

PUBLIC SUMMARY DOCUMENT

Product: ALOGLIPTIN with METFORMIN, tablet, 12.5mg/500mg, 12.5mg/850mg, 12.5mg/ 1000mg, Nesina Met[®]

Sponsor: Takeda Pharmaceuticals Australia Pty Ltd

Date of PBAC Consideration: November 2013

1. Purpose of Application

The major submission requested an Authority required (STREAMLINED) listing for treatment of type 2 diabetes in a patient whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor, a thiazolidinedione or a glucagon-like peptide-1, despite treatment with metformin and where a combination of metformin and sulfonylurea is contraindicated or not tolerated.

2. Background

The PBAC had not previously considered these alogliptin/metformin fixed dose combinations FDCs.

At the April 2013 special meeting, the PBAC considered the ‘DUSC Analysis of Medicines for Type II Diabetes’ noting that ‘intolerance’ to sulfonylurea is being interpreted more broadly in practice than was anticipated. The DUSC analysis showed that a high percentage of patients overall (41%) started third-line agents without a trial of a sulfonylurea (a population in which cost-effectiveness has not been established). In its consideration of the DUSC analysis, the PBAC recommended that restrictions for gliptin products could be amended to remove the requirement for the patient to be intolerant to a sulfonylurea. However, the PBAC considered that this change should be contingent on a price reduction to account for the likely non-cost-effective use, and that approximately 40% of use should be cost-minimised to the average daily dose of a sulfonylurea.

Listing of single agent alogliptin was recommended by the PBAC at the July 2013 meeting. A Public Summary Document is available on the [PBS website](#).

3. Registration Status

The submission was lodged under TGA/PBAC parallel process.

Alogliptin/metformin FDCs were TGA registered on 22 October 2013 and are indicated to improve glycaemic control in adult patients greater than or equal to 18 years old) with type 2 diabetes mellitus when diet and exercise do not provide adequate glycaemic control and treatment with both alogliptin and metformin is appropriate, when treatment with metformin alone does not provide adequate control, or in combination with a thiazolidinedione or with insulin, when dual therapy does not provide adequate control.

Alogliptin/metformin FDCs can also be used to replace separate tablets of alogliptin and metformin in patients already being treated with this combination.

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), despite treatment with metformin, without a requirement for 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 HbA1c must be documented in the patient's medical records at the time treatment with a gliptin is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin 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 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 alogliptin

Note

Alogliptin 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.

Listing was requested on a cost-minimisation basis with the individual components included in the fixed dose combination pack (i.e. alogliptin and metformin).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

The submission stated that the alogliptin/metformin FDC will provide a treatment alternative to concurrent use of alogliptin and metformin tablets for type 2 diabetes patients who have inadequate glycaemic control despite using metformin.

There are currently three other FDCs that have a dipeptidyl peptidase-4 (DPP-4) inhibitor or a thiazolidinedione in combination with metformin for the treatment of type 2 diabetes listed

on the PBS: rosiglitazone/metformin FDC, sitagliptin/metformin FDC, and vildagliptin/metformin FDC; and two others recommended at the April 2013 PBAC Special meeting: linagliptin/metformin FDC and saxagliptin/metformin FDC.

6. Comparator

The submission nominated three comparisons for the main comparator:

1. Alogliptin/metformin FDC compared to alogliptin plus metformin individual tablets
2. Alogliptin and metformin individual tablets compared to metformin alone (alogliptin single agent PBAC submission)
3. Alogliptin and metformin individual tablets compared to sitagliptin and metformin individual tablets (alogliptin single agent PBAC submission)

The submission presented analyses to support the first comparison only (using bioequivalence studies).

The PBAC agreed with the commentary and ESC advice that alogliptin, recommended at the July 2013 PBAC meeting, and metformin individual tablets, was a relevant comparator. The PBAC considered that this FDC would also replace other gliptin/metformin FDCs and that these other FDCs are also appropriate comparators.

7. Clinical Trials

The submission presented:

- Two randomised pharmacokinetic studies both comparing the alogliptin/metformin FDC to the individual alogliptin and metformin tablets. Data was presented for bioequivalence for the 12.5 mg alogliptin/500 mg metformin and 12.5 mg alogliptin/1000 mg metformin FDC, but was not provided for the 12.5 mg alogliptin/850 mg metformin FDC tablet.
- Two supplementary studies, one pharmacokinetic and one phase 3 clinical study, to demonstrate that alogliptin can be dosed either in a once daily or twice daily regimen.

Details are presented in the table below.

Trials and associated reports presented in the submission

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MET-103	An open-label, randomised, 2-cohort, 4-sequence, 4-period crossover study to determine the bioequivalence of alogliptin 6.25 mg and 12.5 mg and glucophage (metformin HCl) 500 mg and 1000 mg when administered as individual tablets and as a fixed-dose combination tablet.	28 February 2012 Protocol number SYR-322MET_103

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MET-101	An open-label, randomised, 2-cohort, 4-sequence, 4-period crossover study to determine the bioequivalence of alogliptin 6.25 mg and 12.5 mg and metformin 500 mg and 1000 mg when administered as individual tablets and as a fixed-dose combination tablet.	08 March 2010 Protocol number SYR-322MET_101
Supplementary randomised trials		
322-101	An open-label, multiple-dose, randomised cross-over study to determine the pharmacokinetics and pharmacodynamics of SYR-322 twice daily versus once-daily dosing in healthy male and female subjects.	07 February 2008 Protocol number SYR-322_101
MET-302	A multicentre, randomised, double-blind, placebo-controlled study to determine the efficacy and safety of alogliptin plus metformin, alogliptin alone, or metformin alone in subjects with type 2 diabetes.	24 October 2011 Protocol number SYR-322MET_302

8. Results of Trials

With regards to comparative effectiveness, bioequivalence was demonstrated with the alogliptin 12.5mg/metformin 500mg FDC, and alogliptin 12.5mg/metformin 1,000mg FDC compared to the use of individual tablets. The primary endpoints for these pharmacokinetics studies were $AUC_{(0-t_{1/2c}, 0-inf)}$ and C_{max} for alogliptin and metformin. The acceptable range for bioequivalence was the 90% confidence interval of the geometric mean ratios between 80% and 125%.

There were no head-to-head trials of the alogliptin/metformin FDC and the individual components in patients with type 2 diabetes.

With regards to comparative harms, in studies MET-103 and MET-101, there were no differences in adverse events (AEs) between subjects who received the alogliptin/metformin FDC compared with subjects who received the individual components. No deaths or serious adverse events occurred in the bioequivalence studies. Two subjects experienced AEs leading to discontinuation of the study drug. Both events were considered by the investigator to be not related to study drug and moderate in intensity.

The most commonly experienced treatment-related AEs in the pharmacokinetic studies were headache, nausea and abdominal pain.

The PBAC noted the ESC advice that the only outcome data that had previously been presented for DPP-4 inhibitors has been based on surrogate endpoints (in particular HbA1c), and considered that patient relevant outcomes would be more informative.

The PBAC noted recent publications that evaluated gliptins in high-risk cardiovascular patients. White, W et al. (Alogliptin after Acute Coronary Syndrome in Patients with Type 2

Diabetes. *N Eng J Med.* 369(14):1327-1335, October 3, 2013) found rates of major adverse cardiovascular events were not increased with alogliptin as compared with placebo. This is in contrast to a 25% increased rate of hospitalisation for heart failure with saxagliptin (Scirica, B et al. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *N Eng J Med* 369(14):1317-1325, October 3, 2013), or the unknown cardiovascular risk with other gliptins.

Benefit/harms summary: Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes

Outcome ¹	Number of participants (studies)	Relative effect from trial(s) (HR for alogliptin group)	Control event rate per 100 patients over trial duration ^b	Intervention event rate per 100 patients over trial duration ^b	Increment
Efficacy and safety					
Composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	5,380 (1)	HR: 0.96 (<=1.16 ^a)	11.8	11.3	NS
Death from cardiovascular causes	5,380 (1)	HR: 0.79 (0.60-1.04)	4.1	3.3	NS
Nonfatal MI	5,380 (1)	HR: 1.08 (0.88-1.33)	6.5	6.9	NS
Nonfatal stroke	5,380 (1)	HR: 0.91 (0.55-1.50)	1.2	1.1	NS
Death from any cause	5,380 (1)	HR: 0.88 (0.71-1.09)	6.5	5.7	NS

Note this trial population is significantly different to the alogliptin trials previously seen by PBAC, which have generally listed cardiac disorders as exclusion criteria.

^aThe parenthetical value is the upper boundary of the one-sided repeated CI, at an alpha level of 0.01.

^b Median follow-up of 18 months.

NS = non-significant

The PBAC noted a non-significant increase in the rate of pancreatitis in the alogliptin and saxagliptin trials. The PBAC considered that this important safety signal requires ongoing monitoring and review.

9. Clinical Claim

The submission claimed that alogliptin/metformin FDC is equivalent in terms of efficacy and safety with the individual components of alogliptin and metformin taken concomitantly.

The submission also claimed that alogliptin and metformin is non-inferior to sitagliptin and metformin (demonstrated in the alogliptin single agent submission, but not reported in this submission). The July 2013 alogliptin submission provided equi-effective doses of alogliptin 25 mg daily and sitagliptin 100 mg daily.

The PBAC accepted these claims.

10. Economic Analysis

The submission presents a cost-minimisation analysis of alogliptin/metformin FDC compared to the individual components. The PBAC agreed that a cost-minimisation approach is appropriate.

11. Estimated PBS Usage and Financial Implications

The submission estimated that the likely number of prescriptions on the PBS with the listing of alogliptin/metformin to be between 100,000 and 200,000 in Year 5, and a total of greater than 200,000 scripts over the first 5 years of listing.

The submission claimed that the listing of alogliptin/metformin FDC will not expand the current gliptin FDC market. The PBAC recalled the Drug Utilisation Sub-Committee (DUSC) Analysis of Medicines for Type II Diabetes (April 2013 special meeting) where “PBAC noted the use of gliptin FDC products substantially exceeds the expected utilisation”. However, the PBAC considered that the listing of the alogliptin/metformin FDC as recommended would not be expected to increase the gliptin/metformin FDC market, but take a share of the existing market. Thus, any financial impact would be limited and result from substitution of gliptin medicines in packs containing 28 days of supply with those containing 30 days of supply, and vice versa.

12. Recommendation and Reasons

The PBAC recommended listing the alogliptin/metformin FDC, as an Authority Required (STREAMLINED) benefit for treatment of patients whose HbA1c is greater than 7% prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin), despite treatment with metformin, without the requirement for patients to be contraindicated or intolerant of a combination of metformin and a sulfonylurea.

The PBAC noted that the restriction originally proposed required the prior intolerance or contra-indication of a combination of metformin and a sulfonylurea, and was made prior to the outcome of the July 2013 PBAC alogliptin submission being known. The PBAC acknowledged that the pre-PBAC response had indicated the willingness of the sponsor to align the price of the FDC with the price of alogliptin alone should the PBAC recommend a listing restriction that aligns with the single agent listing restriction.

The PBAC considered that the cost-effectiveness of the alogliptin/metformin FDC would be acceptable if it were cost-minimised against the ex-manufacturer prices corresponding to the component prices for alogliptin and metformin.

The PBAC considered that the proliferation of available gliptin/metformin FDCs and the range of doses of both gliptin and metformin components, creates the potential for prescriber and patient confusion. The PBAC was concerned there are potential for Quality Use of Medicines issues arising from the number and variety of gliptin FDCs available now and in the future on the PBS.

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

The PBAC advised the Minister that under Section 101 3BA of the National Health Act, alogliptin/metformin FDC should be treated as interchangeable on an individual patient basis with:

- i. Sitagliptin/metformin FDC; and
- ii. Vildagliptin/metformin FDC; and
- iii. Linagliptin/metformin FDC; and
- iv. Saxagliptin/metformin FDC.

Outcome:

Recommended

Name, Restriction, Manner of administration and form	Max. Qty	Nº. of Rpts	Proprietary Name and Manufacturer	
ALOGLIPTIN + METFORMIN Alogliptin 12.5 mg + metformin hydrochloride 500 mg, tablet, 56	1	5	Nesina Met	TK
Alogliptin 12.5 mg + metformin hydrochloride 850 mg, tablet, 56	1	5	Nesina Met	TK
Alogliptin 12.5 mg + metformin hydrochloride 1000 mg, tablet, 56	1	5	Nesina Met	TK

Condition/Indication:	Diabetes mellitus type 2
Restriction:	Authority required (STREAMLINED)
Clinical criteria:	<p>Patient must have, or have had, a HbA1c measurement greater than 7% despite treatment with metformin; 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 despite treatment with metformin.</p>

Prescriber Instructions	<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 gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 inhibitor is initiated.</p> <p>The HbA1c must be no more than 4 months old at the time treatment with a gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 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 gliptin, a glitazone, a glucagon-like peptide-1 or an SGLT2 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>
Administrative Advice	<p>This fixed dose combination is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy), as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.</p>

Condition/Indication:	Diabetes mellitus type 2
Treatment Phase	Continuing
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 alogliptin
Administrative Advice	This fixed dose combination is not PBS-subsidised for use in combination with a sulfonylurea (triple oral therapy), as initial therapy or in combination with a thiazolidinedione (glitazone), a glucagon-like peptide-1 or an SGLT2 inhibitor.

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 comment.