

**6.13 SAXAGLIPTIN AND METFORMIN XR**  
**5 mg/500 mg tablet, 28; 5 mg/1000 mg tablet, 28; 2.5 mg/1000 mg tablet, 56**  
**KOMBIGLYZE<sup>®</sup>, AstraZeneca**

**1 Purpose of Application**

1.1 The minor submission requested that the PBS indication for saxagliptin+metformin (MET) XR (KOMBIGLYZE<sup>®</sup> XR) be extended to include use with a sulfonylurea (SU) (triple oral therapy) for the treatment of type 2 diabetes mellitus (T2DM). This would align the PBS listings for saxagliptin and the saxagliptin+MET fixed dose combination (FDC).

**2 Requested listing**

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
SAXAGLIPTIN+METFORMIN				Kombiglyze XR AZ
saxagliptin 5 mg + metformin hydrochloride 500 mg tablet: modified release, 28	1	5	\$ [REDACTED]	
saxagliptin 5 mg + metformin hydrochloride 1 g tablet: modified release, 28	1	5	\$ [REDACTED]	
saxagliptin 2.5 mg + metformin hydrochloride 1 g tablet: modified release, 56	1	5	\$ [REDACTED]	
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)			
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners			
<b>PBS Indication:</b>	Diabetes mellitus type 2			
<b>Restriction Level / Method:</b>	Authority required (Streamlined)			
<b>Clinical criteria:</b>	The treatment must be in combination with a sulfonylurea  AND  Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase-4 (DPP4) inhibitor despite treatment with maximally tolerated doses of metformin and a sulfonylurea; OR  Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a DPP4 inhibitor despite treatment			

	<p>with maximally tolerated doses of metformin and a sulfonylurea.</p> <p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a DPP4 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a DPP4 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a DPP4 inhibitor, must be documented in the patient's medical records.</p> <p><i>A patient whose diabetes was previously demonstrated unable to be controlled with metformin does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.</i></p>
<p><i>Administrative advice</i></p>	<p><i>This fixed dose combination tablet is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.</i></p>

### 3 Background

- 3.1 Saxagliptin+MET (Kombiglyze® XR ) is TGA indicated as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both saxagliptin and MET is appropriate.
- 3.2 Saxagliptin+MET immediate release (IR) FDC was considered by the PBAC at the March 2013 meeting for an Authority required (STREAMLINED) listing for treatment of type 2 diabetes mellitus 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 MET and where a combination of MET and a SU is contraindicated or not tolerated. The submission presented a cost-minimisation analysis based on non-inferiority between saxagliptin+MET FDC and the individual components, on grounds of bioequivalence. The PBAC deferred making a recommendation at the March 2013 meeting 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 from a DUSC utilisation analysis.
- 3.3 Saxagliptin+MET IR was subsequently recommended for listing at the April 2013 PBAC Special meeting as an Authority Required (STREAMLINED) listing 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 MET. Based on information from the DUSC utilisation analysis, listing was recommended at a lower price and with a different restriction than requested, with the PBAC noting that:

...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 SUs) but at a reduced price, noting that the Committee had not been provided with any evidence to support cost-effectiveness in this expanded population.

- 3.4 Saxagliptin+MET extended release (XR) FDC was recommended by the PBAC at the November 2013 meeting for an Authority required (STREAMLINED) listing for the treatment of Type II diabetes in a patient whose HbA1c is greater than 7% despite treatment with MET. The submission presented a cost-minimisation analysis based on non-inferiority between saxagliptin+MET XR FDC and the individual components, on grounds of bioequivalence. The submission stated that if saxagliptin+MET XR FDC received a positive recommendation that the saxagliptin+MET IR FDC (which was recommended for listing at the April 2013 special meeting) would not be marketed in Australia. The PBAC re-confirmed its April 2013 recommendation that an amended listing with removal of the requirement for patients to be contraindicated or intolerant of SUs was appropriate for this FDC. In regards to pricing, the PBAC considered that the cost-effectiveness of saxagliptin+MET XR FDC would be acceptable if it were cost-minimised against the alogliptin+MET FDC. In making this decision the PBAC considered:

That saxagliptin offers no improvement in efficacy or reduction in toxicity over alogliptin, and noting that saxagliptin may be associated with increased cardiac failure hospitalisations, the PBAC considered it is therefore appropriate for the subsidy price for the saxagliptin component of the FDC, to be cost minimised against alogliptin; and that:

With respect to the price of the metformin component of the FDC...a price for the metformin component that is equal to the corresponding amount of metformin IR in the other gliptin/metformin FDCs would be consistent with its recommendation for the metformin XR/sitagliptin FDC. Additionally this approach to pricing the metformin XR component is appropriate in the absence of any evidence that this FDC is associated with an improvement in efficacy or a reduction in toxicity compared to other FDCs of a gliptin and metformin.

- 3.5 Saxagliptin (2.5mg and 5mg tablets) is currently listed on the PBS for dual oral therapy in combination with MET or a SU in patients inadequately controlled on either MET or a SU alone. The sponsor has submitted a major submission for consideration at the July 2015 PBAC meeting (agenda item 6.02) to request extension of the PBS listing of saxagliptin to include an Authority Required (Streamlined) listing for saxagliptin 2.5mg and 5mg tablets for the treatment of patients with type 2 diabetes in combination with MET and a SU (triple oral therapy).

#### 4 Consideration of the evidence

##### **Sponsor hearing**

4.1 There was no hearing for this item as it was a minor submission.

##### **Consumer comments**

4.2 The PBAC noted that no consumer comments were received for this item.

##### **Clinical trials**

4.3 As a minor submission, no new clinical trials were presented in the submission. The basis of the submission is the evidence presented in previous submissions for the FDC that demonstrated bioequivalence with the mono-components given concomitantly. The submission stated that an updated literature search did not identify any additional evidence regarding bioequivalence.

##### **Drug cost/patient/year**

4.4 The submission assumed that the price of saxagliptin+MET XR FDC in triple oral therapy would be identical to the dual therapy indication. The submission noted that this is consistent with the outcomes for dapagliflozin in triple oral therapy from the March 2015 meeting.

4.5 The requested price for saxagliptin+MET XR FDC (based on the then DPMQ for the dual therapy indication) is summarised in the following table.

**Table 1: Requested price by dose for 28 days of treatment as triple oral therapy in combination with a sulfonylurea**

	DPMQ	Drug cost/patient/year*
5 mg saxagliptin / 500 mg metformin XR, 28	\$ [REDACTED]	\$ [REDACTED]
5 mg saxagliptin / 1000 mg metformin XR, 28	\$ [REDACTED]	\$ [REDACTED]
2.5 mg saxagliptin / 1000 mg metformin XR, 56	\$ [REDACTED]	\$ [REDACTED]

Adapted from Table 2, pg.4 of the submission. Abbreviations: DPMQ, dispensed price maximum quantity; mg, milligrams; XR, extended release.

\*Assuming 13.04 packs per year

##### **Estimated PBS usage & financial implications**

4.6 The submission presented a market share approach. This was consistent with the saxagliptin (triple oral therapy) major submission to the March 2015 meeting. The submission assumed that PBS listing of the saxagliptin+MET XR FDC would not grow the T2DM market or the saxagliptin/DPP4 market.

4.7 The submission estimated there would be minimal financial implications to the PBS if saxagliptin+MET XR FDC is listed, as it anticipated that saxagliptin+MET XR FDC will substitute for saxagliptin and MET mono-components over time. The proposed substitution rate, summarised in Table 2 below, was based on PBS usage data for sitagliptin and sitagliptin+MET over a four year period.

**Table 2: Market share split between saxagliptin and saxagliptin+metformin FDC in triple oral therapy**

	2015	2016	2017	2018	2019	2020
Saxagliptin share of saxagliptin services	█%	█%	█%	█%	█%	█%
Saxagliptin+metformin share of saxagliptin services#	█%	█%	█%	█%	█%	█%

Source: Table 4, pg.6 of the submission.

Abbreviations: TOT, triple oral therapy; FDC, fixed dose combination; XR, extended release

# Sitagliptin mono-component vs FDC ratio (see paragraph 4.5)

- 4.8 The estimated use and financial implications of listing saxagliptin+MET XR FDC on the PBS is summarised in the following table.

**Table 3: Estimated use and financial implications**

	Year 1	Year 2	Year 3	Year 4	Year 5	Total
<b>Extent of use</b>						
Number treated	█	█	█	█	█	█
Number of services	█	█	█	█	█	█
<b>Cost of listing saxagliptin+metformin on the PBS/RPBS</b>						
Cost to the PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Savings to PBS/RPBS from substitution of saxagliptin and metformin mono-components</b>						
Savings to the PBS/RPBS	\$ █	\$ █	\$ █	\$ █	\$ █	\$ █
<b>Net cost of listing saxagliptin+metformin on the PBS/RPBS</b>						
Net cost to the PBS/RPBS	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █	-\$ █

Source: Tables 6 and 7, pp 9-10 of the submission.

- 4.9 The redacted table above shows that at year 5, the estimated number of patients was less than 10,000 and the net save to the RPBS/PBS would be less than \$10 million.

## 5 PBAC Outcome

- 5.1 The PBAC recommended that the listing of saxagliptin+MET XR for the treatment of T2DM be extended to include use in combination with a SU (triple oral therapy).
- 5.2 The PBAC recalled that at its November 2013 meeting it had accepted that saxagliptin+MET XR is similar in efficacy and safety to the co-administration of the same doses of the individual components.
- 5.3 The PBAC recommended the inclusion of a grandfather clause, consistent with the current restriction for saxagliptin, to enable patients whose diabetes has previously been demonstrated unable to be controlled with MET or a SU to be eligible for PBS-subsidised treatment with saxagliptin without having to requalify with respect to glycosylated haemoglobin levels (HbA1c).
- 5.4 The PBAC recommended that the listing for saxagliptin+MET XR should be consistent with the triple oral therapy restriction for sitagliptin+MET. The PBAC further recommended that this restriction wording should apply to other DPP-4 inhibitors and SGLT2 inhibitors (including FDCs) listed for triple oral therapy in T2DM to ensure consistency across listings. The PBAC recommended the following wording to replace the words at the end of one of the clinical criteria: "...despite

treatment with ~~maximally tolerated doses of metformin and a sulfonylurea~~ *either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug*” (with suggested additions in italics and deletions crossed out with strikethrough).

- 5.5 The PBAC considered that the submission’s assumption that the price of saxagliptin+MET XR FDC in triple oral therapy would be identical to the dual therapy indication was reasonable.
- 5.6 The PBAC advised the Minister that, under Section 101(3BA) of the National Health Act 1953, the saxagliptin+MET FDC should be treated as interchangeable on an individual patient basis with the sitagliptin+MET FDC for triple oral therapy for T2DM.
- 5.7 The PBAC advised that the NOTE in the current restriction of saxagliptin+MET XR dual therapy will need to be amended to allow for triple oral combination therapy.
- 5.8 The PBAC advised that saxagliptin is suitable for prescribing by nurse practitioners within collaborative arrangements.
- 5.9 The PBAC recommended that the Safety Net 20 Day Rule should apply.

**Outcome:**

Recommended

**6 Recommended listing**

6.1 Amend existing listing as follows:

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer	
SAXAGLIPTIN+METFORMIN			Kombiglyze XR	AZ
saxagliptin 5 mg + metformin hydrochloride 500 mg tablet: modified release, 28	1	5		
saxagliptin 5 mg + metformin hydrochloride 1 g tablet: modified release, 28	1	5		
saxagliptin 2.5 mg + metformin hydrochloride 1 g tablet: modified release, 56	1	5		
<b>Category / Program</b>	GENERAL – General Schedule (Code GE)			
<b>Prescriber type:</b>	<input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners			
<b>PBS Indication:</b>	Diabetes mellitus type 2			
<b>Restriction Level / Method:</b>	Authority required (Streamlined)			

<p><b>Clinical criteria:</b></p>	<p>The treatment must be in combination with a sulfonylurea</p> <p>AND</p> <p>Patient must have, or have had, a HbA1c measurement greater than 7% prior to the initiation of a dipeptidyl peptidase-4 (DPP4) inhibitor (gliptin), a thiazolidinedione (glitazone), a glucagon-like peptide-1 or a sodium-glucose co-transporter 2 (SGLT2) inhibitor despite treatment with either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug;</p> <p>OR</p> <p>Patient must have, or have had, where HbA1c measurement is clinically inappropriate, blood glucose levels greater than 10 mmol per L in more than 20% of tests over a 2 week period prior to initiation with a DPP4 inhibitor despite treatment with either metformin and a sulfonylurea, or metformin and this drug, or a sulfonylurea and this drug.</p> <p>The date and level of the qualifying HbA1c measurement must be, or must have been, documented in the patient's medical records at the time treatment with a DPP4 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a DPP4 inhibitor was initiated.</p> <p>Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances:</p> <p>(a) A clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies; and/or</p> <p>(b) Had red cell transfusion within the previous 3 months.</p> <p>The results of the blood glucose monitoring, which must be no more than 4 months old at the time of initiation of treatment with a DPP4 inhibitor, must be documented in the patient's medical records.</p> <p>A patient whose diabetes was previously demonstrated unable to be controlled with metformin does not need to requalify on this criterion before being eligible for PBS-subsidised treatment with this fixed dose combination.</p>
<p>Administrative advice</p>	<p>This fixed dose combination tablet is not PBS-subsidised for use as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.</p>

## 7 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.

**8 Sponsor's Comment**

The sponsor had no comment.