Public Summary Document

Product: Alogliptin, tablets, 6.25 mg, 12.5 mg, 25 mg Nesina®
Sponsor: Takeda Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: July 2013

1. Purpose of Application

The submission requested an Authority required (Streamlined) listing for the treatment of patients with type 2 diabetes in combination with metformin or a sulfonylurea.

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

At the time of PBAC consideration in July 2013, Alogliptin was yet to be TGA registered for treatment of type 2 diabetes in combination with metformin or a sulfonylurea.

The PBAC noted that the TGA regulatory application was still pending; however, the Clinical Evaluation Report and TGA Delegates Summary were available to the PBAC at the time of consideration in July 2013.

4. Listing Requested and PBAC's View

Authority required (Streamlined)

Dual oral combination therapy with metformin or a sulfonylurea.
Type 2 diabetes, in combination with either metformin or 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 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 HbA1c must be documented in the patient's medical records at the time therapy with a gliptin, a glitazone or a glucagon-like peptide-1 is initiated. The HbA1c must be no greater 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 anaemia and haemoglobinopathies; and/or
b) red cell transfusion within the previous 3 months.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Type 2 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia resulting from resistance to the action of insulin, insufficient insulin secretion or both. Diet and

lifestyle modifications are the first steps in managing the disease, followed by the addition of drug therapy with metformin. When diet, lifestyle modifications and metformin monotherapy is inadequate in controlling blood sugar levels, current treatment guidelines recommend adding a sulfonylurea. For refractory patients, or those intolerant to a combination of metformin and a sulfonylurea, the addition of a gliptin is a further therapeutic option. Other options include thiazolidinediones, acarbose, and incretins.

If listed, alogliptin will be the fifth dipeptidyl peptidase 4 inhibitor listed on the PBS following the listing of sitagliptin, saxagliptin, linagliptin and vildagliptin.

The PBAC recalled the Drug Utilisation Sub-Committee (DUSC) Analysis of Medicines for type 2 diabetes, considered at the April 2013 PBAC Special meeting, showed that gliptins, glitazones and exenatide are used extensively in patients without contraindications or intolerance to either metformin or a sulfonylurea, despite the restrictions requiring one of these conditions. The PBAC considered that, should alogliptin be listed on the PBS, it would also be likely to be used outside the current proposed restriction.

6. Comparator

The submission nominated sitagliptin as the main comparator. The PBAC considered this was the appropriate comparator for the population of patients where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The PBAC agreed that an alternative comparator would be sulfonylureas, given the likely use of alogliptin in patients without contraindications or intolerance to either metformin or a sulfonylurea.

7. Clinical Trials

No head-to-head trials were presented in the submission. The submission was based on an indirect comparison of alogliptin and sitagliptin using placebo as the common comparator.

For the indirect comparison, the submission, alogliptin versus sitagliptin with metformin as background therapy, the submission presented:
For this indirect comparison, the submission presented:

- three randomised placebo controlled trials of alogliptin 25 mg per day, in a total of 405 alogliptin treated patients, and 302 placebo-treated patients with a background dose of greater than or equal to 1,500 mg per day of metformin (MET-008, CCT-006, 308), indirectly compared to:

- three randomised placebo controlled trials of sitagliptin 100 mg per day, in a total of 654 sitagliptin-treated patients, and 423 placebo-treated patients, with standard doses of a sulfonylurea (Charbonnel et al., 2006; Scott et al., 2008; Raz et al., 2008).

For the indirect comparison, alogliptin versus sitagliptin with a sulfonylurea as background therapy, the submission presented:
For this indirect comparison, the submission presented:

- two randomised placebo controlled trials of alogliptin 25 mg per day, in a total of 604 alogliptin-treated patients, and 103 placebo-treated patients with a background therapy of a sulfonylurea (SULF-007, CCT-005), indirectly compared to:
- one randomised placebo controlled trial of sitagliptin 100mg per day, in 222 patients treated with sitagliptin and 219 placebo-treated patients, as an add-on therapy to a sulfonylurea (Hermansen et al., 2007).

The table below details the published trials presented in the submission.

Trial ID/ First author	Protocol title/ Publication title	Publication citation
MET-008, Nauck et al. (2009)	"Efficacy and safety of adding the dipeptidyl peptidase-4 inhibitor alogliptin to metformin therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: A multicentre, randomised, double-blind, placebo-controlled trial."	International Journal of Clinical Practice 63(1): 46-55.
CCT-006, Seino et al. (2012)	"Efficacy and safety of alogliptin added to metformin in Japanese patients with type 2 diabetes: A randomized, double-blind, placebo-controlled study with an open-label, long-term extension study."	Diabetes, Obesity and Metabolism 14(10): 927-936.
SULF-007, Pratley et al. (2009)	"Efficacy and safety of the dipeptidyl peptidase-4 inhibitor alogliptin in patients with type 2 diabetes inadequately controlled by glyburide monotherapy."	Diabetes, Obesity and Metabolism 11(2): 167-176.
Sitagliptin trials		
Charbonnel et al. (2006)	"Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone."	Diabetes Care. 29(12): 2638-2643.
Scott et al. (2008)	"Efficacy and safety of sitagliptin when added to ongoing metformin therapy in patients with type 2 diabetes."	Diabetes Obes Metab. 10(10): 959-969. Epub 2008 Jan 2014.
Raz et al. (2008)	A 30 week double blind study of patients with T2DM who were	"Efficacy and safety of sitagliptin added to ongoing metformin

	randomised to metformin plus either sitagliptin (n=96) placebo (n=94)	therapy in patients with type 2 diabetes." Curr Med Res Opin. 24(2): 537-550.
Added-on to sulfonylurea - placebo as common reference		
Hermansen, K., M. Kipnes, et al. (2007).	"Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin."	Diabetes, Obesity and Metabolism 9(5): 733-745.

The PBAC noted that compared to the likely PBS population, the trial populations were younger (patients in the trials were generally in their mid-50s), had a shorter duration of diabetes (mean duration of diabetes of 4.9 to 10.4 years in the trials) and had lower BMIs (mean BMI in the trials of 25.5 – 32.4 kg/m2). In addition, it was not clear how comparable the background doses of metformin and sulfonylureas were to those likely to be used in Australian clinical practice.

The PBAC considered that while the populations in the trials were probably not directly representative of the proposed PBS population, the analyses presented in the submission provided reasonable support for the submission's clinical claims.

Given the potential for use of alogliptin outside the proposed treatment algorithm, based on the DUSC Analysis of Medicines for Type II Diabetes the PBAC noted with interest that a number of trials are on-going that compare alogliptin to sulfonylureas.

8. Results of Trials

For the comparison of alogliptin versus sitagliptin with metformin as background therapy, the pooled results of the indirect comparison showed the least squares mean difference versus placebo for alogliptin and sitagliptin was similar for reduction of HbA1c from baseline (-0.68 vs. -0.65 respectively). The indirect mean difference was -0.03 (95% CI: -0.31, 0.25; p=0.9), and within the pre-defined non-inferiority margin of <0.4%, and supportive of the submission's claim of non-inferiority. The upper 95% CI was also within the nominated 0.4% non-inferiority margin.

For the comparison of alogliptin versus sitagliptin with a sulfonylurea as background therapy, the pooled results of the indirect comparison showed the LS mean difference versus placebo for alogliptin and sitagliptin was similar for reduction of HbA1c from baseline (-0.77 vs. -0.57 respectively). The indirect mean difference was -0.20 (95% CI: -0.72, 0.32; p=0.46), and within the pre-defined non-inferiority margin of <0.4%, and supportive of the submission's claim of non-inferiority.

With regard to comparative harms, the PBAC noted in the indirect comparison, there were no statistically significant differences in the rate of drug-related adverse events between alogliptin and sitagliptin. Overall, the adverse event profile was similar for active treatments

and placebo patients including; serious adverse events, gastrointestinal adverse events, abdominal pain, diarrhoea, nausea, and vomiting.

Few patients reported hypoglycaemic events. The PBAC noted that there was a higher rate of serious adverse events for alogliptin, compared to sitagliptin, in the sulfonylurea trials [OR: 3.5 (0.5, 22.00), pooled analysis of SULF-007, CCT-005 and Hermansen et al 2007], but that this difference was not statistically significant. The PBAC also noted the current regulatory concerns about pancreatic problems with gliptins, noting this was a drug class issue.

9. Clinical Claim

The submission described alogliptin (25 mg/day) as non-inferior in terms of comparative effectiveness and non-inferior in terms of comparative safety to sitagliptin (100 mg/day) as dual oral combination therapy with metformin, and as dual oral combination therapy with a sulfonylurea, for the treatment of patients with type II diabetes where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The PBAC considered the submission's claims to be adequately supported by the evidence presented.

10. Economic Analysis

The submission presented a cost-minimisation analysis of alogliptin dual therapy compared to sitagliptin dual therapy. The analysis was based on the clinical claim of non-inferiority to sitagliptin. The trial-based estimates of equi-effective doses were alogliptin 25 mg daily and sitagliptin 100 mg daily. No additional costs or cost off-sets were considered.

The PBAC considered that should alogliptin be used in clinical practice earlier in the treatment algorithm and substitute for sulfonylureas, the cost-effective price would be substantially lower than that proposed in the submission. Calculation of this price would be based on a percentage of the alogliptin price being cost-minimised to the gliptin component, and a percentage of the price being cost-minimised to the average daily dose of a sulfonylurea.

11. Estimated PBS Usage and Financial Implications

The submission claimed that listing of alogliptin would be cost-neutral to the PBS as the cost of each pack of alogliptin would be off-set in full by the cost of the gliptin that would otherwise have been prescribed. The submission assumed that as the fifth gliptin to be listed, there would be no growth in the market from listing alogliptin.

The PBAC noted that the estimates over the first 5 years of listing were based on a linear projection of total gliptin packs sold on the PBS for the calendar years 2009-2012 (Medicare online data).

The PBAC noted that the impact of fitting an exponential function to the Medicare data resulted in estimated increased costs to the PBS of less than $10 million in Year 5.

The PBAC acknowledged that the estimates calculated during the evaluation were a likely over-estimate, but agreed that alogliptin would contribute to some growth of the gliptin market, should it be listed on the PBS. Further, the PBAC considered that some of this growth may be substitution from sulfonylureas, rather than other gliptins.

12. Recommendation and Reasons

The PBAC recommended listing of alogliptin as an Authority required (Streamlined) benefit for treatment in combination with metformin or a sulfonylurea of 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 or a sulfonylurea, without the requirement for patients to have contraindications to, or be intolerant of a combination of metformin and a sulfonylurea. Listing should be at a reduced price, which takes into account the likely proportion of use in patients who have not trialled a sulfonylurea and where cost-effectiveness has not been established.

The PBAC recalled its consideration in relation to the DUSC Analysis of Medicines for Type II Diabetes 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 price of the average daily dose of a sulfonylurea.

The PBAC considered that it was reasonable to extrapolate the risk of use outside the restriction earlier in the treatment algorithm in patients not supplied a sulfonylurea, as seen for currently listed gliptin products, to alogliptin. The PBAC therefore considered that listing at a price where a percentage of use is cost-minimised to sitagliptin and a percentage of use is cost-minimised to the average daily dose of a sulfonylurea in combination with metformin, with a restriction without the requirement for patients to be contraindicated/intolerant of a combination of metformin and a sulfonylurea, was appropriate.

The PBAC considered the indirect comparison presented in the submission adequately supported the submission's claim that alogliptin 25 mg was non-inferior in terms of comparative effectiveness and comparative safety to sitagliptin 100 mg as dual oral combination therapy with metformin, and as dual oral combination therapy with a sulfonylurea.

The PBAC recommended that alogliptin 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 should be treated as interchangeable on an individual patient basis with:

i. linagliptin; and
ii. saxagliptin; and
iii. sitagliptin; and
iv. vildagliptin.

Outcome:
Recommended

Recommended listing

Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
ALOGLIPTIN			
Alogliptin 25 mg, tablet	28	5	Nesina TK
Alogliptin 12.5 mg, tablet	28	5	Nesina TK
Alogliptin 6.25 mg, tablet	28	5	Nesina TK

Condition:	Diabetes mellitus Type 2
Restriction:	Authority required (STREAMLINED) *TO BE FINALISED*

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 comments.