PUBLIC SUMMARY DOCUMENT

Product: Saxagliptin with Metformin, tablet, 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg, Kombiglyze®
Sponsor: Bristol-Myers Squibb Australia Pty Ltd and AstraZeneca 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 HbA1c 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 product. Saxagliptin 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.

Kombiglyze was registered by the TGA on 13 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.

Note: Saxagliptin 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.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy

Saxagliptin/metformin FDC will provide a treatment alternative to concurrent use of saxagliptin 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 proposed that saxagliptin with metformin would be used as third line treatment. The algorithm indicated that first line pharmacological therapy is metformin or a sulfonylurea. If glycaemic control was not achieved, dual combination therapy should be considered, including metformin+sulfonylurea, metformin/sulfonylurea with either a DPP4-inhibitor, a thiazolidinedione, arcabose, GLP1 agonist, or insulin.

The submission claimed that listing the saxagliptin/metformin FDC on the PBS will not change the current treatment algorithm, as saxagliptin/metformin FDC will be prescribed to patients who would otherwise be prescribed saxagliptin and metformin as separate tablets.

6. Comparator

The submission nominated the individual components, saxagliptin 5 mg and metformin 500 mg, 850 mg and 1000 mg, as the appropriate main comparator. The PBAC accepted this as the appropriate comparator.

For PBAC's view, see Recommendation and Reasons.

7. Clinical Trials

The submission presented four unpublished bioequivalence trials (Studies 081, 092, 120 and 152) in healthy subjects and one unpublished head-to-head randomised controlled trial (RCT) (Study 080) comparing saxagliptin 2.5mg BID in combination with metformin to metformin alone in patients with T2DM.

Details of the studies are presented in the table below.

Course of treatment in clinical trials and economic evaluation

		Drug 1	Drug 2	Subjects
Bioequivalence data	Study 081	Saxagliptin/metformin FDC 2.5 mg/500 mg BID	Saxagliptin 2.5mg BID + metformin 500 mg BID	24 healthy subjects
	Study 092	Saxagliptin/metformin FDC 2.5mg/1000mg BID	Saxagliptin 2.5 mg BID + metformin 1000 mg BID	24 healthy subjects
	Study 120	Diabex metformin (500 mg, 1000mg)	Glucophage metformin (500 mg, 1000 mg)	28 healthy subjects

	Study 152	Saxagliptin 2.5 mg BID	Saxagliptin 5 mg QD	16 healthy subjects
Efficacy and safety data	Study 080	Saxagliptin 2.5 mg BID + metformin BID (1500-3000 mg/day)	Placebo + metformin BID (1500-3000 mg/ day)	160 patients with T2DM

BID: twice daily, QD: once daily.
Source: Compiled during evaluation

The four bioequivalence trials were open-label, cross-over randomised controlled trials (RCTs) with washout periods between treatment arms. The trials were analysed on the basis of treated patients (had received a dose during the treatment period), but this also corresponded with the ITT population in two trials (Study 081 and 152). No adjustments were made for missing data. The efficacy trial was a double-blind, multi-centre RCT. The trial was analysed on an "all randomised patients who took at least 1 dose" basis. Last observation carried forward (LOCF) was used to adjust for missing data.

The clinically relevant outcomes for benefits and harms were overall survival, cardiovascular disease, diabetic retinopathy, kidney failure, amputations etc. The PBAC recalled that it had previously accepted the relevance of the change in HbA1c as a surrogate outcome for assessing efficacy[1].

8. Results of Trials

From the bioequivalence studies, the results showed that the saxagliptin maximum observed plasma concentration (Cmax), metformin Cmax, saxagliptin area under the plasma concentration-time curve from time zero extrapolated to infinite time (AUC(INF)) and metformin AUC(INF) met the criteria for bioequivalence in all trials.

The results of Study 080 showed that there was a statistically significant reduction in the adjusted mean change in HbA1c from baseline to week 12 in the saxagliptin 2.5 mg BID + metformin treatment arm compared to metformin alone. The submission noted that the placebo response in Study 080 was unusually high and may be attributed to biological variability.

Additionally, there was a numerically greater decrease in the adjusted mean change in fasting plasma glucose (FPG, not statistically significant) from baseline to week 12 in the saxagliptin 2.5mg BID + metformin treatment arm compared to metformin alone.

There was a statistically significant greater proportion of patients who achieved an HbA1C less than 7% in the saxagliptin 2.5 mg BID + metformin treatment arm compared to metformin alone. A similar result was also observed for HbA1C less than 6.5 %.

In study 080, the incidence of adverse events (AEs) was lower or comparable with saxagliptin 2.5 mg BID + metformin versus metformin alone with the exception of hypoglycaemic AEs. Patients treated with saxagliptin 2.5 mg BID + metformin experienced more hypoglycaemia than metformin alone (all events were mild or moderate). The incidence of confirmed hypoglycaemia[2] was lower with saxagliptin 2.5 mg BID + metformin but the incidence of hypoglycaemic AEs was higher.

[1] PBAC (March 2009) Sitagliptin with metformin FDC, extract of March 2009 PBAC minutes.
PBAC (Nov 2010) Vildagliptin with metformin FDC, extract of November 2010 PBAC minutes.
[2] Fingerstick glucose value ≤ 50mg/dL with associated hypoglycaemia symptoms.

An extended assessment of comparative harms was not presented.

For PBAC's view, see Recommendations and Reasons.

9. Clinical Claim

The submission described saxagliptin/metformin FDC as bioequivalent in terms of the pharmacodynamics and pharmacokinetics to concomitant administration of the individual tablets of saxagliptin and metformin at the corresponding dose strengths. The PBAC considered the claim was adequately supported, but noted that the final assessment of bioequivalence was a TGA matter.

The submission further described saxagliptin/metformin FDC as safe and effective in the treatment of patients with T2DM, although it did not specify the comparator to which claim this claim related. In terms of reduction of HbA1c, the PBAC considered that Study 080 provided adequate evidence of an additional clinical effect compared to metformin alone.

The PBAC considered that the submission did not provide evidence that at the corresponding dose strengths, that the efficacy and safety of saxagliptin/metformin FDC are the same as concomitant administration of the individual tablets of saxagliptin and metformin. The submission also did not provide adequate evidence that the efficacy and safety of saxagliptin 5 mg QD (once daily) are the same as that of saxagliptin 2.5 mg BID (twice daily). A visual comparison of the efficacy results reported by Study 080 to other studies was presented.

10. Economic Analysis

A cost-minimisation analysis was presented, based on non-inferiority between saxagliptin/metformin FDC and the individual components, on grounds of bioequivalence, and not including any additional costs/offsets. The equi-effective doses were estimated as:

- Saxagliptin/metformin FDC: saxagliptin 2.5 mg BID plus either metformin 500 mg, 850 mg or 1000 mg BID, whichever appropriate.
- Individual components form: saxagliptin 5 mg QD plus either metformin 500 mg, 850 mg or 1000 mg BID, whichever appropriate.

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

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated to be between 10,000 and 50,000 in Year 5. The total number of prescriptions supplied was estimated to be more than 200, 000 in Year 5. The submission claimed a nil net cost to the PBS/RPBS, as a result of a directly proportional decrease in the use of the single-drug items.

The PBAC considered that the submission's estimate of usage was uncertain and would likely be an underestimate given the potential for leakage beyond the requested PBS population for the saxagliptin/metformin FDC, to patients without a contraindication or intolerance to sulfonylurea therapy. In addition, the PBAC noted that experience with other PBS listed gliptin/metformin FDCs indicated potential for higher uptake than anticipated, and that a proportional decrease in the proposed substituted therapies may not eventuate in practice.

Therefore, the PBAC did not consider that the listing of saxagliptin/metformin FDC would result in an overall net nil cost to the PBS.

The PBAC also noted the potential for use outside of the PBS subsidy criteria, including as triple oral therapy with sulfonylurea, metformin and a gliptin, and a proportion of patients where a gliptin is added to metformin, where the patient does not have a contraindication or intolerance to a sulfonylurea.

The PBAC also considered the submission's assumption that patient's will switch from other gliptin/metformin FDC combinations uncertain.

The PBAC noted the following concerns with the saxagliptin/metformin FDC with respect to meeting submission guidelines for listing 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 saxagliptin/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 not result in inappropriate dosing of either component, nor contain components that require individual dose titration. The PBAC considered that there was risk of inappropriate dosing with saxagliptin/metformin FDC as the metformin component requires titration.
- Criterion (h) requires that the combination product not result in unnecessary proliferation of product and/or dose forms. The PBAC was not convinced of a pressing clinical need for a saxagliptin/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, confirmation of bioequivalence with the single components given concomitantly, 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 (DUSC) from its February 2013 meeting on the utilisation of gliptins and gliptin-metformin FDCs.

The DUSC utilisation analysis, which 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 saxagliptin/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 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 fixed dose combination of gliptin with metformin could promote the current rapid growth in utilisation of gliptins.

The PBAC further noted that the final report from DUSC would be provided to PBAC for consideration at a PBAC Special meeting in April 2013, and agreed to re-consider this listing at the meeting.

The application was subsequently considered at the April 2013 PBAC Special 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 if the saxagliptin/metformin FDC is used in the same way as currently PBS listed dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptin)/metformin FDCs.

If the PBS indication was approved as proposed, the PBAC noted that it would be reasonable to extrapolate the risk of use outside the restriction seen for currently listed gliptin/metformin FDCs, to saxagliptin/metformin FDC.

The PBAC noted that whilst the requested listing of saxagliptin/metformin FDC on the PBS would allow prescribing to patients who would otherwise be prescribed saxagliptin 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 replaced in practice.

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 notes that this submission was subsequently considered at the April 2013 PBAC Special meeting.