PUBLIC SUMMARY DOCUMENT
Product: SAXAGLIPTIN, tablets, 5 mg, Onglyza®
Sponsor: Bristol-Myers Squibb Pharmaceuticals
Date of PBAC Consideration: March 2010

1. Purpose of Application.

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

2. Background

This drug had not previously been considered by the PBAC.

3. Registration Status

At the time of consideration, saxagliptin was not registered with the Therapeutic Goods Administration (TGA).

Listing on the PBS is contingent upon successful TGA registration.

4. Listing Requested and PBAC's View.

Authority required (STREAMLINED)
Dual oral combination therapy with metformin or a sulfonylurea.

Type 2 diabetes mellitus, in combination with metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7 % prior to initiation of saxagliptin 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 saxagliptin treatment is initiated. The HbA1c must be no more than 4 months old at the time saxagliptin treatment 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 saxagliptin therapy, must be documented in the patient's medical records.

Note:
Saxagliptin is not PBS-subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with a thiazolidinedione (glitazone).

The PBAC recommended the restriction wording for saxagliptin and all currently PBS subsidised dipeptidyl peptidase 4 inhibitors (gliptins) and thiazolidinediones (glitazones) be modified to allow patients to switch between agents in these two classes without having to requalify with respect to glycosylated haemoglobin levels (HbA1c). Although the evidence to support switches from a gliptin to a glitazone, and vice versa, is limited, the Committee considered it unreasonable to require a loss of diabetic control prior to switching.

5. Clinical Place for the Proposed Therapy

Type 2 diabetes 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. If dual therapy with metformin and a sulfonylurea is unsuccessful, insulin can be added. Other options include thiazolidinediones, acarbose, incretins, glitinides and gliptins. Saxagliptin would provide another gliptin option.

6. Comparator

The submission nominated sitagliptin as the main comparator. The PBAC considered this appropriate.

7. Clinical Trials

The submission presented one unpublished randomised head-to-head trial comparing saxagliptin 5 mg/day with sitagliptin 100 mg/day each in combination with metformin 1,500 mg to 3,000 mg daily in patients with type 2 diabetes mellitus (T2DM) not adequately controlled by metformin alone over an 18-week study period.

The submission also presented an indirect comparison of saxagliptin and sitagliptin in combination with a sulfonylurea (glyburide or glimepiride) based on the results of two 24-week duration, multi-centre, randomised double-blind, placebo-controlled phase III trials (Hermansen et al. 2007 and an unpublished trial) using placebo as the common reference. The unpublished trial compared saxagliptin (2.5 mg/day or 5 mg/day plus glyburide 7.5 mg) to placebo (plus glyburide 7.5 mg). Hermansen et al. (2007) compared sitagliptin (100 mg/day plus glimepiride 4 – 8 mg/day) to placebo (plus glimepiride 4 – 8 mg/day).

One trial had been published at the time of the submission, as follows:

Trial ID / First author	Protocol title/ Publication title	Publication citation
Indirect comparison – saxagliptin as add-on to a sulfonylurea versus a sulfonylurea		
Hermansen 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* 2007; 9 (5): 733-745.

In addition, an indirect comparison of sitagliptin plus metformin (Charbonnel et al. 2006) versus saxagliptin plus metformin (an unpublished trial) using metformin (placebo) as the common comparator was presented in the submission.

The PBAC noted concerns about whether the patients included in the clinical trials were representative of those for whom PBS listing was sought, and whether the results of the indirect comparison were sufficient to support a listing for use in combination with a sulfonylurea. Despite this the PBAC accepted that the data supported the clinical claim.

8. Results of Trials

In the unpublished, direct head-to-head comparison of saxagliptin versus sitagliptin (either agent added to metformin), the change in HbA1c % from baseline at week 18 was the primary outcome.

Based on the upper limit of the 95 % confidence interval (i.e. 0.2 %), the mean difference in HbA1c was below the pre-defined non-inferiority margin of less than 0.3 %, indicating saxagliptin 5 mg/day was non-inferior to sitagliptin 100 mg/day when added to metformin, in reducing HbA1c from baseline.

The results of the indirect comparison of saxagliptin to sitagliptin (either agent added to a sulfonylurea) showed that there was no statistically significant difference between saxagliptin 5 mg and sitagliptin 100 mg for the reduction in HbA1c from baseline at Week 24.

The PBAC accepted that saxagliptin is no worse in terms of efficacy than sitagliptin when either agent is used in combination with metformin or a sulfonylurea. However, the Committee noted concerns about the limited data on the long term durability of effect of saxagliptin.

In the unpublished, direct head-to-head trial of saxagliptin versus sitagliptin (both agents added to metformin), there were no statistically significant differences between the two treatments in the number of adverse events reported, the proportion of subjects experiencing serious adverse events, drug related adverse events, or serious drug-related adverse events. The numbers of hypoglycaemic events with saxagliptin and sitagliptin were low and there was no statistically significant difference in the number of hypoglycaemic events experienced between the two treatment arms.

With the exception of 'Any adverse event', the indirect comparison of safety outcomes from the unpublished indirect comparison of saxagliptin versus sitagliptin (either agent added to a sulfonylurea) and Hermansen et al. (2007) showed that there were no statistically significant differences between saxagliptin 5 mg/day and sitagliptin 100 mg/day in the occurrence of adverse events or safety related outcomes. The relative risk (RR) for the occurrence of 'any adverse event' was statistically significantly lower for saxagliptin 5 mg/day than sitagliptin 100 mg/day. However, the adverse event rates (i.e. for 'any adverse event') in the placebo arms across trials were significantly different. A similarly large difference in the placebo arms for 'drug-related adverse events' was also observed.

There appeared to be no statistically significant differences between treatment (saxagliptin 5 mg/sitagliptin 100 mg) and placebo for any of the other reported adverse

events across the randomised controlled trials including; all hypoglycaemic events, confirmed hypoglycaemic events, gastrointestinal adverse events, abdominal pain, diarrhoea, nausea, and vomiting.

The extended assessment of comparative harms suggested that there was no evidence of dependence or abuse developing for saxagliptin. Further, there was no evidence that saxagliptin increased cardio vascular risk.

The PBAC accepted that saxagliptin is no worse in terms of safety than sitagliptin when either agent is used in combination with metformin or a sulfonylurea. However, the Committee noted concerns about the long term safety of the dipeptidyl peptidase inhibitors (gliptins) in general.

9. Clinical Claim

The submission described saxagliptin (5 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, for the treatment of patients with type 2 diabetes mellitus where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The submission also described saxagliptin (5 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 sulfonylurea, for the treatment of patients with type 2 diabetes mellitus where a combination of metformin and a sulfonylurea is contraindicated or not tolerated.

The PBAC accepted that saxagliptin is no worse in terms of efficacy and safety than sitagliptin when either agent is used in combination with metformin or a sulfonylurea.

10 Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were estimated as saxagliptin 5 mg/day and sitagliptin 100 mg/day.

11. Estimated PBS Usage and Financial Implications

The likely number of packs dispensed/year was estimated by the submission to be in the range of 100,000 – 200,000 prescriptions in Year 5.

The financial cost/year to the PBS of listing saxagliptin on the BPS was predicted by the submission to be less than $15,000 in Year 1 to Year 5. The submission anticipated the listing of saxagliptin on the PBS will be cost-neutral to the Government as it will directly substitute for sitagliptin, pioglitazone or rosiglitazone.

12. Recommendation and Reasons

The PBAC recommended the listing of saxagliptin as an Authority required (Streamlined) benefit for the treatment of type 2 diabetes mellitus, in combination with metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7 % despite treatment with either metformin or a sulfonylurea and where a combination of metformin and a sulfonylurea is contraindicated or not tolerated. Listing was recommended on a cost-minimisation basis with sitagliptin with the equi-effective doses of saxagliptin 5 mg/day and sitagliptin 100 mg/day.

Despite concerns about whether the patients included in the clinical trials were representative of those for whom PBS listing is sought, and whether the results of the indirect comparison were sufficient to support a listing for use combination with a sulfonylurea, the PBAC accepted that saxagliptin is no worse in terms of efficacy and safety than sitagliptin when either agent is used in combination with metformin or a sulfonylurea. However, the Committee noted concerns about the limited data on the long term durability of effect of saxagliptin, and about the long term safety of the dipeptidyl peptidase inhibitors (gliptins) in general.

The PBAC recommended the restriction wording for saxagliptin and all currently PBS subsidised dipeptidyl peptidase 4 inhibitors (gliptins) and thiazolidinediones (glitazones) be modified to allow patients to switch between agents in these two classes without having to requalify with respect to glycosylated haemoglobin levels (HbA1c). Although the evidence to support switches from a gliptin to a glitazone, and vice versa, is limited, the Committee considered it unreasonable to require a loss of diabetic control prior to switching.

The PBAC also noted that the listing of saxagliptin is contingent upon successful TGA registration.

Recommendation:
SAXAGLIPTIN, tablet, 5 mg

Restriction:

NOTE:
Saxagliptin is not PBS-subsidised for use in combination with metformin and a sulfonylurea (triple oral therapy), as monotherapy or in combination with a thiazolidinedione (glitazone).

Authority required (STREAMLINED)
Dual oral combination therapy with metformin or a sulfonylurea.

Type 2 diabetes mellitus, in combination with metformin or a sulfonylurea, in a patient whose HbA1c is greater than 7 % prior to initiation of a dipeptidyl peptidase 4 inhibitor (gliptin) or a thiozolidinedione (glitazone) 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 or glitazone is initiated. The HbA1c must be no more than 4 months old at the time treatment with a gliptin or glitazone 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 or glitazone, must be documented in the patient's medical records.

Maximum quantity: 28
Repeats: 5

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 has no comment.