PUBLIC SUMMARY DOCUMENT
Product: SAXAGLIPTIN, tablet, 5 mg (as hydrochloride), Onglyza®
Sponsor: Bristol-Myers Squibb Australia Pty Ltd
Date of PBAC Consideration: July 2012

1. Purpose of Application

To extend the current Authority Required (Streamlined) listing to include treatment of patients with type 2 diabetes in combination with insulin.

2. Background

This drug has not previously been considered by the PBAC for this indication.

At the March 2010 meeting, 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. Listing was effective 1 June 2011.

3. Registration Status

At the time of PBAC consideration saxagliptin was not TGA registered for the proposed indication:

> Saxagliptin is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with insulin (with or without metformin), as an adjunct to diet and exercise, when insulin alone does not provide adequate glycaemic control.

Saxagliptin was TGA registered on 18 March 2011 for the indications:

- Add-on combination - in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.
- Initial combination - for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).

4. Listing Requested and PBAC's View

Authority Required (STREAMLINED)
Combination therapy with insulin

Type 2 diabetes, in combination with insulin, 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 insulin and oral anti-diabetic agents, or insulin alone where metformin is contraindicated.

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.

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

There is estimated to be between 45,000 and 100,000 new diagnoses of diabetes each year in Australia, with Type 2 making up the majority. 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 exercise are the first steps in managing the disease, followed by the addition of drug therapy with metformin. When diet and exercise modifications and metformin monotherapy is inadequate in controlling blood glucose, current treatment guidelines recommend adding a sulfonylurea. If dual therapy with metformin and a sulfonylurea is unsuccessful, insulin can be added. Other options include glucagon like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, alpha-glucosidase inhibitors, or meglitinides.

The submission proposed that the place in therapy of saxagliptin is as an alternative treatment option to pioglitazone for use as add-on combination therapy with insulin for the treatment of type 2 diabetes.

6. Comparator

The submission nominated pioglitazone as the comparator.

The PBAC considered that pioglitazone is not the only appropriate comparator and that some of the use of saxagliptin would be in patients with the objective of reducing the dose of concomitant insulin, reducing hypoglycaemia and/or improving diabetes control. Therefore insulin should also be considered as a comparator.

7. Clinical Trials

The submission presented an indirect comparison of two randomised trials of saxagliptin 5 mg + insulin with or without metformin (CT-057) and pioglitazone 30 mg + insulin (Mattoo 2005) with placebo + insulin as a common comparator.

Trial CT-057 was conducted over 24 weeks, allowed insulin dose changes according to pre-specified protocols and allowed patients to continue taking metformin in combination with

insulin in both treatment arms. Mattoo (2005) was conducted over 26 weeks, allowed insulin titration by investigator discretion and required patients to cease all oral anti-diabetes drugs (OADs) other than pioglitazone.

The submission excluded Rosenstock (2002) from consideration due to short trial duration (16 weeks), age of the trial and differences in baseline HbA1c compared to Trial CT-057 and Mattoo (2005). Rosenstock (2002) was the pivotal trial in the September 2001 re-submission of pioglitazone for the combination therapy with insulin listing. The results for mean change in HbA1c from baseline are included in analyses conducted during the evaluation.

The PBAC did not accept the submission's argument that the Rosenstock (2002) trial should be excluded from the primary indirect analysis. *For PBAC's view see Recommendation and Reasons.*

Details of the trials and associated reports published at the time of submission are in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
Common reference: placebo + insulin		
Saxagliptin + insulin		
Trial 057	A multicenter, randomized, double-blind, phase 3 trial to evaluate the efficacy and safety of saxagliptin added to insulin monotherapy or to insulin in combination with metformin in subjects with type 2 diabetes who have inadequate glycemic control on insulin alone or on insulin in combination with metformin.	29th April 2011.
Barnett, A. H., et al. (2011)	Saxagliptin add-on therapy to insulin with or without metformin for type 2 diabetes mellitus: 52-week safety and efficacy.	Diabetologia 54: S108-S109
Charbonnel, B., et al. (2011)	Saxagliptin (SAXA) add-on therapy improves glycemic control in patients (Pts) with poorly controlled type 2 diabetes (T2D) on insulin (INS) alone or INS combined with metformin (MET).	Diabetes 60: A304
Pioglitazone + insulin		
Mattoo, V., et al. (2005)	Metabolic effects of pioglitazone in combination with insulin in patients with type 2 diabetes mellitus whose disease is not adequately controlled with insulin therapy: Results of a six-month, randomized, double-blind, prospective, multicenter, parallel-group trial.	Clinical Therapeutics 27(5): 554-567

8. Results of Trials

The primary outcome reported was mean change in HbA1c from baseline at 24 weeks (and 52 weeks CT-057 only). Key secondary outcomes reported were the proportions of patients achieving an HbA1c <7%, proportion of patients experiencing one or more hypoglycaemic events, mean change in the insulin dose; mean change from baseline in patient weight (kg), and mean change from baseline in FPG (mmol/L). Data from patients requiring rescue medication for uncontrolled hyperglycaemia were not considered in the analyses of the primary outcome. Missing data were imputed using the last post-baseline measure prior to the use of rescue medication (LOCF).

CHANGE IN HBA1C FROM BASELINE

The results of the indirect analysis presented in the submission (CT-057 vs Mattoo) show no statistically significant difference in reduction in HbA1c between saxagliptin and pioglitazone. The point estimate favours pioglitazone and the upper bound of the 95% CI meets the nominated MCID of 0.4% suggesting non-inferiority of saxagliptin.

Differences between trials (CT-057 and Mattoo et al 2005) in terms of insulin dosage, diabetes management and concomitant OAD use (i.e. metformin) make comparability of the trials uncertain, and in some outcomes may bias results in favour of saxagliptin.

In the indirect analysis using pooled pioglitazone data from Mattoo (2005) and Rosenstock (2002) conducted during the evaluation, there is no statistically significant difference between saxagliptin and pioglitazone, the point estimate favours pioglitazone treatment and the upper bound of the 95% CI no longer meets the MCID of 0.4%.

PATIENTS ACHIEVING AN HBA1C <7%

Similar proportions of patients achieved an HbA1c <7% with saxagliptin and pioglitazone (CT-057 vs Mattoo). However, results of Trial CT-057 stratified by concomitant use of metformin showed more metformin treated patients achieved an HbA1c <7% than those not receiving metformin and the placebo adjusted treatment effect was also higher in the metformin treated subgroup.

INSULIN REQUIREMENTS

There was a statistically significant reduction in insulin utilisation in pioglitazone treated patients, compared to saxagliptin. Interpretation of this outcome may be confounded by differences between trials; protocol driven changes in insulin dose in CT-057, and investigator discretion in Mattoo 2005.

Patients in Trial CT-057 used primarily pre-mixed insulin formulations (59.9%), intermediate-acting insulins (17.8%) and long-acting insulins (17.1%). Mattoo (2005) did not report insulin types used.

OTHER OUTCOMES

Differences in rates of hypoglycaemic events between saxagliptin and pioglitazone were confounded by differences in the definition and counting of hypoglycaemic events between the two trials. CT-057 only included hypoglycaemic events reported as adverse events; Mattoo (2005) reported all hypoglycaemic events including those based on subjective symptoms.

All groups reported weight gain within and across trials; saxagliptin 0.39 kg and pioglitazone 4.05 kg. The indirect analysis of the mean change in body weight from baseline showed less weight gain with saxagliptin + insulin ± metformin compared to pioglitazone + insulin.

There were statistically significantly larger reductions in fasting blood glucose in

pioglitazone + insulin treated patients compared with saxagliptin + insulin ± metformin patients.

The most commonly reported adverse events in saxagliptin treated patients were infections and infestations (26%), gastro-intestinal disturbances (14%) and skin and subcutaneous tissue disorders (2%). The incidence and seriousness of adverse events was similar to placebo (insulin ± metformin), and not statistically significantly different from patients taking pioglitazone. The incidence of reported adverse events in Trial CT-057 was generally higher at 52 weeks compared to 24 weeks.

Commonly reported adverse events in saxagliptin treated patients are shown below.

	Study 057 24-Week		**Study 057 52-Week**	
	Saxa + INS	**PBO + INS**	**Saxa + INS**	**PBO + INS**
Infections and infestations	26%	29%	36%	41%
Gastro-intestinal disturbances	14%	14%	19%	17%
Skin and subcutaneous tissue disorders	2%	2%	5%	5%

Abbreviations: SAXA – saxagliptin, INS – insulin, PBO – placebo

Long term reporting of adverse events in the PSUR was consistent with the clinical trials and a comprehensive review of cardiovascular risk factors found no evidence of increased cardiovascular risk in patients with type 2 diabetes exposed to saxagliptin for up to 2.5 years. The clinical trials excluded patients with serious cardiovascular co-morbidities and risk factors.

For PBAC's view, see Recommendation and Reasons.

9. Clinical Claim

The submission described saxagliptin (in combination with insulin) as non-inferior in terms of comparative effectiveness and equivalent in terms of comparative safety over pioglitazone (in combination with insulin).

The PBAC considered there was insufficient evidence to accept the submission's clinical claim that saxagliptin (in combination with insulin) is non-inferior in terms of comparative effectiveness to pioglitazone (in combination with insulin). In terms of safety, the PBAC accepted the submission's claim that saxagliptin (in combination with insulin) is equivalent to pioglitazone (in combination with insulin), based on currently available data.

10. Economic Analysis

The submission presented a cost minimisation analysis based on the claim of non-inferiority of saxagliptin 5 mg to pioglitazone 30 mg.

For PBAC's view, see Recommendation and Reasons.

11. Estimated PBS Usage and Financial Implications

The submission estimated the total net financial cost to the PBS to be less than $10 million in Year 5.

The submission's estimates are uncertain due to the uncertainty in estimated prescription numbers and application of the F1 rather than F2 Formulary price for pioglitazone ($91.19 instead of $77.62). Cost estimates did not include possible substitution of saxagliptin for metformin in combination with insulin.

The Pre-Sub-Committee Response presented sensitivity analyses to inform the PBAC with respect to uncertainty in substitution for pioglitazone and market uptake of saxagliptin.

The market uptake estimate suggested that saxagliptin will replace pioglitazone as the most commonly prescribed authority required OAD in combination with insulin. The assumption of a higher market share for saxagliptin compared to pioglitazone in this population could be possible given the safety concerns of pioglitazone.

For PBAC's view, see Recommendation and Reasons.

12. Recommendation and Reasons

The PBAC noted that this submission is being considered under the TGA/PBAC parallel process and that the recently received TGA Delegates overview was negative, due to poor efficacy and lack of data beyond 24 weeks.

The PBAC considered that pioglitazone is not the only appropriate comparator and that some of the use of saxagliptin would be in patients with the objective of reducing the dose of concomitant insulin, reducing hypoglycaemia and/or improving diabetes control. Therefore insulin should also be considered as a comparator.

The PBAC noted that the basis of submission was an indirect comparison of saxagliptin 5 mg plus insulin with or without metformin (Trial CT-057) with pioglitazone 30 mg plus insulin (Mattoo 2005) using placebo plus insulin as a common comparator. The submission specifies a non-inferiority margin of 0.4% for the primary outcome of change in HbA1c from baseline.

The PBAC did not accept the submission's argument that the Rosenstock (2002) trial should be excluded from the primary indirect analysis. The PBAC noted that this was the pivotal trial used in the resubmission for listing pioglitazone for combination therapy with insulin. The PBAC agreed with the ESC that there was not a strong basis for the selective inclusion/exclusion of trials in the pivotal indirect analysis particularly as this could affect the conclusions drawn from the results.

For the primary outcome of mean change in HbA1c levels from baseline, the PBAC noted that the indirect comparison of CT-057 versus Mattoo shows no statistically significant difference between saxagliptin and pioglitazone (mean difference: 0.14, 95% CI: -0.12, 0.40) and the upper bound of the 95% CI meets the nominated minimum clinically important difference (MCID) of 0.4%, suggesting non-inferiority of saxagliptin. However, the PBAC also noted that an indirect comparison of CT-057 and Rosenstock would suggest inferiority of saxagliptin, similar to the analysis conducted during the evaluation using the pooled pioglitazone data from Mattoo (2005) and Rosenstock (2002), with the upper bound of the 95% CI not meeting the MCID of 0.4% (mean difference: 0.35%, 95% CI: -0.12%. 0.83%).

Further, the PBAC agreed that differences between the trials in terms of insulin dose (protocol driven regimen versus investigator's discretion), diabetes management (use of

rescue medication and definitions of hypoglycaemia), and concomitant metformin use in Trial CT-057 add more uncertainty to the indirect comparison results. Therefore, the PBAC was not convinced that saxagliptin is non-inferior compared with pioglitazone.

The PBAC noted that there were no statistically significant differences between saxagliptin and pioglitazone (in combination with insulin) in relation to adverse events. The PBAC acknowledged the ongoing long term safety concerns with pioglitazone, and that prescribers may prefer an alternative oral treatment to pioglitazone.

The PBAC considered there was insufficient evidence to accept the submission's clinical claim that saxagliptin (in combination with insulin) is non-inferior in terms of comparative effectiveness to pioglitazone (in combination with insulin). In terms of safety, the PBAC accepted the submission's claim that saxagliptin (in combination with insulin) is equivalent to pioglitazone (in combination with insulin), based on currently available data.

The PBAC noted the submission presented a cost minimisation analysis of saxagliptin 5 mg versus pioglitazone 30 mg. The PBAC considered that on the basis of inadequate clinical evidence to support a claim of non-inferiority, the cost minimisation analysis was not valid.

The PBAC was unconvinced by the submission's justifications that the price of saxagliptin (for the indication in combination with insulin) should be based on the current PBS price for saxagliptin for the dual therapy indication (DPMQ $91.19), which is equivalent to the F1 price of pioglitazone prior to the statutory 16% price decrease. The PBAC considered this effectively requests a price premium for saxagliptin over the current PBS price for pioglitazone (DPMQ $77.62) for the indication in combination with insulin. The PBAC agreed this was not justified as saxagliptin provides no improvement in efficacy or safety over pioglitazone.

The PBAC considered that the estimates of use and financial implications presented in the submission were uncertain due to the effect that safety concerns regarding pioglitazone may have on saxagliptin usage in the future, the issues discussed above regarding price and possible use of saxagliptin in combination with metformin and insulin.

Therefore, the PBAC rejected the submission on the basis of an inadequate comparison across appropriate comparators, uncertain comparative clinical effectiveness and uncertain cost effectiveness.

The PBAC noted that the submission meets the criteria for an independent review.

Recommendation:
Reject

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 is disappointed with the PBAC decision and will explore available options to make Saxagliptin available on the PBS for eligible Australian patients who require an alternative to pioglitazone in achieving HbA1c control whilst being treated with insulin.

The sponsor would like to note, that saxagliptin has since been ARTG listed for this indication.