.

6. PBAC consideration of the evidence

Refer to the March 2013 Public Summary Document.

Drug Utilisation sub-Committee (DUSC) Analysis of Medicines for Type 2 diabetes

The PBAC noted that the October 2012 and February 2013 DUSC utilisation analyses had been provided to the sponsor.

The PBAC noted the following findings from the February 2013 DUSC analysis of utilisation of PBS listed medicines for type 2 diabetes:

- There is extensive use of gliptins, glitazones and exenatide beyond the PBS restrictions;
- When considering medicines that can or cannot be prescribed in combination for PBS subsidy, 27.9% of patient medication regimens that include a gliptin, glitazone or exenatide do not meet the restrictions, that is:

    - The combination of a gliptin or rosiglitazone with both metformin and a sulfonylurea accounts for almost half of the patient medication regimens that are beyond the PBS restriction;
    - Monotherapy with a gliptin or a glitazone or exenatide is the next most frequent regimen that is non-compliant with PBS restrictions, accounting for 23%;
    - 34.6% of regimens containing gliptins do not comply with PBS criteria.
- When considering whether prescribing of gliptins, glitazones and exenatide complies with the requirements for patients to be contraindicated or intolerant to either metformin or a sulfonylurea:
    - Overall, 47.7% of patients initiated on a gliptin, glitazone or exenatide had not received a supply of both metformin and a sulfonylurea in the previous two years. A proportion of these patients may have a contraindication to one or both of these agents, but the rate is higher than plausible based on the likely frequency of true contraindications.
    - 4.9% of patients had no evidence of a supply of metformin or a sulfonylurea in the 2 years prior to the index prescription of a gliptin, glitazone, or exenatide. This group may represent patients who have contraindications to both metformin and a sulfonylurea. To comply with the conditions for PBS subsidy, however, the gliptins should be used in combination with either metformin or a sulfonylurea, and exenatide should be used with one or both of metformin and sulfonylurea. This group is unlikely to meet PBS criteria for co-administered therapy.
    - 6.7% of patients had a sulfonylurea supplied, but no metformin, which is consistent with reported rates of metformin contraindication.
    - 36.1% of patients had metformin supplied, but not a sulfonylurea, which is not consistent with the rate of contraindication to sulfonylurea.
    - Of all patient initiations to gliptins, glitazones or exenatide between July-December 2011, 85% were for gliptins. Although it is acknowledged that there are safety concerns with the glitazones, which is probably reducing their use, it is inconsistent that 85% of initiations are for gliptins, which are only subsidised where there is a contraindication or intolerance to metformin of sulfonylurea, whereas pioglitazone has two additional indications covering a larger population.

With specific regard to gliptins, the PBAC noted that for all regimens containing a gliptin the total non-compliance with PBS criteria was 34.6%. 18.5% of use of gliptins was in combination with BOTH metformin and a sulfonylurea. The cost-effectiveness of this treatment regimen has not been established.

With specific regard to gliptin+metformin FDCs, the PBAC noted that 46.7% of patients initiated on a regimen containing a gliptin+metformin FDC had been supplied only metformin as pre-initiation treatment (i.e., they had not been supplied a sulfonylurea). While the PBAC acknowledged that a proportion of these patients may have a true contraindication to sulfonylureas, the PBAC considered that this proportion would be small, and the majority of the 46.7% were probably supplied gliptin+metformin FDCs under circumstances that were non-compliant with PBS criteria. Again, the PBAC noted that the cost-effectiveness of this treatment regimen (i.e., dual therapy as an alternative to sulfonylureas in a population WITHOUT contraindications) has not been established.

The findings of the DUSC review confirmed the PBAC's concerns, expressed during the March 2013 consideration of the submission, that there was significant potential for use of the proposed linagliptin+metformin FDC outside the requested PBS population.

The PBAC considered that this concern was well supported by observed experience with the currently PBS listed gliptin+metformin FDCs, where the review of utilisation of the products showed that utilisation had been substantially greater than anticipated.

Similarly, the PBAC considered that it was, highly likely, that utilisation of linagliptin+metformin FDC would also be considerably higher than predicted, and therefore the submission's estimated costs to the PBS and Government were underestimated and highly uncertain.

7. Recommendation and Reasons

The PBAC noted that the ACPM had found that linagliptin+metformin FDC had a favourable risk-benefit profile for the requested indication. Therefore, the PBAC was satisfied that the TGA registration was consistent with the requested PBS listing.

As in March 2013, the PBAC remained concerned regarding linagliptin+metformin FDC with respect to completely meeting the guidelines for FDCs. (Refer to the March 2013 Public Summary Document).

The PBAC reiterated its position that it considered the submission's estimates of utilisation and financial implications to be highly uncertain and likely to be significantly underestimated should the linagliptin+metformin FDC be used in the same way as currently PBS listed gliptin+metformin FDCs, based on the DUSC utilisation analysis, and experience with currently listed gliptin+metformin FDCs.

The PBAC remained confident that it was reasonable to extrapolate the risk of use outside the restriction seen for currently listed gliptin+metformin FDCs to linagliptin+metformin FDC, should the PBS indication be approved as proposed. The PBAC noted that the majority of use outside the requested PBS indication was likely to be use earlier in the treatment algorithm, in place of sulfonylureas, in patients who are not intolerant of sulfonylureas or in whom sulfonylureas are not contraindicated.

The PBAC considered that there was no compelling clinical need for an additional gliptin+metformin FDC on the PBS, and had significant concerns regarding the highly uncertain and underestimated usage and financial implications. The PBAC gave consideration to the following two options that it thought might provide a reasonable basis of approval of the submission, and ensure the cost to the PBS and Government was acceptable.

<u>Option 1</u>
As the PBAC did not have confidence in the predictions of use beyond Year 1, and noting that the gliptin+FDC market is expanding, the PBAC considered that one option was to approve linagliptin+metformin FDC for listing with the requested restriction, (i.e., limiting use to patients in whom combination treatment with metformin and a sulfonylurea is contraindicated or not tolerated), at the price proposed in the submission, with a risk sharing arrangement involving a hard cap based on Year 1 utilisation estimates beyond which a

100% rebate would apply. However, the PBAC did not have any confidence in the predicted estimates of use in year 2 and did not consider it was able to advise the Minister or the Department of what the financial cap should be in year 2 and beyond.

Option 2

Taking into account the findings of the DUSC utilisation analysis with regard to the use of gliptin+FDCs earlier in the treatment algorithm in patients not supplied a sulfonylurea, the PBAC considered it would be reasonable to recommend listing with a restriction more reflective of the likely use of this combination product (i.e., remove the requirement for patients to have a contraindication or be intolerant of sulfonylureas) but at a reduced price, noting that the Committee had not been provided with any evidence to support cost-effectiveness in this expanded population.

The PBAC noted the DUSC utilisation analysis finding that 46.7% of patients initiating on a gliptin+metformin FDC were not supplied a prior sulfonylurea. The PBAC considered whether it could estimate the likely true frequency of patients who are intolerant to sulfonylureas, or in whom the class of drugs is contraindicated. No precise estimates were identified in the review, and the product information documents for existing sulfonylureas include only general warning statements without quantification. While noting prescriber concerns about risk of hypoglycaemia particularly in the elderly with some sulfonylureas, the PBAC considered that the rate of true contraindication or intolerance would be very small, less than 5% of the patient population. With this assumption, it remained that usage in approximately 40% of patients initiated on a gliptin+metformin FDC has not been demonstrated to be cost-effective. Therefore, the PBAC considered that listing under these circumstances would require a price reduction to account for the likely non-cost-effective use, and that approximately 40% of use should be cost-minimised to the price of the average daily dose of a sulfonylurea in combination with metformin.

Overall, given the unknown likely utilisation, the PBAC considered that Option 2 was preferred, and recommended listing of linagliptin+metformin FDC as an Authority Required (STREAMLINED) benefit in patients 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 metformin, at a reduced price which takes into account the proportion of use in patients where the cost-effectiveness of this combination has not been established, as described above.

The PBAC recommended that an amended listing with removal of the requirement for patients to be contraindicated or intolerant of sulfonylureas for single ingredient linagliptin was appropriate, should a similar price reduction be agreed for the single ingredient formulation.

The PBAC noted the correspondence from the sponsor, drawing comparisons with the PBAC's November 2012 recommendation for sitagliptin with simvastatin for patients with type 2 diabetes and elevated cholesterol. The PBAC did not consider this comparison to be relevant, as the recommendation referred to was for use of sitagliptin with simvastatin in a different patient population. In addition, the sitagliptin/simvastatin combination was not likely to replace the use of a sulfonylurea, which is the relevant issue for the consideration of the proposed linagliptin/metformin FDC.

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

Recommendation:
Recommended

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
LINAGLIPTIN + METFORMIN			Trajentamet BY
Linagliptin 2.5 mg + metformin hydrochloride 500 mg, tablet	60	5	
Linagliptin 2.5 mg + metformin hydrochloride 850 mg, tablet	60	5	
Linagliptin 2.5 mg + metformin hydrochloride 1000 mg, tablet	60	5	

Condition/Indication:	Type 2 diabetes
Treatment phase:	Initial treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have an HbA1c 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 metformin; OR The patient must show blood glucose levels greater than 10 mmol per L in more than 20% of blood glucose monitoring tests over a 2-week period despite treatment with metformin in circumstances where assessment of HbA1c is not appropriate.
Prescriber Instructions	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. 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.
Administrative Advice	Linagliptin with metformin fixed dose combination tablet is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy), as initial therapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1.

Condition/Indication:	Type 2 diabetes
Treatment phase:	Continuing treatment
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	Patient must have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines which includes metformin and linagliptin.
Administrative Advice	Linagliptin with metformin fixed dose combination tablet is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy), as initial therapy or in combination with a thiazolidinedione (glitazone) or a glucagon-like peptide-1.

8. 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.

9. Sponsor's Comment

The sponsor has no comment